Tab 1

CHROMOSOME

A chromosome is a package of DNA with part or all of the genetic material of an organism. In most chromosomes, the very long thin DNA fibers are coated with nucleosome-forming packaging proteins; in eukaryotic cells the most important of these proteins are the histones. These proteins, aided by chaperone proteins, bind to and condense the DNA molecule to maintain its integrity. These chromosomes display a complex three-dimensional structure, which plays a significant role in transcriptional regulation.

A replicated and condensed metaphase eukaryotic chromosome:

1) ***Chromatid***
2) ***Centromere***
3) *Short arm*
4) *Long arm*

Chromosomes are normally visible under a light microscope only during the metaphase of cell division (where all chromosomes are aligned in the center of the cell in their condensed form). Before this happens, each chromosome is duplicated (S phase), and both copies are joined by a centromere, resulting either in an X-shaped structure (pictured above), if the centromere is located equatorially, or a two-arm structure, if the centromere is located distally. The joined copies are now called sister chromatids. During metaphase, the X-shaped structure is called a metaphase chromosome, which is highly condensed and thus easiest to distinguish and study. In animal cells, chromosomes reach their highest compaction level in anaphase during chromosome segregation.

Chromosomal recombination during meiosis and subsequent sexual reproduction play a significant role in genetic diversity. If these structures are manipulated incorrectly, through processes known as chromosomal instability and translocation, the cell may undergo mitotic catastrophe. Usually, this will make the cell initiate apoptosis leading to its own death, but sometimes mutations in the cell hamper this process and thus cause progression of cancer.
Some use the term chromosome in a wider sense, to refer to the individualized portions of chromatin in cells, either visible or not under light microscopy. Others use the concept in a narrower sense, to refer to the individualized portions of chromatin during cell division, visible under light microscopy due to high condensation.

Etymology

The word chromosome (/ˈkroʊməˌsoʊm, -ˌzoʊm/) comes from the Greek χρῶμα (chroma, "colour") and σῶμα (soma, "body"), describing their strong staining by particular dyes. The term was coined by the German anatomist Heinrich Wilhelm Waldeyer, referring to the term chromatin, which was introduced by Walther Flemming.
Some of the early karyological terms have become outdated. For example, Chromatin (Flemming 1880) and Chromosom (Waldeyer 1888), both ascribe color to a non-colored state.

History Of Discovery

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

Otto Bütschli was the first scientist to recognize the structures now known as chromosomes.
In a series of experiments beginning in the mid-1880s, Theodor Boveri gave definitive contributions to elucidating that chromosomes are the vectors of heredity, with two notions that became known as 'chromosome continuity' and 'chromosome individuality'.
Wilhelm Roux suggested that each chromosome carries a different genetic configuration, and Boveri was able to test and confirm this hypothesis. Aided by the rediscovery at the start of the 1900s of Gregor Mendel's earlier work, Boveri was able to point out the connection between the rules of inheritance and the behaviour of the chromosomes. Boveri influenced two generations of American cytologists: Edmund Beecher Wilson, Nettie Stevens, Walter Sutton and Theophilus Painter were all influenced by Boveri (Wilson, Stevens, and Painter actually worked with him).
In his famous textbook The Cell in Development and Heredity, Wilson linked together the independent work of Boveri and Sutton (both around 1902) by naming the chromosome theory of inheritance the Boveri–Sutton chromosome theory (the names are sometimes reversed). Ernst Mayr remarks that the theory was hotly contested by some famous geneticists: William Bateson, Wilhelm Johannsen, Richard Goldschmidt and T.H. Morgan, all of a rather dogmatic turn of mind. Eventually, complete proof came from chromosome maps in Morgan's own lab.
The number of human chromosomes was published in 1923 by Theophilus Painter. By inspection through the microscope, he counted twenty-four pairs, which would mean forty-eight chromosomes. His error was copied by others and it was not until 1956 that the true number, forty-six, was determined by Indonesian-born cytogeneticist Joe Hin Tjio.

Prokaryotes

The prokaryotes – bacteria and archaea – typically have a single circular chromosome, but many variations exist. The chromosomes of most bacteria, which some authors prefer to call genophores, can range in size from only 130,000 base pairs in the endosymbiotic bacteria Candidatus Hodgkinia cicadicola and Candidatus Tremblaya princeps, to more than 14,000,000 base pairs in the soil-dwelling bacterium Sorangium cellulosum. Spirochaetes of the genus Borrelia are a notable exception to this arrangement, with bacteria such as Borrelia burgdorferi, the cause of Lyme disease, containing a single linear chromosome.

Structure In Sequences

Prokaryotic chromosomes have less sequence-based structure than eukaryotes. Bacteria typically have a one-point (the origin of replication) from which replication starts, whereas some archaea contain multiple replication origins. The genes in prokaryotes are often organized in operons, and do not usually contain introns, unlike eukaryotes.

DNA packaging

Prokaryotes do not possess nuclei. Instead, their DNA is organized into a structure called the nucleoid. The nucleoid is a distinct structure and occupies a defined region of the bacterial cell. This structure is, however, dynamic and is maintained and remodeled by the actions of a range of histone-like proteins, which associate with the bacterial chromosome. In archaea, the DNA in chromosomes is even more organized, with the DNA packaged within structures similar to eukaryotic nucleosomes.

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Certain bacteria also contain plasmids or other extrachromosomal DNA. These are circular structures in the cytoplasm that contain cellular DNA and play a role in horizontal gene transfer. In prokaryotes (see nucleoids) and viruses, the DNA is often densely packed and organized; in the case of archaea, by homology to eukaryotic histones, and in the case of bacteria, by histone-like proteins. Bacterial chromosomes tend to be tethered to the plasma membrane of the bacteria. In molecular biology application, this allows for its isolation from plasmid DNA by centrifugation of lysed bacteria and pelleting of the membranes (and the attached DNA).
Prokaryotic chromosomes and plasmids are, like eukaryotic DNA, generally supercoiled. The DNA must first be released into its relaxed state for access for transcription, regulation, and replication.

Eukaryotes

Each eukaryotic chromosome consists of a long linear DNA molecule associated with proteins, forming a compact complex of proteins and DNA called chromatin. Chromatin contains the vast majority of the DNA in an organism, but a small amount inherited maternally can be found in the mitochondria. It is present in most cells, with a few exceptions, for example, red blood cells. Histones are responsible for the first and most basic unit of chromosome organization, the nucleosome.
Eukaryotes (cells with nuclei such as those found in plants, fungi, and animals) possess multiple large linear chromosomes contained in the cell's nucleus. Each chromosome has one centromere, with one or two arms projecting from the centromere, although, under most circumstances, these arms are not visible as such. In addition, most eukaryotes have a small circular mitochondrial genome, and some eukaryotes may have additional small circular or linear cytoplasmic chromosomes.
In the nuclear chromosomes of eukaryotes, the uncondensed DNA exists in a semi-ordered structure, where it is wrapped around histones (structural proteins), forming a composite material called chromatin.

Interphase chromatin

The packaging of DNA into nucleosomes causes a 10 nanometer fibre which may further condense up to 30 nm fibres Most of the euchromatin in interphase nuclei appears to be in the form of 30-nm fibers. Chromatin structure is the more decondensed state, i.e. the 10-nm conformation allows transcription.
During interphase (the period of the cell cycle where the cell is not dividing), two types of chromatin can be distinguished:

- ***Euchromatin**, which consists of DNA that is active, e.g., being expressed as protein.*
- ***Heterochromatin**, which consists of mostly inactive DNA. It seems to serve structural purposes during the chromosomal stages. Heterochromatin can be further distinguished into two types:*

1) *Constitutive heterochromatin, which is never expressed. It is located around the centromere and usually contains repetitive sequences.*
2) *Facultative heterochromatin, which is sometimes expressed.*

Metaphase Chromatin And Division

In the early stages of mitosis or meiosis (cell division), the chromatin double helix becomes more and more condensed. They cease to function as accessible genetic material (transcription stops) and
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become a compact transportable form. The loops of thirty-nanometer chromatin fibers are thought to fold upon themselves further to form the compact metaphase chromosomes of mitotic cells. The DNA is thus condensed about ten-thousand-fold.
The chromosome scaffold, which is made of proteins such as condensin, TOP2A and KIF4, plays an important role in holding the chromatin into compact chromosomes. Loops of thirty-nanometer structure further condense with scaffold into higher order structures.
This highly compact form makes the individual chromosomes visible, and they form the classic four-arm structure, a pair of sister chromatids attached to each other at the centromere. The shorter arms are called p arms (from the French petit, small) and the longer arms are called q arms (q follows p in the Latin alphabet; q-g "grande"; alternatively it is sometimes said q is short for queue meaning tail in French). This is the only natural context in which individual chromosomes are visible with an optical microscope.
Mitotic metaphase chromosomes are best described by a linearly organized longitudinally compressed array of consecutive chromatin loops.
During mitosis, microtubules grow from centrosomes located at opposite ends of the cell and also attach to the centromere at specialized structures called kinetochores, one of which is present on each sister chromatid. A special DNA base sequence in the region of the kinetochores provides, along with special proteins, longer-lasting attachment in this region. The microtubules then pull the chromatids apart toward the centrosomes, so that each daughter cell inherits one set of chromatids. Once the cells have divided, the chromatids are uncoiled and DNA can again be transcribed. In spite of their appearance, chromosomes are structurally highly condensed, which enables these giant DNA structures to be contained within a cell nucleus.

Human Chromosomes

Chromosomes in humans can be divided into two types: autosomes (body chromosome(s)) and allosome (sex chromosome(s)). Certain genetic traits are linked to a person's sex and are passed on through the sex chromosomes. The autosomes contain the rest of the genetic hereditary information. All act in the same way during cell division. Human cells have 23 pairs of chromosomes (22 pairs of autosomes and one pair of sex chromosomes), giving a total of 46 per cell. In addition to these, human cells have many hundreds of copies of the mitochondrial genome. Sequencing of the human genome has provided a great deal of information about each of the chromosomes. Below is a table compiling statistics for the chromosomes, based on the Sanger Institute's human genome information in the Vertebrate Genome Annotation (VEGA) database. Number of genes is an estimate, as it is in part based on gene predictions. Total chromosome length is an estimate as well, based on the estimated size of unsequenced heterochromatin regions.

Chromosome	Genes[39]	Total base pairs	% of bases
1	2000	247,199,719	8.0
2	1300	242,751,149	7.9
3	1000	199,446,827	6.5
4	1000	191,263,063	6.2
5	900	180,837,866	5.9
6	1000	170,896,993	5.5

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7	*900*	*158,821,424*	*5.2*
8	*700*	*146,274,826*	*4.7*
9	*800*	*140,442,298*	*4.6*
10	*700*	*135,374,737*	*4.4*
11	*1300*	*134,452,384*	*4.4*
12	*1100*	*132,289,534*	*4.3*
13	*300*	*114,127,980*	*3.7*
14	*800*	*106,360,585*	*3.5*
15	*600*	*100,338,915*	*3.3*
16	*800*	*88,822,254*	*2.9*
17	*1200*	*78,654,742*	*2.6*
18	*200*	*76,117,153*	*2.5*
19	*1500*	*63,806,651*	*2.1*
20	*500*	*62,435,965*	*2.0*
21	*200*	*46,944,323*	*1.5*
22	*500*	*49,528,953*	*1.6*
X	*800*	*154,913,754*	*5.0*
(sex chromosome)			
Y	*200[40]*	*57,741,652*	*1.9*
(sex chromosome)			
Total	*21,000*	*3,079,843,747*	*100.0*

Based on the micrographic characteristics of size, position of the centromere and sometimes the presence of a chromosomal satellite, the human chromosomes are classified into the following groups:

Group	***Chromosomes***	***Features***
A	*1–3*	*Large, metacentric or submetacentric*
B	*4–5*	*Large, submetacentric*
C	*6–12, X*	*Medium-sized, submetacentric*
D	*13–15*	*Medium-sized, acrocentric, with satellite*
E	*16–18*	*Small, metacentric or submetacentric*
F	*19–20*	*Very small, metacentric*
G.	*21–22, Y*	*Very small, acrocentric (and 21, 22 with satellite)*

Karyotypes *:- In general, the karyotype is the characteristic chromosome complement of a eukaryote species. The preparation and study of karyotypes is part of cytogenetics.*
Although the replication and transcription of DNA is highly standardized in eukaryotes, the same cannot be said for their karyotypes, which are often highly variable. There may be variation between species in chromosome number and in detailed organization. In some cases, there is significant variation within species. Often there is:

1. variation between the two sexes

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2. variation between the germline and soma (between gametes and the rest of the body)
3. variation between members of a population, due to balanced genetic polymorphism
4. geographical variation between races
5. mosaics or otherwise abnormal individuals.

Also, variation in karyotype may occur during development from the fertilized egg.
The technique of determining the karyotype is usually called karyotyping. Cells can be locked part-way through division (in metaphase) in vitro (in a reaction vial) with colchicine. These cells are then stained, photographed, and arranged into a karyogram, with the set of chromosomes arranged, autosomes in order of length, and sex chromosomes (here X/Y) at the end.
Like many sexually reproducing species, humans have special gonosomes (sex chromosomes, in contrast to autosomes). These are XX in females and XY in males.

History And Analysis Techniques

Investigation into the human karyotype took many years to settle the most basic question: How many chromosomes does a normal diploid human cell contain? In 1912, Hans von Winiwarter reported 47 chromosomes in spermatogonia and 48 in oogonia, concluding an XX/XO sex determination mechanism. In 1922, Painter was not certain whether the diploid number of man is 46 or 48, at first favouring 46. He revised his opinion later from 46 to 48, and he correctly insisted on humans having an XX/XY system.
New techniques were needed to definitively solve the problem:

1) *Using cells in culture*
2) *Arresting mitosis in metaphase by a solution of colchicine*
3) *Pretreating cells in a hypotonic solution 0.075 M KCl, which swells them and spreads the chromosomes*
4) *Squashing the preparation on the slide forcing the chromosomes into a single plane*
5) *Cutting up a photomicrograph and arranging the result into an indisputable karyogram.*

It took until 1954 before the human diploid number was confirmed as 46. Considering the techniques of Winiwarter and Painter, their results were quite remarkable. Chimpanzees, the closest living relatives to modern humans, have 48 chromosomes as do the other great apes: in humans two chromosomes fused to form chromosome 2.

Aberrations

Chromosomal aberrations are disruptions in the normal chromosomal content of a cell. They can cause genetic conditions in humans, such as Down syndrome, although most aberrations have little to no effect. Some chromosome abnormalities do not cause disease in carriers, such as translocations, or chromosomal inversions, although they may lead to a higher chance of bearing a child with a chromosome disorder.[citation needed] Abnormal numbers of chromosomes or chromosome sets, called aneuploidy, may be lethal or may give rise to genetic disorders. Genetic counseling is offered for families that may carry a chromosome rearrangement.
The gain or loss of DNA from chromosomes can lead to a variety of genetic disorders. Human examples include:

- ***Cri du chat**, which is caused by the deletion of part of the short arm of chromosome 5. "Cri du chat" means "cry of the cat" in French; the condition was so-named because affected babies make high-pitched cries that sound like those of a cat. Affected individuals have wide-set eyes, a small head and jaw, moderate to severe mental health problems, and are very short.*
- ***Down syndrome**, the most common trisomy, usually caused by an extra copy of chromosome 21 (trisomy 21). Characteristics include decreased muscle tone, stockier build, asymmetrical skull, slanting eyes and mild to moderate developmental disability.*
- ***Edwards syndrome**, or trisomy-18, the second most common trisomy. Symptoms include motor retardation, developmental disability and numerous congenital anomalies causing serious health problems. Ninety percent of those affected die in infancy. They have characteristic clenched hands and overlapping fingers.*
- ***Isodicentric 15,** also called idic(15), partial tetrasomy 15q, or inverted duplication 15 (inv dup 15).*
- ***Jacobsen syndrome**, which is very rare. It is also called the 11q terminal deletion disorder. Those affected have normal intelligence or mild developmental disability, with poor expressive language skills. Most have a bleeding disorder called Paris-Trousseau syndrome.*
- ***Klinefelter syndrome (XXY).** Men with Klinefelter syndrome are usually sterile and tend to be taller and have longer arms and legs than their peers. Boys with the syndrome are often shy and quiet and have a higher incidence of speech delay and dyslexia. Without testosterone treatment, some may develop gynecomastia during puberty.*
- ***Patau Syndrome**, also called D-Syndrome or trisomy-13. Symptoms are somewhat similar to those of trisomy-18, without the characteristic folded hand.*
- ***Small supernumerary marker chromosome.** This means there is an extra, abnormal chromosome. Features depend on the origin of the extra genetic material. Cat-eye syndrome and isodicentric chromosome 15 syndrome (or Idic15) are both caused by a supernumerary marker chromosome, as is Pallister–Killian syndrome.*
- ***Triple-X syndrome (XXX).** XXX girls tend to be tall and thin and have a higher incidence of dyslexia.*
- ***Turner syndrome (X instead of XX or XY)**. In Turner syndrome, female sexual characteristics are present but underdeveloped. Females with Turner syndrome often have a short stature, low hairline, abnormal eye features and bone development and a "caved-in" appearance to the chest.*
- ***Wolf–Hirschhorn syndrome**, which is caused by partial deletion of the short arm of chromosome 4. It is characterized by growth retardation, delayed motor skills development, "Greek Helmet" facial features, and mild to profound mental health problems.*
- ***XYY syndrome**. XYY boys are usually taller than their siblings. Like XXY boys and XXX girls, they are more likely to have learning difficulties.*

Sperm Aneuploidy

Exposure of males to certain lifestyle, environmental and/or occupational hazards may increase the risk of aneuploid spermatozoa. In particular, risk of aneuploidy is increased by tobacco smoking, and

occupational exposure to benzene, insecticides, and perfluorinated compounds. Increased aneuploidy is often associated with increased DNA damage in spermatozoa.

Number In Various Organisms

In Eukaryotes

The number of chromosomes in eukaryotes is highly variable (see table). In fact, chromosomes can fuse or break and thus evolve into novel karyotypes. Chromosomes can also be fused artificially. For example, the 16 chromosomes of yeast have been fused into one giant chromosome and the cells were still viable with only somewhat reduced growth rates.

The tables below give the total number of chromosomes (including sex chromosomes) in a cell nucleus. For example, most eukaryotes are diploid, like humans who have 22 different types of autosomes, each present as two homologous pairs, and two sex chromosomes. This gives 46 chromosomes in total. Other organisms have more than two copies of their chromosome types, such as bread wheat, which is hexaploid and has six copies of seven different chromosome types – 42 chromosomes in total.

Species #	*Chromosome numbers (2n) in some animals*
★ *Indian muntjac*	*6♀, 7♂*
★ *Common fruit fly*	*8*
★ *Pill millipede*	*30*
★ *Earthworm*	*36*
★ *Tibetan fox*	*36*
★ *Domestic cat*	*38*
★ *Domestic pig*	*38*
★ *Laboratory mouse*	*40*
★ *Laboratory rat*	*42*
★ *Rabbit*	*44*
★ *Syrian hamster*	*44*
★ *Guppy*	*46*
★ *Human*	*46*
★ *Hare*	*48*
★ *Gorilla*	*48*
★ *Chimpanzee*	*48*
★ *Domestic sheep*	*54*
★ *Garden snail*	*54*
★ *Silkworm*	*56*
★ *Elephant*	*56*
★ *Cow*	*60*
★ *Donkey*	*62*
★ *Guinea pig*	*64*
★ *Horse*	*64*
★ *Dog*	*78*
★ *Hedgehog*	*90*

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★ *Goldfish* *100–104*
★ *Kingfisher* *132*

Chromosome numbers in other organisms

Species	Largechromosomes	Intermediatechromosomes	Microchromosomes
Trypanosoma brucei	11	6	≈100
Domestic pigeon[88]	18	–	59–63
Chicken.	8	2 sex chromosomes	60

Normal members of a particular eukaryotic species all have the same number of nuclear chromosomes (see the table). Other eukaryotic chromosomes, i.e., mitochondrial and plasmid-like small chromosomes, are much more variable in number, and there may be thousands of copies per cell.

The 23 human chromosome territories during prometaphase in fibroblast cells

Asexually reproducing species have one set of chromosomes that are the same in all body cells. However, asexual species can be either haploid or diploid.
Sexually reproducing species have somatic cells (body cells), which are diploid [2n] having two sets of chromosomes (23 pairs in humans), one set from the mother and one from the father. Gametes, reproductive cells, are haploid [n]: They have one set of chromosomes. Gametes are produced by meiosis of a diploid germline cell. During meiosis, the matching chromosomes of father and mother can exchange small parts of themselves (crossover), and thus create new chromosomes that are not inherited solely from either parent. When a male and a female gamete merge (fertilization), a new diploid organism is formed.

Some animal and plant species are polyploid [Xn]: *They have more than two sets of homologous chromosomes. Plants important in agriculture such as tobacco or wheat are often polyploid, compared to their ancestral species. Wheat has a haploid number of seven chromosomes, still seen in some cultivars as well as the wild progenitors. The more-common pasta and bread wheat types are polyploid, having 28 (tetraploid) and 42 (hexaploid) chromosomes, compared to the 14 (diploid) chromosomes in the wild wheat.*

In Prokaryotes
Prokaryote species generally have one copy of each major chromosome, but most cells can easily survive with multiple copies. For example, Buchnera, a symbiont of aphids has multiple copies of its chromosome, ranging from 10–400 copies per cell. However, in some large bacteria, such as Epulopiscium fishelsoni up to 100,000 copies of the chromosome can be present. Plasmids and plasmid-like small chromosomes are, as in eukaryotes, highly variable in copy number. The number of plasmids in the cell is almost entirely determined by the rate of division of the plasmid – fast division causes high copy number.

List Of Chromones
Human chromosomes, each of which contains an incomplete list of genes located on that chromosome, are as follows:

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★ Chromosome 1 :- Chromosome 1 is the designation for the largest human chromosome. Humans have two copies of chromosome 1, as they do with all of the autosomes, which are the non-sex chromosomes. Chromosome 1 spans about 249 million nucleotide base pairs, which are the basic units of information for DNA. It represents about 8% of the total DNA in human cells.
★ Chromosome 2 :- Chromosome 2 is one of the twenty-three pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 2 is the second-largest human chromosome, spanning more than 242 million base pairs and representing almost eight percent of the total DNA in human cells.
★ Chromosome 3 :- Chromosome 3 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 3 spans more than 198 million base pairs and represents about 6.5 percent of the total DNA in cells.
★ Chromosome 4 :- Chromosome 4 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 4 spans more than 190 million base pairs and represents between 6 and 6.5 percent of the total DNA in cells.
★ Chromosome 5 :- Chromosome 5 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 5 spans about 182 million base pairs and represents almost 6% of the total DNA in cells. Chromosome 5 is the 5th largest human chromosome, yet has one of the lowest gene densities. This is partially explained by numerous gene-poor regions that display a remarkable degree of non-coding and syntenic conservation with non-mammalian vertebrates, suggesting they are functionally constrained.
★ Chromosome 6 :- Chromosome 6 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 6 spans nearly 171 million base pairs and represents between 5.5 and 6% of the total DNA in cells. It contains the major histocompatibility complex, which contains over 100 genes related to the immune response, and plays a vital role in organ transplantation.
★ Chromosome 7 :- Chromosome 7 is one of the 23 pairs of chromosomes in humans, who normally have two copies of this chromosome. Chromosome 7 spans about 160 million base pairs and represents between 5 and 5.5 percent of the total DNA in cells.
★ Chromosome 8 :- Chromosome 8 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 8 spans about 146 million base pairs and represents between 4.5 and 5.0% of the total DNA in cells.
★ Chromosome 9 :- Chromosome 9 is one of the 23 pairs of chromosomes in humans. Humans normally have two copies of this chromosome, as they normally do with all chromosomes. Chromosome 9 spans about 138 million base pairs of nucleic acids and represents between 4.0 and 4.5% of the total DNA in cells.
★ Chromosome 10 :- Chromosome 10 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 10 spans about 134 million base pairs and represents between 4 and 4.5 percent of the total DNA in cells.
★ Chromosome 11 :- Chromosome 11 is one of the 23 pairs of chromosomes in humans. Humans normally have two copies of this chromosome. Chromosome 11 spans about 135 million base pairs and represents between 4 and 4.5 percent of the total DNA in cells. The shorter arm is termed 11p while the longer arm is 11q. At about 21.5 genes per megabase, chromosome 11 is one of the most gene-rich, and disease-rich, chromosomes in the human genome.
★ Chromosome 12 :- Chromosome 12 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 12 spans about 133 million base pairs and represents between 4 and 4.5 percent of the total DNA in cells.
★ Chromosome 13 :- Chromosome 13 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 13 spans about 113 million base pairs and represents between 3.5 and 4% of the total DNA in cells.
★ Chromosome 14 :- Chromosome 14 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 14 spans about 107 million base pairs and represents between 3 and 3.5% of the total DNA in cells.

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★ *Chromosome 15 :- Chromosome 15 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 15 spans about 99.7 million base pairs and represents between 3% and 3.5% of the total DNA in cells. Chromosome 15 is an acrocentric chromosome, with a very small short arm, which contains few protein coding genes among its 19 million base pairs. It has a larger long arm that is gene rich, spanning about 83 million base pairs.*

★ *Chromosome 16 :- Chromosome 16 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 16 spans about 90 million base pairs and represents just under 3% of the total DNA in cells.*

★ *Chromosome 17 :- Chromosome 17 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 17 spans more than 84 million base pairs and represents between 2.5 and 3% of the total DNA in cells.*

★ *Chromosome 18 :- Chromosome 18 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 18 spans about 80 million base pairs and represents about 2.5 percent of the total DNA in cells.*

★ *Chromosome 19 :- Chromosome 19 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 19 spans more than 61.7 million base pairs, the building material of DNA. It is considered the most gene-rich chromosome containing roughly 1,500 genes, despite accounting for only 2 percent of the human genome.*

★ *Chromosome 20 :- Chromosome 20 is one of the 23 pairs of chromosomes in humans. Chromosome 20 spans around 66 million base pairs and represents between 2 and 2.5 percent of the total DNA in cells. Chromosome 20 was fully sequenced in 2001 and was reported to contain over 59 million base pairs. Since then, due to sequencing improvements and fixes, the length of chromosome 20 has been updated to just over 66 million base pairs.*

★ *Chromosome 21 :- Chromosome 21 is one of the 23 pairs of chromosomes in humans. Chromosome 21 is both the smallest human autosome and chromosome, with 46.7 million base pairs representing about 1.5 percent of the total DNA in cells. Most people have two copies of chromosome 21, while those with three copies of chromosome 21 have Down syndrome.*

★ *Chromosome 22 :- Chromosome 22 is one of the 23 pairs of chromosomes in human cells. Humans normally have two copies of chromosome 22 in each cell. Chromosome 22 is the second smallest human chromosome, spanning about 51 million DNA base pairs and representing between 1.5 and 2% of the total DNA in cells.*

★ *X Chromosome :- The X chromosome is one of the two sex chromosomes in many organisms, including mammals, and is found in both males and females. It is a part of the XY sex-determination system and XO sex-determination system. The X chromosome was named for its unique properties by early researchers, which resulted in the naming of its counterpart Y chromosome, for the next letter in the alphabet, following its subsequent discovery.*

★ *Y Chromosome :- The Y chromosome is one of two sex chromosomes in therian mammals and other organisms. Along with the X chromosome, it is part of the XY sex-determination system, in which the Y is the sex-determining chromosome because the presence of the Y chromosome causes offspring produced in sexual reproduction to be of male sex. In mammals, the Y chromosome contains the SRY gene, which triggers development of male gonads. The Y chromosome is passed only from male parents to male offspring.*

RELATED EXTENSIONS

- *Aneuploidy*
- *Chromomere*
- *Chromosome segregation*
- *Cohesin*
- *Condensin*
- *DNA*
- *Genetic deletion*

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

- *Epigenetics*
- *Chromosomes in genetic algorithm*
- ♦ *Genetic genealogy*
  - ★ *Genealogical DNA test*
- *Lampbrush chromosome*
- *List of number of chromosomes of various organisms*
- *Locus (explains gene location nomenclature)*
- *Maternal influence on sex determination*
- *Microchromosome*
- *Minichromosome*
- *Non-disjunction*
- *Secondary chromosome*
- *Sex-determination system*
  - ♦ *XY sex-determination system*
    - ♣ *X-chromosome*
      - ★ *X-inactivation*
    - ♣ *Y-chromosome*
      - ★ *Y-chromosomal Aaron*
      - ★ *Y-chromosomal Adam*
  - ♦ *ZO sex-determination system*
  - ♦ *ZW sex-determination system*
  - ♦ *XO sex-determination system*
  - ♦ *Temperature-dependent sex determination*
  - ♦ *Haplodiploid sex-determination system*
- *Polytene chromosome*
- *Protamine*
- *Neochromosome*
- *Parasitic chromosome*

CHROMATID

*A **chromatid** (Greek khrōmat- 'color' + -id) is one half of a duplicated chromosome. Before replication, one chromosome is composed of one DNA molecule. In replication, the DNA molecule is copied, and the two molecules are known as chromatids. During the later stages of cell division these chromatids separate longitudinally to become individual chromosomes.*

Chromatid pairs are normally genetically identical, and said to be homozygous. However, if mutations occur, they will present slight differences, in which case they are heterozygous. The pairing of chromatids should not be confused with the ploidy of an organism, which is the number of homologous versions of a chromosome.

Chromatids may be sister or non-sister chromatids. A sister chromatid is either one of the two chromatids of the same chromosome joined together by a common centromere. A pair of sister chromatids is called a dyad. Once sister chromatids have separated (during the anaphase of mitosis

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or the anaphase II of Meiosis during sexual reproduction), they are again called chromosomes, each having the same genetic mass as one of the individual chromatids that made up its parent. The DNA sequence of two sister chromatids is completely identical (apart from very rare DNA copying errors).

Sister chromatid exchange (SCE) is the exchange of genetic information between two sister chromatids. SCEs can occur during mitosis or meiosis. SCEs appear to primarily reflect DNA recombinational repair processes responding to DNA damage (see article Sister chromatid exchange).

Non-sister chromatids, on the other hand, refers to either of the two chromatids of paired homologous chromosomes, that is, the pairing of a paternal chromosome and a maternal chromosome. In chromosomal crossovers, non-sister (homologous) chromatids form chiasmata to exchange genetic material during the prophase I of meiosis (See Homologous chromosome pair).

Sister Chromatid

A sister chromatid refers to the identical copies (chromatids) formed by the DNA replication of a chromosome, with both copies joined together by a common centromere. In other words, a sister chromatid may also be said to be 'one-half' of the duplicated chromosome. A pair of sister chromatids is called a dyad. A full set of sister chromatids is created during the synthesis (S) phase of interphase, when all the chromosomes in a cell are replicated. The two sister chromatids are separated from each other into two different cells during mitosis or during the second division of meiosis.

Compare sister chromatids to homologous chromosomes, which are the two different copies of a chromosome that diploid organisms (like humans) inherit, one from each parent. Sister chromatids are by and large identical (since they carry the same alleles, also called variants or versions, of genes) because they derive from one original chromosome. An exception is towards the end of meiosis, after crossing over has occurred, because sections of each sister chromatid may have been exchanged with corresponding sections of the homologous chromatids with which they are paired during meiosis. Homologous chromosomes might or might not be the same as each other because they derive from different parents.

There is evidence that, in some species, sister chromatids are the preferred template for DNA repair. Sister chromatid cohesion is essential for the correct distribution of genetic information between daughter cells and the repair of damaged chromosomes. Defects in this process may lead to aneuploidy and cancer, especially when checkpoints fail to detect DNA damage or when incorrectly attached mitotic spindles do not function properly.

Mitosis

Mitotic recombination is primarily a result of DNA repair processes responding to spontaneous or induced damages. Homologous recombinational repair during mitosis is largely limited to interaction between nearby sister chromatids that are present in a cell subsequent to DNA replication but prior to cell division. Due to the special nearby relationship they share, sister chromatids are not only preferred over distant homologous chromatids as substrates for recominational repair, but have the capacity to repair more DNA damage than do homologs.

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Meiosis

Studies with the budding yeast Saccharomyces cerevisiae indicate that inter-sister recombination occurs frequently during meiosis, and up to one-third of all recombination events occur between sister chromatids.

Homologous Chromosomes

A pair of homologous chromosomes, or homologs, is a set of one maternal and one paternal chromosome that pair up with each other inside a cell during meiosis. Homologs have the same genes in the same loci, where they provide points along each chromosome that enable a pair of chromosomes to align correctly with each other before separating during meiosis. This is the basis for Mendelian inheritance, which characterizes inheritance patterns of genetic material from an organism to its offspring parent developmental cell at the given time and area .

Chromosomes are linear arrangements of condensed deoxyribonucleic acid (DNA) and histone proteins, which form a complex called chromatin. Homologous chromosomes are made up of chromosome pairs of approximately the same length, centromere position, and staining pattern, for genes with the same corresponding loci. One homologous chromosome is inherited from the organism's mother; the other is inherited from the organism's father. After mitosis occurs within the daughter cells, they have the correct number of genes which are a mix of the two parents' genes. In diploid (2n) organisms, the genome is composed of one set of each homologous chromosome pair, as compared to tetraploid organisms which may have two sets of each homologous chromosome pair. The alleles on the homologous chromosomes may be different, resulting in different phenotypes of the same genes. This mixing of maternal and paternal traits is enhanced by crossing over during meiosis, wherein lengths of chromosomal arms and the DNA they contain within a homologous chromosome pair are exchanged with one another.

History

Early in the 1900s, William Bateson and Reginald Punnett were studying genetic inheritance and they noted that some combinations of alleles appeared more frequently than others. That data and information was further explored by Thomas Morgan. Using test cross experiments, he revealed that, for a single parent, the alleles of genes near to one another along the length of the chromosome move together. Using this logic he concluded that the two genes he was studying were located on homologous chromosomes. Later on during the 1930s, Harriet Creighton and Barbara McClintock were studying meiosis in corn cells and examining gene loci on corn chromosomes. Creighton and McClintock discovered that the new allele combinations present in the offspring and the event of crossing over were directly related. This proved interchromosomal genetic recombination.

Structure

Homologous chromosomes are pairs of chromosomes in a diploid organism that have similar genes, although not necessarily identical. There are two main properties of homologous chromosomes: 1) the length of chromosomal arms and 2) the placement of the centromere.

The actual length of the arm, in accordance with the gene locations, is critically important for proper alignment. Centromere placement on the chromosome can be characterized by four main

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arrangements, either metacentric, submetacentric, acrocentric, or telocentric. Both of these properties (i.e., the length of chromosomal arms, and the placement of the chromosomal centromere) are the main factors for creating structural homology between chromosomes. Therefore, when two chromosomes containing the relatively same structure exist (e.g., maternal chromosome 15 and paternal chromosome 15), they are able to pair together via the process of synapsis to form homologous chromosomes.

Since homologous chromosomes are not identical and do not originate from the same organism, they are different from sister chromatids. Sister chromatids result after DNA replication has occurred, and thus are identical, side-by-side duplicates of each other.

In humans

Humans have a total of 46 chromosomes, but there are only 22 pairs of homologous autosomal chromosomes. The additional 23rd pair is the sex chromosomes, X and Y.Note that the pair of sex chromosomes may or may not be homologous, depending on the sex of the individual. For instance, females contain XX, thus have a homologous pair of sex chromosomes. This means that females have 23 pairs of homologous chromosomes in total (i.e., 22 pairs of non-sex chromosomes (autosomes), 1 pair of sex chromosomes). Conversely, males contain XY, which means that they have a non-homologous pair of sex chromosomes as their 23rd pair of chromosomes.

In humans, the 22 pairs of homologous autosomal chromosomes contain the same genes but code for different traits in their allelic forms, as one was inherited from the mother and one from the father.

So, humans have two sets of 23 chromosomes in each cell that contains a nucleus. One set of 23 chromosomes (n) is from the mother (22 autosomes, 1 sex chromosome (X only)) and one set of 23 chromosomes (n) is from the father (22 autosomes, 1 sex chromosome (X or Y)). Ultimately, this means that humans are diploid (2n) organisms.

Functions

Homologous chromosomes are important in the processes of meiosis and mitosis. They allow for the recombination and random segregation of genetic material from the mother and father into new cells.

In meiosis

Meiosis is a round of two cell divisions that results in four haploid daughter cells that each contain half the number of chromosomes as the parent cell. It reduces the chromosome number in a germ cell by half by first separating the homologous chromosomes in meiosis I and then the sister chromatids in meiosis II. The process of meiosis I is generally longer than meiosis II because it takes more time for the chromatin to replicate and for the homologous chromosomes to be properly oriented and segregated by the processes of pairing and synapsis in meiosis I. During meiosis, genetic recombination (by random segregation) and crossing over produces daughter cells that each contain different combinations of maternally and paternally coded genes. This recombination of genes allows for the introduction of new allele pairings and genetic variation. Genetic variation among organisms helps make a population more stable by providing a wider range of genetic traits for natural selection to act on.

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Prophase I

In prophase I of meiosis I, each chromosome is aligned with its homologous partner and pairs completely. In prophase I, the DNA has already undergone replication so each chromosome consists of two identical chromatids connected by a common centromere. During the zygotene stage of prophase I, the homologous chromosomes pair up with each other. This pairing occurs by a synapsis process where the synaptonemal complex – a protein scaffold – is assembled and joins the homologous chromosomes along their lengths. Cohesin crosslinking occurs between the homologous chromosomes and helps them resist being pulled apart until anaphase. Genetic crossing-over, a type of recombination, occurs during the pachytene stage of prophase I. In addition, another type of recombination referred to as synthesis-dependent strand annealing (SDSA) frequently occurs. SDSA recombination involves information exchange between paired homologous chromatids, but not physical exchange. SDSA recombination does not cause crossing-over.

In the process of crossing-over, genes are exchanged by the breaking and union of homologous portions of the chromosomes' lengths. Structures called chiasmata are the site of the exchange. Chiasmata physically link the homologous chromosomes once crossing over occurs and throughout the process of chromosomal segregation during meiosis. Both the non-crossover and crossover types of recombination function as processes for repairing DNA damage, particularly double-strand breaks. At the diplotene stage of prophase I the synaptonemal complex disassembles before which will allow the homologous chromosomes to separate, while the sister chromatids stay associated by their centromeres.

Metaphase I

In metaphase I of meiosis I, the pairs of homologous chromosomes, also known as bivalents or tetrads, line up in a random order along the metaphase plate. The random orientation is another way for cells to introduce genetic variation. Meiotic spindles emanating from opposite spindle poles attach to each of the homologs (each pair of sister chromatids) at the kinetochore.

Anaphase I

In anaphase I of meiosis I the homologous chromosomes are pulled apart from each other. The homologs are cleaved by the enzyme separase to release the cohesin that held the homologous chromosome arms together. This allows the chiasmata to release and the homologs to move to opposite poles of the cell. The homologous chromosomes are now randomly segregated into two daughter cells that will undergo meiosis II to produce four haploid daughter germ cells.

Meiosis II

After the tetrads of homologous chromosomes are separated in meiosis I, the sister chromatids from each pair are separated. The two haploid daughter cells (the number of chromosomes has been reduced to half: earlier two sets of chromosomes were present, but now each set exists in two different daughter cells that have arisen from the single diploid parent cell by meiosis I) resulting from meiosis I undergo another cell division in meiosis II but without another round of chromosomal replication. The sister chromatids in the two daughter cells are pulled apart during anaphase II by nuclear spindle fibers, resulting in four haploid daughter cells.

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In mitosis

Homologous chromosomes do not function the same in mitosis as they do in meiosis. Prior to every single mitotic division a cell undergoes, the chromosomes in the parent cell replicate themselves. The homologous chromosomes within the cell will ordinarily not pair up and undergo genetic recombination with each other. Instead, the replicants, or sister chromatids, will line up along the metaphase plate and then separate in the same way as meiosis II – by being pulled apart at their centromeres by nuclear mitotic spindles. If any crossing over does occur between sister chromatids during mitosis, it does not produce any new recombinant genotypes.

In somatic cells

Homologous pairing in most contexts will refer to germline cells, however also takes place in somatic cells. For example, in humans, somatic cells have very tightly regulated homologous pairing (separated into chromosomal territories, and pairing at specific loci under control of developmental signalling). Other species however (notably Drosophila) exhibit homologous pairing much more frequently. In Drosophila the homologous pairing supports a gene regulatory phenomenon called transvection in which an allele on one chromosome affects the expression of the homologous allele on the homologous chromosome. One notable function of this is the sexually dimorphic regulation of X-linked genes.

Problems

There are severe repercussions when chromosomes do not segregate properly. Faulty segregation can lead to fertility problems, embryo death, birth defects, and cancer. Though the mechanisms for pairing and adhering homologous chromosomes vary among organisms, proper functioning of those mechanisms is imperative in order for the final genetic material to be sorted correctly.

Nondisjunction

Proper homologous chromosome separation in meiosis I is crucial for sister chromatid separation in meiosis II. A failure to separate properly is known as nondisjunction. There are two main types of nondisjunction that occur: trisomy and monosomy. Trisomy is caused by the presence of one additional chromosome in the zygote as compared to the normal number, and monosomy is characterized by the presence of one fewer chromosome in the zygote as compared to the normal number. If this uneven division occurs in meiosis I, then none of the daughter cells will have proper chromosomal distribution and non-typical effects can ensue, including Down's syndrome. Unequal division can also occur during the second meiotic division. Nondisjunction which occurs at this stage can result in normal daughter cells and deformed cells.

Other uses

While the main function of homologous chromosomes is their use in nuclear division, they are also used in repairing double-strand breaks of DNA. These double-stranded breaks may occur in replicating DNA and are most often the result of interaction of DNA with naturally occurring damaging molecules such as reactive oxygen species. Homologous chromosomes can repair this damage by aligning themselves with chromosomes of the same genetic sequence. Once the base pairs have been matched and oriented correctly between the two strands, the homologous chromosomes

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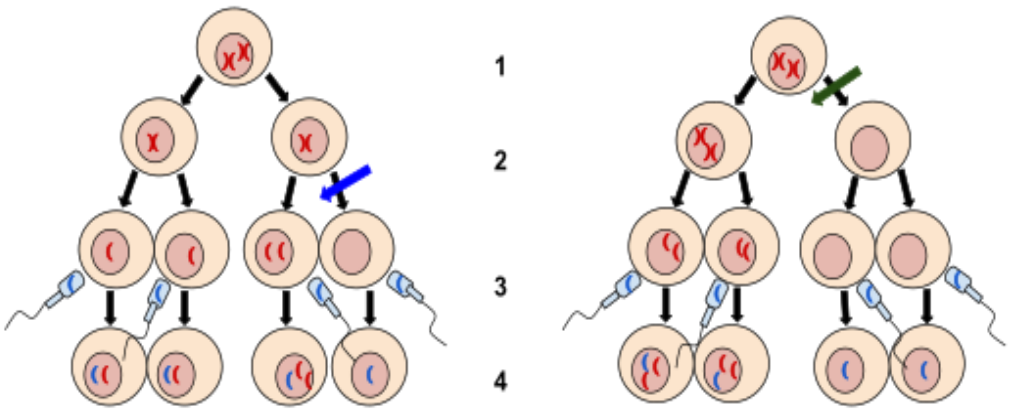
perform a process that is very similar to recombination, or crossing over as seen in meiosis. Part of the intact DNA sequence overlaps with that of the damaged chromosome's sequence. Replication proteins and complexes are then recruited to the site of damage, allowing for repair and proper replication to occur. Through this functioning, double-strand breaks can be repaired and DNA can function normally.

Relevant research

Current and future research on the subject of homologous chromosome is heavily focused on the roles of various proteins during recombination or during DNA repair. In a recently published article by Pezza et al.[which?] the protein known as HOP2 is responsible for both homologous chromosome synapsis as well as double-strand break repair via homologous recombination. The deletion of HOP2 in mice has large repercussions in meiosis. Other current studies focus on specific proteins involved in homologous recombination as well.

There is ongoing research concerning the ability of homologous chromosomes to repair double-strand DNA breaks. Researchers are investigating the possibility of exploiting this capability for regenerative medicine. This medicine could be very prevalent in relation to cancer, as DNA damage is thought to be contributor to carcinogenesis. Manipulating the repair function of homologous chromosomes might allow for bettering a cell's damage response system. While research has not yet confirmed the effectiveness of such treatment, it may become a useful therapy for cancer.



1. Meiosis I 2. Meiosis II 3. Fertilization 4. Zygote Nondisjunction is when chromosomes fail to separate normally resulting in a gain or loss of chromosomes. In the left image the blue arrow indicates nondisjunction taking place during meiosis II. In the right image the green arrow is indicating nondisjunction taking place during meiosis I.

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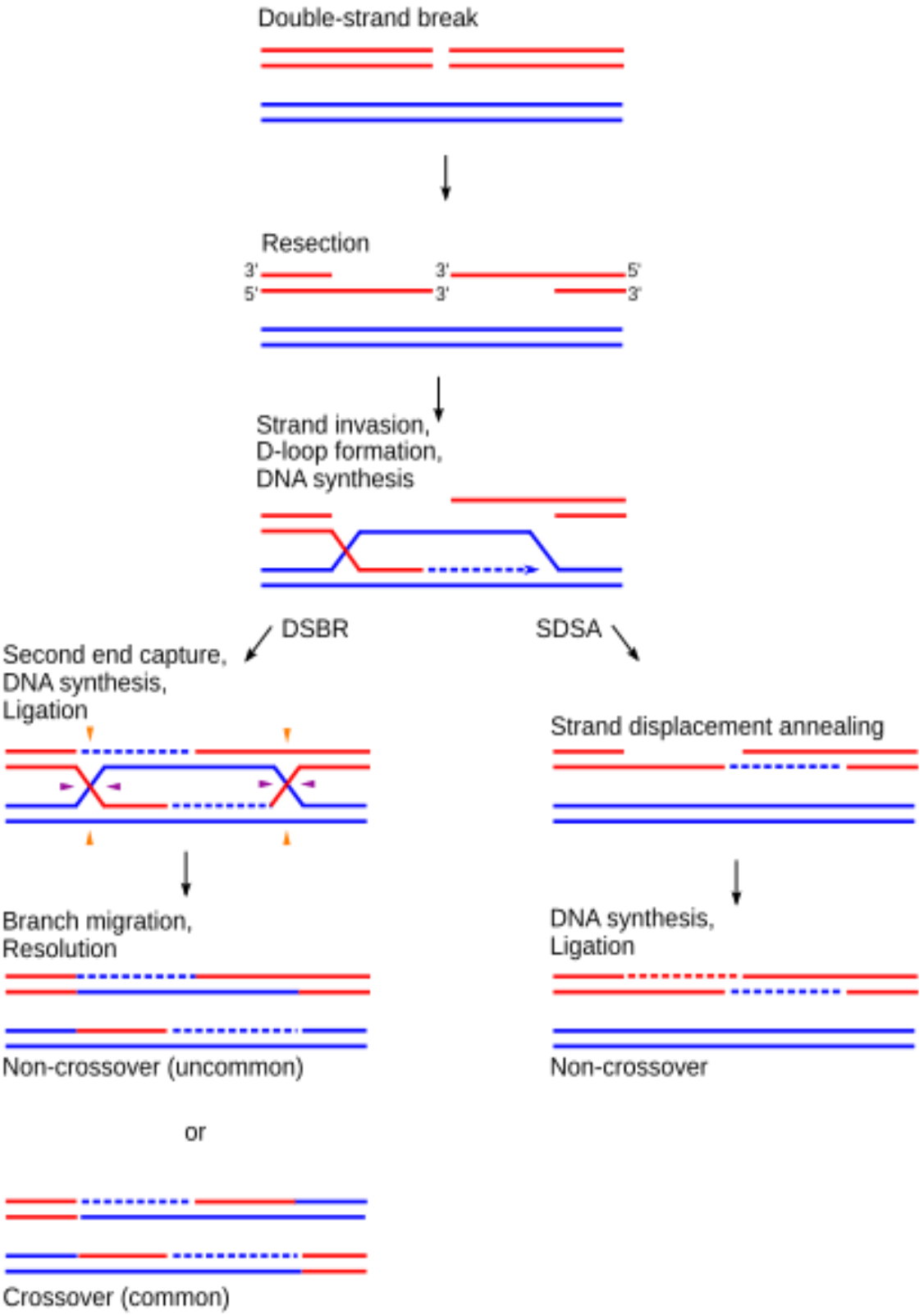

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Diagram of the general process for double-stranded break repair as well as synthesis-dependent strand annealing.

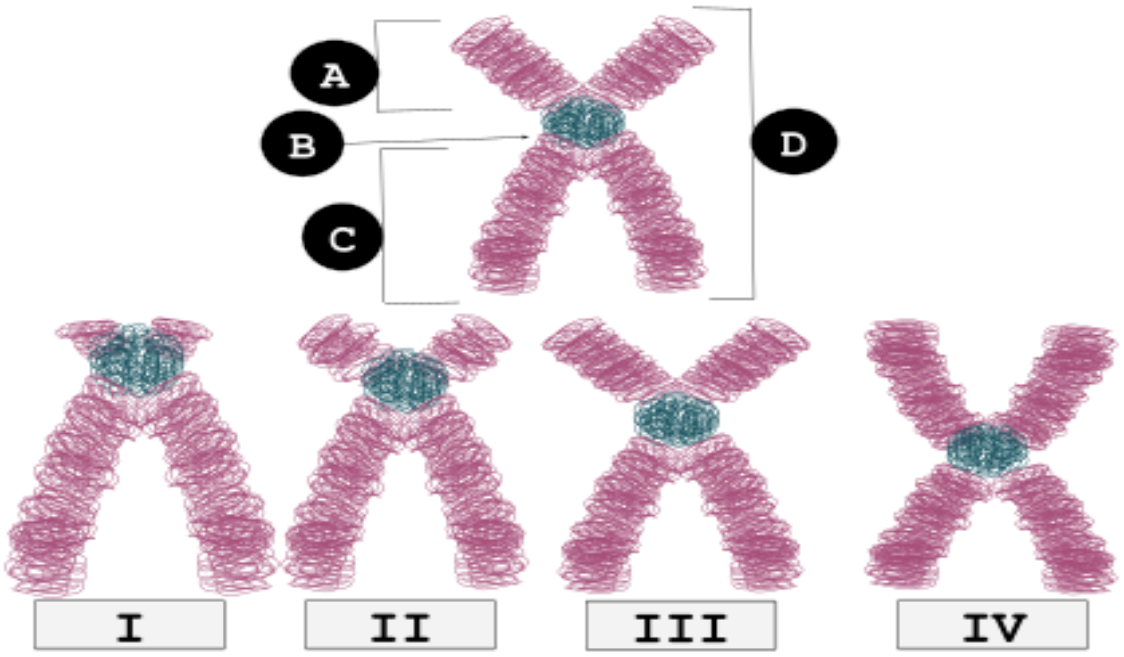
CENTROMERE

The centromere links a pair of sister chromatids together during cell division. This constricted region of chromosome connects the sister chromatids, creating a short arm (p) and a long arm (q) on the chromatids. During mitosis, spindle fibers attach to the centromere via the kinetochore.

The physical role of the centromere is to act as the site of assembly of the kinetochores – a highly complex multiprotein structure that is responsible for the actual events of chromosome segregation – i.e. binding microtubules and signaling to the cell cycle machinery when all chromosomes have adopted correct attachments to the spindle, so that it is safe for cell division to proceed to completion and for cells to enter anaphase.

There are, broadly speaking, two types of centromeres. "Point centromeres" bind to specific proteins that recognize particular DNA sequences with high efficiency. Any piece of DNA with the point centromere DNA sequence on it will typically form a centromere if present in the appropriate species. The best characterized point centromeres are those of the budding yeast, Saccharomyces cerevisiae. "Regional centromeres" is the term coined to describe most centromeres, which typically form on regions of preferred DNA sequence, but which can form on other DNA sequences as well. The signal for formation of a regional centromere appears to be epigenetic. Most organisms, ranging from the fission yeast Schizosaccharomyces pombe to humans, have regional centromeres.

Regarding mitotic chromosome structure, centromeres represent a constricted region of the chromosome (often referred to as the primary constriction) where two identical sister chromatids are most closely in contact. When cells enter mitosis, the sister chromatids (the two copies of each chromosomal DNA molecule resulting from DNA replication in chromatin form) are linked along their length by the action of the cohesin complex. It is now believed that this complex is mostly released from chromosome arms during prophase, so that by the time the chromosomes line up at the mid-plane of the mitotic spindle (also known as the metaphase plate), the last place where they are linked with one another is in the chromatin in and around the centromere.



Classifications of Chromosomes

I	*Telocentric*	*Centromere placement very close to the top, p arms barely visible if visible at all.*
II	*Acrocentric*	*q arms are still much longer than the p arms, but the p arms are longer than those in telocentric.*
III	*Submetacentric*	*p and q arms are very close in length but not equal.*
IV	*Metacentric*	*p and q arms are equal in length.*

A: Short arm (p arm)
B: Centromere
C: Long arm (q arm)
D: Sister Chromatids

In humans, centromere positions define the chromosomal karyotype, in which each chromosome has two arms, p (the shorter of the two) and q (the longer). The short arm 'p' is reportedly named for the French word "petit" meaning 'small'. The position of the centromere relative to any particular linear chromosome is used to classify chromosomes as metacentric, submetacentric, acrocentric, telocentric, or holocentric.

Categorization of chromosomes according to the relative arms length

Centromere position	*Arms length ratio*	*Sign*	*Description*
Medial sensu stricto	*1.0 – 1.6*	*M*	*Metacentric*
Medial region	*1.7*	*m*	*Metacentric*
Submedial	*3.0*	*sm*	*Submetacentric*
Subterminal	*3.1 – 6.9*	*st*	*Subtelocentric*
Terminal region	*7.0*	*t*	*Acrocentric*
Terminal sensu stricto	*∞*	*T*	*Telocentric*
Notes	*–*	*Metacentric:M+m*	*Atelocentric:*

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Metacentric

Metacentric means that the centromere is positioned midway between the chromosome ends, resulting in the arms being approximately equal in length. When the centromeres are metacentric, the chromosomes appear to be "x-shaped."

Submetacentric

Submetacentric means that the centromere is positioned below the middle, with one chromosome arm shorter than the other, often resulting in an L shape.

Acrocentric

An acrocentric chromosome's centromere is situated so that one of the chromosome arms is much shorter than the other. The "acro-" in acrocentric refers to the Greek word for "peak." The human genome has six acrocentric chromosomes, including five autosomal chromosomes (13, 14, 15, 21, 22) and the Y chromosome.

Short acrocentric p-arms contain little genetic material and can be translocated without significant harm, as in a balanced Robertsonian translocation. In addition to some protein coding genes, human acrocentric p-arms also contain Nucleolus organizer regions (NORs), from which ribosomal RNA is transcribed. However, a proportion of acrocentric p-arms in cell lines and tissues from normal human donors do not contain detectable NORs.[4] The domestic horse genome includes one metacentric chromosome that is homologous to two acrocentric chromosomes in the conspecific but undomesticated Przewalski's horse. This may reflect either fixation of a balanced Robertsonian translocation in domestic horses or, conversely, fixation of the fission of one metacentric chromosome into two acrocentric chromosomes in Przewalski's horses. A similar situation exists between the human and great ape genomes, with a reduction of two acrocentric chromosomes in the great apes to one metacentric chromosome in humans (see aneuploidy and the human chromosome 2).

Many diseases from the result of unbalanced translocations more frequently involve acrocentric chromosomes than other non-acrocentric chromosomes. Acrocentric chromosomes are usually located in and around the nucleolus. As a result, these chromosomes tend to be less densely packed than chromosomes in the nuclear periphery. Consistently, chromosomal regions that are less densely packed are also more prone to chromosomal translocations in cancers.

Telocentric

Telocentric chromosomes have a centromere at one end of the chromosome and therefore exhibit only one arm at the cytological (microscopic) level. They are not present in humans but can form through cellular chromosomal errors. Telocentric chromosomes occur naturally in many species, such as the house mouse, in which all chromosomes except the Y are telocentric.

Subtelocentric

Subtelocentric chromosomes' centromeres are located between the middle and the end of the chromosomes, but reside closer to the end of the chromosomes.

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Centromere types

Acentric

An acentric chromosome is fragment of a chromosome that lacks a centromere. Since centromeres are the attachment point for spindle fibers in cell division, acentric fragments are not evenly distributed to daughter cells during cell division. As a result, a daughter cell will lack the acentric fragment and deleterious consequences could occur.

Chromosome-breaking events can also generate acentric chromosomes or acentric fragments.

Dicentric

A dicentric chromosome is an abnormal chromosome with two centromeres, which can be unstable through cell divisions. It can form through translocation between or fusion of two chromosome segments, each with a centromere. Some rearrangements produce both dicentric chromosomes and acentric fragments which can not attach to spindles at mitosis. The formation of dicentric chromosomes has been attributed to genetic processes, such as Robertsonian translocation[6] and paracentric inversion. Dicentric chromosomes can have a variety of fates, including mitotic stability. In some cases, their stability comes from inactivation of one of the two centromeres to make a functionally monocentric chromosome capable of normal transmission to daughter cells during cell division

For example, human chromosome 2, which is believed to be the result of a Robertsonian translocation at some point in the evolution between the great apes and Homo, has a second, vestigial, centromere near the middle of its long arm.

Monocentric

The monocentric chromosome is a chromosome that has only one centromere in a chromosome and forms a narrow constriction.

Monocentric centromeres are the most common structure on highly repetitive DNA in plants and animals.

Holocentric

Holocentric chromosome

Unlike monocentric chromosomes, holocentric chromosomes have no distinct primary constriction when viewed at mitosis. Instead, spindle fibers attach along almost the entire (Greek: holo-) length of the chromosome. In holocentric chromosomes centromeric proteins, such as CENPA (CenH3) are spread over the whole chromosome. The nematode, Caenorhabditis elegans, is a well-known example of an organism with holocentric chromosomes, but this type of centromere can be found in various species, plants, and animals, across eukaryotes. Holocentromeres are actually composed of multiple distributed centromere units that form a line-like structure along the chromosomes during mitosis. Alternative or nonconventional strategies are deployed at meiosis to achieve the homologous chromosome pairing and segregation needed to produce viable gametes or gametophytes for sexual reproduction.

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Different types of holocentromeres exist in different species, namely with or without centromeric repetitive DNA sequences and with or without CenH3. Holocentricity has evolved at least 13 times independently in various green algae, protozoans, invertebrates, and different plant families. Contrary to monocentric species where acentric fragments usually become lost during cell division, the breakage of holocentric chromosomes creates fragments with normal spindle fiber attachment sites. Because of this, organisms with holocentric chromosomes can more rapidly evolve karyotype variation, able to heal fragmented chromosomes through subsequent addition of telomere caps at the sites of breakage.

Polycentric

Polycentric chromosomes have several kinetochore clusters, i.e. centromes. The term overlaps partially with "holocentric", but "polycentric" is clearly preferred when discussing defectively formed monocentric chromosomes. There is some actual ambiguity as well, as there is no clear line dividing up the transition from kinetochores covering the whole chromosome to distinct clusters. In other words, the difference between "the whole chromosome is a centrome" and "the chromosome has no centrome" is hazy and usage varies. Beyond "polycentricity" being used more about defects, there is no clear preference in other topics such as evolutionary origin or kinetochore distribution and detailed structure (e.g. as seen in tagging or genome assembly analysis).

Even clearly distinct clusters of kinetochore proteins do not necessarily produce more than one constriction: "Metapolycentric" chromosomes feature one elongated constriction of the chromosome, joining a longer segment which is still visibly shorter than the chromatids. Metapolycentric chromosomes may be a step in the emergence and suppression of centromere drive, a type of meiotic drive that disrupts parity by monocentric centromeres growing additional kinetochore proteins to gain an advantage during meiosis.

Human chromosomes

Table of human chromosomes with data on centromeres and sizes.

Chromosome	Centromereposition (Mbp)	Category	Chromosome Size (Mbp)	Centromere size (Mbp)
1	125.0	metacentric	247.2	7.4
2	93.3	submetacentric	242.8	6.3
3	91.0	metacentric	199.4	6.0
4	50.4	submetacentric	191.3	—
5	48.4	submetacentric	180.8	—
6	61.0	submetacentric	170.9	—
7	59.9	submetacentric	158.8	—
8	45.6	submetacentric	146.3	—
9	49.0	submetacentric	140.4	—

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10	40.2	submetacentric	135.4	—
11	53.7	submetacentric	134.5	—
12	35.8	submetacentric	132.3	—
13	17.9	acrocentric	114.1	—
14	17.6	acrocentric	106.3	—
15	19.0	acrocentric	100.3	—
16	36.6	metacentric	88.8	—
17	24.0	submetacentric	78.7	—
18	17.2	submetacentric	76.1	—
19	26.5	metacentric	63.8	—
20	27.5	metacentric	62.4	—
21	13.2	acrocentric	46.9	—
22	14.7	acrocentric	49.5	—
X	60.6	submetacentric	154.9	—
Y	12.5	acrocentric	57.7	—

Based on the micrographic characteristics of size, position of the centromere and sometimes the presence of a chromosomal satellite, the human chromosomes are classified into the following groups.

	Group	Chromosomes	Features
•	Group A	Chromosome 1–3	Large, metacentric and submetacentric
•	Group B	Chromosome 4–5	Large, submetacentric
•	Group C	Chromosome 6–12, X	Medium-sized, submetacentric
•	Group D	Chromosome 13–15	Medium-sized, acrocentric, with satellite
•	Group E	Chromosome 16–18	Small, metacentric and submetacentric
•	Group F	Chromosome 19–20	Very small, metacentric
•	Group G	Chromosome 21–22, Y	Very small, acrocentric, with satellite

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Sequence

There are two types of centromeres. In regional centromeres, DNA sequences contribute to but do not define function. Regional centromeres contain large amounts of DNA and are often packaged into heterochromatin. In most eukaryotes, the centromere's DNA sequence consists of large arrays of repetitive DNA (e.g. satellite DNA) where the sequence within individual repeat elements is similar but not identical. In humans, the primary centromeric repeat unit is called α-satellite (or alphoid), although a number of other sequence types are found in this region. Centromere satellites are hypothesized to evolve by a process called layered expansion. They evolve rapidly between species, and analyses in wild mice show that satellite copy number and heterogeneity relates to population origins and subspecies. Additionally, satellite sequences may be affected by inbreeding.

Point centromeres are smaller and more compact. DNA sequences are both necessary and sufficient to specify centromere identity and function in organisms with point centromeres. In budding yeasts, the centromere region is relatively small (about 125 bp DNA) and contains two highly conserved DNA sequences that serve as binding sites for essential kinetochore proteins.

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Inheritance

Since centromeric DNA sequence is not the key determinant of centromeric identity in metazoans, it is thought that epigenetic inheritance plays a major role in specifying the centromere. The daughter chromosomes will assemble centromeres in the same place as the parent chromosome, independent of sequence. It has been proposed that histone H3 variant CENP-A (Centromere Protein A) is the epigenetic mark of the centromere. The question arises whether there must be still some original way in which the centromere is specified, even if it is subsequently propagated epigenetically. If the centromere is inherited epigenetically from one generation to the next, the problem is pushed back to the origin of the first metazoans.

On the other hand, thanks to comparisons of the centromeres in the X chromosomes, epigenetic and structural variations have been seen in these regions. In addition, a recent assembly of the human genome has detected a possible mechanism of how pericentromeric and centromeric structures evolve, through a layered expansion model for αSat sequences. This model proposes that different αSat sequence repeats emerge periodically and expand within an active vector, displacing old sequences, and becoming the site of kinetochore assembly. The αSat can originate from the same, or from different vectors. As this process is repeated over time, the layers that flank the active centromere shrink and deteriorate. This process raises questions about the relationship between this dynamic evolutionary process and the position of the centromere.

Structure

The centromeric DNA is normally in a heterochromatin state, which is essential for the recruitment of the cohesin complex that mediates sister chromatid cohesion after DNA replication as well as coordinating sister chromatid separation during anaphase. In this chromatin, the normal histone H3 is replaced with a centromere-specific variant, CENP-A in humans. The presence of CENP-A is believed to be important for the assembly of the kinetochore on the centromere. CENP-C has been shown to localise almost exclusively to these regions of CENP-A associated chromatin. In human cells, the histones are found to be most enriched for H4K20me3 and H3K9me3 which are known heterochromatic modifications. In Drosophila, Islands of retroelements are major components of the centromeres.

In the yeast Schizosaccharomyces pombe (and probably in other eukaryotes), the formation of centromeric heterochromatin is connected to RNAi. In nematodes such as Caenorhabditis elegans, some plants, and the insect orders Lepidoptera and Hemiptera, chromosomes are "holocentric", indicating that there is not a primary site of microtubule attachments or a primary constriction, and a "diffuse" kinetochore assembles along the entire length of the chromosome.

Centromeric aberrations

In rare cases, neocentromeres can form at new sites on a chromosome as a result of a repositioning of the centromere. This phenomenon is most well known from human clinical studies and there are currently over 90 known human neocentromeres identified on 20 different chromosomes. The formation of a neocentromere must be coupled with the inactivation of the previous centromere, since chromosomes with two functional centromeres (Dicentric chromosome) will result in chromosome

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

breakage during mitosis. In some unusual cases human neocentromeres have been observed to form spontaneously on fragmented chromosomes. Some of these new positions were originally euchromatic and lack alpha satellite DNA altogether. Neocentromeres lack the repetitive structure seen in normal centromeres which suggest that centromere formation is mainly controlled epigenetically. Over time a neocentromere can accumulate repetitive elements and mature into what is known as an evolutionary new centromere. There are several well known examples in primate chromosomes where the centromere position is different from the human centromere of the same chromosome and is thought to be evolutionary new centromeres. Centromere repositioning and the formation of evolutionary new centromeres has been suggested to be a mechanism of speciation.

Centromere proteins are also the autoantigenic target for some anti-nuclear antibodies, such as anti-centromere antibodies.

Dysfunction and disease

It has been known that centromere misregulation contributes to mis-segregation of chromosomes, which is strongly related to cancer and miscarriage. Notably, overexpression of many centromere genes have been linked to cancer malignant phenotypes. Overexpression of these centromere genes can increase genomic instability in cancers. Elevated genomic instability on one hand relates to malignant phenotypes; on the other hand, it makes the tumor cells more vulnerable to specific adjuvant therapies such as certain chemotherapies and radiotherapy. Instability of centromere repetitive DNA was recently shown in cancer and aging.

Repair of centromeric DNA

When DNA breaks occur at centromeres in the G1 phase of the cell cycle, the cells are able to recruit the homologous recombinational repair machinery to the damaged site, even in the absence of a sister chromatid. It appears that homologous recombinational repair can occur at centromeric breaks throughout the cell cycle in order to prevent the activation of inaccurate mutagenic DNA repair pathways and to preserve centromeric integrity.

Etymology and pronunciation

The word centromere (/ˈsɛntrəˌmɪər/ uses combining forms of centro- and -mere, yielding "central part", describing the centromere's location at the center of the chromosome..

CHROMOSOME SEGREGATION

Chromosome segregation is the process in eukaryotes by which two sister chromatids formed as a consequence of DNA replication, or paired homologous chromosomes, separate from each other and migrate to opposite poles of the nucleus. This segregation process occurs during both mitosis and meiosis. Chromosome segregation also occurs in prokaryotes. However, in contrast to eukaryotic chromosome segregation, replication and segregation are not temporally separated. Instead segregation occurs progressively following replication.

Mitotic chromatid segregation

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

During mitosis chromosome segregation occurs routinely as a step in cell division (see mitosis diagram). As indicated in the mitosis diagram, mitosis is preceded by a round of DNA replication, so that each chromosome forms two copies called chromatids. These chromatids separate to opposite poles, a process facilitated by a protein complex referred to as cohesin. Upon proper segregation, a complete set of chromatids ends up in each of two nuclei, and when cell division is completed, each DNA copy previously referred to as a chromatid is now called a chromosome.

Meiotic chromosome and chromatid segregation

Chromosome segregation occurs at two separate stages during meiosis called anaphase I and anaphase II (see meiosis diagram). In a diploid cell there are two sets of homologous chromosomes of different parental origin (e.g. a paternal and a maternal set). During the phase of meiosis labeled "interphase s" in the meiosis diagram there is a round of DNA replication, so that each of the chromosomes initially present is now composed of two copies called chromatids. These chromosomes (paired chromatids) then pair with the homologous chromosome (also paired chromatids) present in the same nucleus (see prophase I in the meiosis diagram). The process of alignment of paired homologous chromosomes is called synapsis (see Synapsis). During synapsis, genetic recombination usually occurs. Some of the recombination events occur by crossing over (involving physical exchange between two chromatids), but most recombination events involve information exchange but not physical exchange between two chromatids (see Synthesis-dependent strand annealing (SDSA)). Following recombination, chromosome segregation occurs as indicated by the stages metaphase I and anaphase I in the meiosis diagram.

Different pairs of chromosomes segregate independently of each other, a process termed "independent assortment of non-homologous chromosomes". This process results in each gamete usually containing a mixture of chromosomes from both original parents.

Improper chromosome segregation (see non-disjunction, disomy) can result in aneuploid gametes having either too few or too many chromosomes.

The second stage at which segregation occurs during meiosis is prophase II (see meiosis diagram). During this stage, segregation occurs by a process similar to that during mitosis, except that in this case prophase II is not preceded by a round of DNA replication. Thus the two chromatids comprising each chromosome separate into different nuclei, so that each nucleus gets a single set of chromatids (now called chromosomes) and each nucleus becomes included in a haploid gamete (see stages following prophase II in the meiosis diagram). This segregation process is also facilitated by cohesin. Failure of proper segregation during prophase II can also lead to aneuploid gametes. Aneuploid gametes can undergo fertilization to form aneuploid zygotes and hence to serious adverse consequences for progeny.

Crossovers facilitate segregation, but are not essential

Meiotic chromosomal crossover (CO) recombination facilitates the proper segregation of homologous chromosomes. This is because, at the end of meiotic prophase I, CO recombination provides a physical link that holds homologous chromosome pairs together. These linkages are established by chiasmata, which are the cytological manifestations of CO recombination. Together with cohesion

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

linkage between sister chromatids, CO recombination may help ensure the orderly segregation of the paired homologous chromosomes to opposite poles. In support of this, a study of aneuploidy in single spermatozoa by whole genome sequencing found that, on average, human sperm cells with aneuploid autosomes exhibit significantly fewer crossovers than normal cells. After the first chromosome segregation in meiosis I is complete, there is further chromosome segregation during the second equational division of meiosis II. Both proper initial segregation of chromosomes in prophase I and the next chromosome segregation during equational division in meiosis II are required to generate gametes with the correct number of chromosomes.

CO recombinants are produced by a process involving the formation and resolution of Holliday junction intermediates. As indicated in the figure titled "A current model of meiotic recombination", the formation of meiotic crossovers can be initiated by a double-strand break (DSB). The introduction of DSBs in DNA often employs the topoisomerase-like protein SPO11. CO recombination may also be initiated by external sources of DNA damage such as X-irradiation, or internal sources.

There is evidence that CO recombination facilitates meiotic chromosome segregation. Other studies, however, indicate that chiasma, while supportive, are not essential to meiotic chromosome segregation. The budding yeast Saccharomyces cerevisiae is a model organism used for studying meiotic recombination. Mutants of S. cerevisiae defective in CO recombination at the level of Holliday junction resolution were found to efficiently undergo proper chromosome segregation. The pathway that produces the majority of COs in S. cerevisiae, and possibly in mammals, involves a complex of proteins including the MLH1-MLH3 heterodimer (called MutL gamma). MLH1-MLH3 binds preferentially to Holliday junctions. It is an endonuclease that makes single-strand breaks in supercoiled double-stranded DNA, and promotes the formation of CO recombinants. Double mutants deleted for both MLH3 (major pathway) and MMS4 (which is necessary for a minor Holliday junction resolution pathway) showed dramatically reduced crossing over compared to wild-type (6- to 17-fold reduction); however spore viability was reasonably high (62%) and chromosomal disjunction appeared mostly functional.[

The MSH4 and MSH5 proteins form a hetero-oligomeric structure (heterodimer) in S. cerevisiae and humans. In S. cerevisiae, MSH4 and MSH5 act specifically to facilitate crossovers between homologous chromosomes during meiosis. The MSH4/MSH5 complex binds and stabilizes double Holliday junctions and promotes their resolution into crossover products. An MSH4 hypomorphic (partially functional) mutant of S. cerevisiae showed a 30% genome-wide reduction in crossover numbers, and a large number of meioses with non-exchange chromosomes. Nevertheless, this mutant gave rise to spore viability patterns suggesting that segregation of non-exchange chromosomes occurred efficiently. Thus it appears that CO recombination facilitates proper chromosome segregation during meiosis in S. cerevisiae, but it is not essential.

The fission yeast Schizosaccharomyces pombe has the ability to segregate homologous chromosomes in the absence of meiotic recombination (achiasmate segregation). This ability depends on the microtubule motor dynein that regulates the movement of chromosomes to the poles of the meiotic spindle.

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

CHROMOMERE

A chromomere, also known as an idiomere, is one of the serially aligned beads or granules of a eukaryotic chromosome, resulting from local coiling of a continuous DNA thread. Chromomeres are regions of chromatin that have been compacted through localized contraction. In areas of chromatin with the absence of transcription, condensing of DNA and protein complexes will result in the formation of chromomeres. It is visible on a chromosome during the prophase of meiosis and mitosis. Giant banded (Polytene) chromosomes resulting from the replication of the chromosomes and the synapsis of homologs without cell division is a process called endomitosis. These chromosomes consist of more than 1000 copies of the same chromatid that are aligned and produce alternating dark and light bands when stained. The dark bands are the chromomere.

It is unknown when chromomeres first appear on the chromosome. Chromomeres can be observed best when chromosomes are highly condensed. The chromomeres are present during leptotene phase of prophase I during meiosis. During zygotene phase of prophase I, the chromomeres of homologs align with each other to form homologous rough pairing (homology searching). These chromomeres helps provide a unique identity for each homologous pairs. They appear as dense granules during leptotene stage

There are more than 2000 chromomeres on 20 chromosomes of maize.

Physical properties

Chromomeres are organized in a discontinuous linear pattern along the condensed chromosomes (pachytene chromosomes) during the prophase stage of meiosis. The linear pattern of chromomeres is linked to the arrangement of genes along the chromosome. Chromomeres contain genes and sometimes clusters of genes within their structure. Aggregates of chromomeres are known as chromonemata.

Cohesive proteins SMC3 and hRAD21(plays a role in sister chromatid cohesion) are found within chromomeres at high concentrations, and maintain the proper structure of chromomeres. The protein XCAP-D2 is also present at high concentrations within the chromomere, and acts as a condensin component. High concentrations of tandem repeats of the heterochromatin protein HP1β builds up within the chromomere. In regions where loops attach to chromomeres, there is hyperacetylation of histone 4. The extra acetylation loosens chromatin from a condensed form, making it more accessible to proteins involved in transcription.

Functions

Chromomeres are known as the structural subunit of a chromosome. The arrangement of chromomere structure can aid in control of gene expression.

Maps of chromomeres can be made for use in genetic and evolutionary studies. Chromomeric maps can be used to locate the exact position of genes on a chromosome. Chromomeric maps can be used to

analyze chromosome aberrations, and find correlations between the aberrations and their effects on genes near breakpoints.

Lampbrush chromosomes and chromomeres

Chromomeres display different properties and behaviours when associated with lampbrush chromosomes. Although found all across the lampbrush chromosome, they are not organized in a clear pattern along as they are in normal pachytene chromosomes of meiosis.[2][5] The two sister chromatids of a lampbrush chromosome separate fully, forming lateral loops that extend from chromomeres, and act as transcription complexes. The lateral loops are areas where the chromosomes are transcriptionally active. The loops define where the chromomere will be positioned. The chromomere is an organization of regions of non-transcribed chromatin. These regions of chromatin that have not been transcribed are located at the ends of the loops that were formed by the sister chromatids of a lampbrush chromosome. Each chromomere can have up to several pairs of loops from lampbrush chromosomes originating from it, as well as micro-loops that cannot be detected with a light microscope.

Chromomeres of lampbrush chromosomes act as structural units, and are not considered to be genetic units participating in transcription. The arrangement of a chromosome into chromomeric units happens almost simultaneously with the start of transcription. The loop structures extending from chromomeres are maintained by a high level of transcriptional activity and structural proteins of the chromosome. Chromatin within the chromomere are held in position by a variety of histone modifications and epigenetic markers.

Methyl-CpG-binding protein 2 (MeCP2) is a protein that binds to methylated DNA. MeCP2 has been found to associate most strongly with transcriptionally inactive chromomere domains. MeCP2 binding patterns to chromomere domains are proportional to the density of chromomeric DNA found on a chromosome. The binding of MeCP2 to chromomeric regions represents regions of chromatin that are highly dynamic on the lampbrush chromosome.

Lampbrush chromosome are a special form of chromosome found in the growing oocytes (immature eggs) of most animals, except mammals. They were first described by Walther Flemming and Ruckert in 1882. Lampbrush chromosomes of tailed and tailless amphibians, birds and insects are described best of all . Chromosomes transform into the lampbrush form during the diplotene stage of meiotic prophase I due to an active transcription of many genes. They are highly extended meiotic half-bivalents, each consisting of 2 sister chromatids. Lampbrush chromosomes are clearly visible even in the light microscope, where they are seen to be organized into a series of chromomeres with large chromatin loops extended laterally. Continuous RNA transcription is required to maintain typical chromomere-loop structure of lampbrush chromosomes. Inhibition of transcription leads to retraction of lateral loops into chromomeres and chromosome condensation.

Lampbrush chromosome

Lampbrush chromosomes produce a large number of mRNAs and non-coding RNAs, which are synthesized on the lateral loops. These transcripts are used during oogenesis and at the early stages

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

of embryogenesis. Each lateral loop contains one or several transcription units with polarized RNP-matrix coating the DNA axis of the loop.

Amphibian and avian lampbrush chromosomes can be microsurgically isolated from oocyte nucleus (germinal vesicle) with either forceps or needles. Giant chromosomes in the lampbrush form are useful model for studying chromosome organization, genome function and gene expression during meiotic prophase, since they allow the individual transcription units to be visualized. Moreover, lampbrush chromosomes are widely used for high-resolution mapping of DNA sequences and construction of detail cytological maps of individual chromosomes.

Minichromosome

A minichromosome is a small chromatin-like structure resembling a chromosome and consisting of centromeres, telomeres and replication origins but little additional genetic material. self-published source?] They replicate autonomously in the cell during cellular division. Minichromosomes may be created by natural processes as chromosomal aberrations or by genetic engineering.

Through the insertion of multiple genes and telomeres, a shortened minichromosome is produced, which can then be inserted into a host cell

Structure

Minichromosomes can be either linear or circular pieces of DNA. By minimizing the amount of unnecessary genetic information on the chromosome and including the basic components necessary for DNA replication (centromere, telomeres, and replication sequences), molecular biologists aim to construct a chromosomal platform which can be utilized to insert or present new genes into a host cell.

Production

Producing minichromosomes by genetic engineering techniques involves two primary methods, the de novo (bottom-up) and the top-down approach.

De novo

The minimum constituent parts of a chromosome (centromere, telomeres, and DNA replication sequences) are assembled by using molecular cloning techniques to construct the desired chromosomal contents in vitro. Next, the desired contents of the minichromosome must be transformed into a host which is capable of assembling the components (typically yeast or mammalian cells[5]) into a functional chromosome. This approach has been attempted for the introduction of minichromosomes into maize for the possibility of genetic engineering, but success has been limited and questionable. In general, the de novo approach is more difficult than the top-down method due to species incompatibility issues and the heterochromatic nature of centromeric regions.

Top-down

This method utilizes the mechanism of telomere-mediated chromosomal truncation (TMCT). This process is the generation of truncation by selective transformation of telomeric sequences into a host

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

genome. This insertion causes the generation of more telomeric sequences and eventual truncation. The newly synthesized truncated chromosome can then be altered through the insertion of new genes for desired traits. The top-down approach is generally considered as the more plausible means of generating extra-numerary chromosomes for the use of genetic engineering of plants. In particular it is useful because their stability during cell division has been demonstrated. The limitation of this approach is that it is labor-intensive.

Role in genetic engineering

Unlike traditional methods of genetic engineering, minichromosomes can be used to transfer and express multiple sets of genes onto one engineered chromosome package. Traditional methods which involve the insertion of novel genes into existing sequences may result in the disruption of endogenous genes and thus negatively affect the host cell. Additionally, with traditional gene insertion methods, scientists have had less ability to control where the newly inserted genes are located on the host cell chromosomes, which makes it difficult to predict inheritance of multiple genes from generation to generation. Minichromosome technology allows for the stacking of genes side-by-side on the same chromosome thus reducing likelihood of segregation of novel traits.

Plants

In 2006, scientists demonstrated the successful use of telomere truncation in maize plants to produce minichromosomes that could be utilized as a platform for inserting genes into the plant genome. In plants, the telomere sequence is conserved, which implies that this strategy can be utilized to successfully construct additional minichromosomes in other plant species.

In 2007, scientists reported success in assembling minichromosomes in vitro using the de novo method.

The use of minichromosomes as a means for generating more desirable crop traits is actively being explored. Major advantages include the ability to introduce genetic information which is highly compatible with the host genome. This eliminates the risk of disrupting various important processes such as cell division and gene expression. With continued development, the future for use of minichromosomes may make a huge impact on the productivity of major crops.

Other organisms

Minichromosomes have also been successfully inserted into yeast and animal cells. These minichromosomes were constructed using the de novo approach.

Microchromosome

A microchromosome is a chromosome defined for its relatively small size. They are typical components of the karyotype of birds, some reptiles, fish, amphibians, and monotremes. As many bird genomes have chromosomes of widely different lengths, the name was meant to distinguish them from the comparatively large macrochromosomes. The distinction referred to the measured size of the chromosome while staining for karyotype, and while there is not a strict definition, chromosomes resembling the large chromosomes of mammals were called macrochromosomes (roughly 3 to 6 μm), while the much smaller ones of less than around 0.5 μm were called microchromosomes. In terms of

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base pairs, by convention, those of less than 20Mb were called microchromosomes, those between 20 and 40 Mb are classified as intermediate chromosomes, and those larger than 40Mb are macrochromosomes. By this definition, all normal chromosomes in organisms with relatively small genomes (less than 100-200Mb) would be considered microchromosomes.

Function

Microchromosomes are characteristically very small and often cytogenetically indistinguishable in a karyotype, which makes ordering and identifying chromosomes into a coherent karyotype particularly difficult. While originally thought to be insignificant fragments of chromosomes, in species where they have been studied they have been found to be rich in genes and high in GC content. In chickens, microchromosomes have been estimated to contain between 50 and 75% of all genes. During metaphase, they appear merely as 0.5-1.5 μm long specks. Their small size and poor condensation into heterochromatin means they generally lack the diagnostic banding patterns and distinct centromere locations used for chromosome identification.

Occurrence

Microchromosomes are found in many vertebrates, but not in most mammals.[1] Important comparisons were made using the genomic organization of the Florida lancelet – part of a sister group to all vertebrates – suggests that the ancestral amniote (and vertebrates in general) genome consisted entirely of microchromosomes. Comparison between lancelet and modern vertebrate chromosomes shows that the macrochromosomes were the result of fusion between ancestral microchromosomes. In addition, retention of microchromosomes is shown to be the norm; the complete loss of them in mammals is the outlier instead.

In birds

Chickens have a diploid number of 78 (2n = 78) chromosomes, and as is usual in birds, the majority are microchromosomes. Classification of chicken chromosomes varies by author. Some classify them as 6 pairs of macrochromosomes, one pair of sex chromosomes, with the remaining 32 pairs being intermediate or microchromosomes. Other arrangements such as that used by the International Chicken Genome Sequencing Consortium include five pairs of macrochromosomes, five pairs of intermediate chromosomes, and twenty-eight pairs of microchromosomes. Microchromosomes represent approximately one third of the total genome size, and have been found to have a much higher gene density than macrochromosomes. Because of this, it is estimated that the majority of genes are located on microchromosomes,[6] though due to the difficulty in physically identifying microchromosomes and the lack of microsatellite markers, it has been difficult to place genes on specific microchromosomes.

Birds (except Falconidae) usually have karyotypes of approximately 80 chromosomes (2n = 80), with only a few being distinguishable macrochromosomes and an average of 60 being microchromosomes. They are more abundant in birds than any other group of animals. Chickens (Gallus gallus) are an important model organism for studying microchromosomes. Examination of microchromosomes in birds has led to the hypotheses that they may have originated as conserved fragments of ancestral macrochromosomes, and conversely that macrochromosomes could have arisen as aggregates of microchromosomes. Comparative genomic analysis shows that microchromosomes contain genetic

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

information which has been conserved across multiple classes of chromosomes. This indicates that at least ten chicken microchromosomes arose from fission of larger chromosomes and that the typical bird karyotype arose 100–250 mya.[6]

Replication timing and recombination rates have been found to differ between micro- and macrochromosomes in chickens. Microchromosomes replicate earlier in the S phase of interphase than macrochromosomes. Recombination rates have also been found to be higher on microchromosomes. Possibly due to the high recombination rates, chicken chromosome 16 (a microchromosome) has been found to contain the most genetic diversity of any chromosome in certain chicken breeds. This is likely due to the presence on this chromosome of the major histocompatibility complex (MHC).

For the many small linkage groups in the chicken genome which have not been placed on chromosomes, the assumption has been made that they are located on the microchromosomes. Groups of these correspond almost exactly with large sections of certain human chromosomes. For example, linkage groups E29C09W09, E21E31C25W12, E48C28W13W27, E41W17, E54 and E49C20W21 correspond with chromosome 7.

Turkey

The turkey has a diploid number of 80 (2n = 80) chromosomes. The karyotype contains an additional chromosomal pair relative to the chicken due to the presence of at least two fission/fusion differences (GGA2 = MGA3 and MGA6 and GGA4 = MGA4 and MGA9). Given these differences involving the macrochromosomes, an additional fission/fusion must also exist between the species involving the microchromosomes if the diploid numbers are valid. Other rearrangements have been identified through comparative genetic maps, physical maps and whole genome sequencing.

In turtles

Microchromosomes play a key role in sex determination in soft-shelled turtles.

In humans and other animals

Microchromosomes are absent from the karyotypes of mammals and some amphibians. (The monotreme platypus has an intermediate karyotype with smaller chromosomes that are not quite "micro".

In rare cases, microchromosomes have been observed in the karotypes of individual humans. A link has been suggested between microchromosome presence and certain genetic disorders like Down syndrome and fragile X syndrome. The smallest chromosome in humans is normally chromosome 21, which is 47 Mb.

Neochromosome

A neochromosome is a chromosome that is not normally found in nature. Cancer-associated neochromosomes are found in some cancer cells.

Neochromosomes have also been created using genetic engineering techniques.

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

Cancer-associated neochromosomes

Cancer-associated neochromosomes are giant supernumerary chromosomes. They harbor the mutations that drive certain cancers (highly amplified copies of key oncogenes, such as MDM2, CDK4, HMGA2). They may be circular or linear chromosomes. They have functional centromeres, and telomeres when linear. They are rare overall, being found in about 3% of cancers, but are common in certain rare cancers. For example, they are found in 90% of parosteal osteosarcomas.

Neochromosomes from well- and de-differentiated liposarcoma have been studied at high resolution by isolation (using flow sorting) and sequencing, as well as microscopy. They consist of hundreds of fragments of DNA, often derived from multiple normal chromosomes, stitched together randomly, and contain high levels of DNA amplification (~30-60 copies of some genes).

Using statistical inference and mathematical modelling, the process of how neochromosomes initially form and evolve has been made clearer. Fragments of DNA produced following chromothriptic shattering of chromosome 12 undergo DNA repair to form of a circular or ring chromosome. This undergoes hundreds of circular breakage-fusion-bridge cycles, causing random amplification and deletion of DNA with selection for the amplification of key oncogenes. DNA from additional chromosomes is somehow added during this process. Erosion of centromeres can lead to the formation of neocentromeres or the capture of new native centromeres from other chromosomes. The process ends when the neochromosome forms a linear chromosome following the capture of telomeric caps, which can be chromothriptically derived.

Parasitic chromosomes

Parasitic chromosomes are "selfish" chromosomes that propagate throughout cell divisions, even if they confer no benefit to the overall organism's survival. Parasitic chromosomes can persist even if slightly detrimental to survival, as is characteristic of some selfish genetic elements. Parasitic chromosomes are often B chromosomes, such that they are not necessarily present in the majority of the species population and are not needed for basic life functions, in contrast to A chromosomes. Parasitic chromosomes are classified as selfish genetic elements.

Parasitic chromosomes, if detrimental to an organism's survival, often are selected against by natural selection over time, but if the chromosome is able to act like a selfish DNA element, it can spread throughout a population. An example of a ***parasitic chromosome*** *is the* ***b24*** *chromosome in* ***grasshoppers****.*

Polytene chromosomes

Polytene chromosomes are large chromosomes which have thousands of DNA strands. They provide a high level of function in certain tissues such as salivary glands of insects.

Polytene chromosomes were first reported by E.G.Balbiani in 1881. Polytene chromosomes are found in dipteran flies: the best understood are those of Drosophila, Chironomus and Rhynchosciara. They are present in another group of arthropods of the class Collembola, a protozoan group Ciliophora,

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mammalian trophoblasts and antipodal, and suspensor cells in plants. In insects, they are commonly found in the salivary glands when the cells are not dividing.

They are produced when repeated rounds of DNA replication without cell division forms a giant chromosome. Thus polytene chromosomes form when multiple rounds of replication produce many sister chromatids which stay fused together.

Polytene chromosomes, at interphase, are seen to have distinct thick and thin banding patterns. These patterns were originally used to help map chromosomes, identify small chromosome mutations, and in taxonomic identification. They are now used to study the function of genes in transcription.

Function

In addition to increasing the volume of the cells' nuclei and causing cell expansion, polytene cells may also have a metabolic advantage as multiple copies of genes permits a high level of gene expression. In Drosophila melanogaster, for example, the chromosomes of the larval salivary glands undergo many rounds of endoreduplication to produce large quantities of adhesive mucoprotein ("glue") before pupation. Another example within the fly itself is the tandem duplication of various polytene bands located near the centromere of the X chromosome which results in the Bar phenotype of kidney-shaped eyes.
The interbands are involved in the interaction with the active chromatin proteins, nucleosome remodeling, and origin recognition complexes. Their primary functions are: to act as binding sites for RNA pol II, to initiate replication and, to start nucleosome remodeling of short fragments of DNA.

Structure

In insects, polytene chromosomes are commonly found in the salivary glands; they are also referred to as "salivary gland chromosomes". The large size of the chromosome is due to the presence of many longitudinal strands called chromonemata; hence the name polytene (many stranded). They are about 0.5 mm in length and 20 µm in diameter. The chromosomal strands are formed after repeated division of the chromosome in the absence of cytoplasmic division. This type of division is called endomitosis. The polytene chromosome contains two types of bands, dark bands and interbands. The dark bands are darkly stained and the inter bands are lightly stained with nuclear stains. The dark bands contain more DNA and less RNA. The interbands contain more RNA and less DNA. The amount of DNA in interbands ranges from 0.8 - 25%..
The bands of polytene chromosomes become enlarged at certain times to form swellings called puffs. The formation of puffs is called puffing. In the regions of puffs, the chromonemata uncoil and open out to form many loops. The puffing is caused by the uncoiling of individual chromomeres in a band. The puffs indicate the site of active genes where mRNA synthesis takes place The chromonemata of puffs give out a series of many loops laterally. As these loops appear as rings, they are called Balbiani rings after the name of the researcher who discovered them. They are formed of DNA, RNA and a few proteins. As they are the site of transcription, transcription mechanisms such as RNA polymerase and ribonucleoproteins are present.

In protozoans, there is no transcription, since the puff consists only of DNA.

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

History

Polytene chromosomes were originally observed in the larval salivary glands of Chironomus midges by Édouard-Gérard Balbiani in 1881. Balbiani described the chromosomal puffs among the tangled thread inside the nucleus, and named it "permanent spireme". In 1890, he observed similar spireme in a ciliated protozoan Loxophyllum meleagris. The existence of such spireme in Drosophila melanogaster was reported by Bulgarian geneticist Dontcho Kostoff in 1930. Kostoff predicted that the discs (bands) which he observed were "the actual packets in which inherited characters are passed from generation to generation."

The hereditary nature of these structures was not confirmed until they were studied in Drosophila melanogaster in the early 1930s by German biologists Emil Heitz and Hans Bauer. In 1930, Heitz studied different species of Drosophila (D. melanogaster, D. simulans, D. hydei, and D. virilis) and found that all their interphase chromatins in certain cells were swollen and messy. In 1932, he collaborated with Karl Heinrich Bauer with whom he discovered that the tangled chromosomes having distinct bands are unique to the cells of the salivary glands, midgut, Malphigian tubules, and brain of the flies Bibio hurtulunus and Drosophila funebris. The two papers were published in the early 1933. Unaware of these papers, an American geneticist Theophilus Shickel Painter reported in December 1933 the existence of giant chromosome in D. melanogaster (followed by a series of papers the following year). Learning of this, Heitz accused Painter of deliberately ignoring their original publication to claim priority of discovery. In 1935, Hermann J. Muller and A.A. Prokofyeva established that the individual band or part of a band corresponds with a gene in Drosophila. The same year, P.C. Koller hesitantly introduced the name "polytene" to describe the giant chromosome, writing:

> ***It seems that we can regard these chromosomes as corresponding with paired pachytene chromosomes at meiosis in which the intercalary parts between chromomeres have been stretched and separated into smaller units, and in which, instead of two threads lying side by side, we have 16 or even more. Hence they are "polytene" rather than pachytene; I do not, however, propose to use this term; I shall refer to them as "multiple threads."***

Occurrence

Polytene chromosomes are present in secretory tissues of dipteran insects such as the Malpighian tubules of Sciara and also in protists, plants, mammals, or in cells from other insects. Some of the largest polytene chromosomes described thus far occur in larval salivary gland cells of the chironomid genus Axarus.

In plants, they are found in only a few species, and are restricted to ovary and immature seed tissues such as in Phaseolus coccineus and P. vulgaris (Nagl, 1981), and the anther tapetum of Vigna unguiculata and of some Phaseolus species.

Polytene chromosomes are also used to identify the species of chironomid larvae that are notoriously difficult to identify. Each morphologically distinct group of larvae consists of a number of morphologically identical (sibling) species that can only be identified by rearing adult males or by cytogenetic analysis of the polytene chromosomes of the larvae. Karyotypes are used to confirm the

presence of specific species and to study genetic diversity in species with a wide range of genetic variation.

SECONDARY CHROMOSOME

Chromids, formerly (and less specifically) secondary chromosomes, are a class of bacterial replicons (replicating DNA molecules). These replicons are called "chromids" because they have characteristic features of both chromosomes and plasmids. Early on, it was thought that all core genes could be found on the main chromosome of the bacteria. However, in 1989 a replicon (now known as a chromid) was discovered containing core genes outside of the main chromosome. These core genes make the chromid indispensable to the organism. Chromids are large replicons, although not as large as the main chromosome. However, chromids are almost always larger than a plasmid (or megaplasmid). Chromids also share many genomic signatures of the chromosome, including their GC-content and their codon usage bias. On the other hand, chromids do not share the replication systems of chromosomes. Instead, they use the replication system of plasmids. Chromids are present in 10% of bacteria species sequenced by 2009.

Bacterial genomes divided between a main chromosome and one or more chromids (and / or megaplasmids) are said to be divided or multipartite genomes. The vast majority of chromid-encoding bacteria only have a single chromid, although 9% have more than one (compared with 12% of megaplasmid-encoding bacteria containing multiple megaplasmids). The genus Azospirillum contains three species which have up to five chromids, the most chromids known in a single species to date. Chromids also appear to be more common in bacteria which have a symbiotic or pathogenic relationship with eukaryotes and with organisms with high tolerance to abiotic stressors.

Chromids were discovered in 1989, in a species of Alphaproteobacteria known as Rhodobacter sphaeroides. However, the formalization of the concept of a "chromid" as an independent type of replicon only came about in 2010. Several classifications further distinguish between chromids depending on conditions of their essentiality, their replication system, and more.

The two hypotheses for the origins of chromids are the "plasmid" and "schism" hypotheses. According to the plasmid hypothesis, chromids originate from plasmids which have acquired core genes over evolutionary time and so stabilized in their respective lineages. According to the schism hypothesis, chromids as well as the main chromosome originate from a schism of a larger, earlier chromosome. The plasmid hypothesis is presently widely accepted, although there may be rare cases where large replicons originate from a chromosomal schism. One finding holds that chromids originated 45 times across bacterial phylogenies and were lost twice.

Discovery and classification

Discovery

Early in the era of bacterial genomics, the genomes of bacteria were thought to have a relatively simple architecture. All known bacteria had circular chromosomes containing all the crucial genes. Some bacteria had additional replicons known as plasmids, and plasmids were characteristically small, circular, and dispensable (meaning that they only encoded non-essential genes). As more

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bacteria and their genomes were studied, many alternative forms of bacterial genomic architecture began to be discovered. Linear chromosomes and linear plasmids were discovered in a number of species. Soon after, bacteria with several large replicons were discovered, leading to the view that bacteria, just like eukaryotes, can have a genome made up of more than one chromosome. The first example of this was Rhodobacter sphaeroides in 1989, but additional discoveries quickly followed with Brucella melitensis in 1993, Burkholderia cepacia complex in 1994, Rhizobium meliloti in 1995, Bacillus thuringiensis in 1996, and now about 10% of bacterial species are known to have large replicons that are separate from the main chromosome.

Definition

With the onset of these discoveries, several approaches in classifying different components of multipartite genomes were proposed. Various terms have been used to describe large replicons other than the main chromosome, including simply designating them as additional chromosomes, or "minichromosomes", "megaplasmids", or "secondary chromosomes". Criteria used to distinguish between these replicons typically revolve around features such as size and the presence of core genes. In 2010, the classification of these genomic elements as chromids was proposed. Previous terms, such as "secondary chromosome", are considered inadequate upon the observation that these replicons contain the replication systems of plasmids and so are a fundamentally different class of replicons than chromosomes. The original definition of a 'chromid' involves meeting three criteria:

1. ***chromids have plasmid-type maintenance and replication systems;***
2. ***chromids have a nucleotide composition close to that of the chromosome;***
3. ***chromids carry core genes that are found on the chromosome in other species.***

While this definition is robust, the authors who proposed it did so with the expectation that some exceptions would be found that would blur the lines between chromids and other replicons. This expectation existed because of the general tendency for evolutionary lineages to produce ambiguous systems, which has resulted in the more well-known issues in formulating a widely-encompassing species definition.

Since the classification of chromids, other replicons have been discovered which share some features of chromids but have been categorized separately. One example is the designated "rrn-plasmid" found in a clade within the bacterial genus Aureimonas. The rrn-plasmid contains the rrn (rRNA) operon (hence its name), and the rrn operon cannot be found on the main chromosome. The main chromosome is therefore termed as an "rrn-lacking chromosome" or RLC, and so the clade of bacteria within Aureimonas which possess the rrn-plasmid is also termed the "RLC clade". Members of the RLC clade have nine replicons, of which the main chromosome is the largest and the rrn-plasmid is the smallest at only 9.4kb. The rrn-plasmid also has a high copy number in RLC bacteria. While this very small size and copy number resembles plasmids moreso than it does chromids, the rrn-plasmid still ahs the only copies of the genes in the rrn operon and for tRNA(Ile). This distinctive collection of features led the scientists discovering this replicon to simply classify it as an rrn-plasmid, which is thought of as a separate classification than a "plasmid" or "chromid".

Additional proposed classifications

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Beyond classifying certain replicons as chromids, a number of scientists have proposed further distinguishing between different types of chromids. One classification distinguishes between primary and secondary chromids. Primary chromids are defined as chromids containing core genes that are always essential for the survival of the bacterium under all conditions. Secondary chromids are defined as chromids essential for survival in the native conditions of the bacterium, but may be non-essential in certain "safe" conditions such as a laboratory environment. Secondary chromids may also have more recent evolutionary origins and may retain some more plasmid-like features as compared with primary chromids. An example of a proposed primary chromid is "chromosome II" of Paracoccus denitrificans PD1222.

Characteristics

Size and copy number

In a bacterial genome, the main chromosome will always be the largest replicon, followed by the chromid and then the plasmid. One exception to this trend is known in Deinococcus deserti VCD115, where both plasmids are larger than the chromid.

Chromids vary considerably in size between organisms. In the bacterial genus Vibrio, the main chromosome varies between 3.0 and 3.3 Mb whereas the chromid varies between 0.8 and 2.4 Mb in size. A replicon in a strain of Buchnera, which encodes some core genes, is only 7.8kb. While the presence of core genes may lead to the classification of this replicon as a chromid, this replicon may also be excluded on certain definitions. Some approaches only categorize certain replicons as chromids if they meet a threshold size of 350kb. It has also been observed that chromids tend to have a low copy number in the cell, as with chromosomes and megaplasmids. On average, chromids are twice as large as megaplasmids (and so the emergence of a chromid from a megaplasmid is associated with a sizable gene accumulation in the aftermath of the conversion). One of the largest chromids is the one in Burkholderia pseudomallei, which exceeds 3.1 million nucleotides in size, i.e. 3.1 megabases or 3.1 Mb.

Genomic features

Chromids more frequently have a lower G + C content compared with the main chromosome, although the strength of this association is not very strong. A chromid will also typically have a G + C content within 1% of that of the main chromosome, reflecting its nearing the base composition equilibrium of the main chromosome after having stably existed within a bacterial lineage for a necessary period of time. Chromids also resemble the main chromosome in their codon usage bias. One analysis found that chromids had a median 0.34% difference in GC content with the main chromosome, compared with values of 1.9% for megaplasmids and 2.8% for plasmids.

Chromids have at least one core gene absent from the main chromosome. (Main chromosomes contain the bulk of the core genes of a bacterium, whereas plasmids contain no core genes.) For example, the chromid in Vibrio cholerae contains genes for the ribosomal subunits L20 and L35. While most chromids have a disproportionately smaller number of essential genes compared to the main chromosome, such as rRNA genes or the genes in the rRNA operon, some may have many more essential genes and may even be considered "equal partners" with the chromosome. In general, chromids also see an enrichment of genes involved in the processes of transport, metabolism,

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

transcription, regulatory functions, signal transduction, and motility-related functions. Proteins located on chromids are involved in processes which can interact with proteins encoded on the main chromosome. Chromids also have more transposase genes than chromosomes, but less than megaplasmids.

Phylogenetic distribution

The presence of core genes makes the chromid essential to the survival of the bacterium. The same core genes will be found on the chromids within a genus but not necessarily between genera. All chromids of a genus may additionally share a large number of conserved but non-essential genes which help define the phenotype of the genus (and the emergence of chromids appears to be the primary evolutionary force in the formation of chromid-encoding bacterial genera, as has been suggested in the case of Vibrio). In contrast, bacterial chromosomes may universally or near-universally share hundreds of conserved core genes. Plasmids contain no core genes, and unlike chromids, plasmids of different species within a bacterial genus (or even just different isolates within the same species) share few genes. This is partly due to the common transfer of gain and loss of plasmids and their transfer between bacteria through conjugation (a form of horizontal gene transfer), while chromids are passed on through cell divisions (vertically) with no evidence of chromids moving through horizontal gene transfer. It has been observed that the chromid in at least one bacterial species could be eliminated without making the bacterium inviable, however, the bacterium did become auxotrophic indicating a severe fitness compromise associated with the loss of the chromid.

Due to their stable presence within a bacterial genus, chromids also have a feature of being phylogenetically restricted to specific genera. Examples of genera of bacteria with chromids include Deinococcus, Leptospira, Cyanothece (a type of cyanobacteria), and an enrichment of genera of the Pseudomonadota. Overall, bacterial genome sequencing indicates that roughly 10% of bacterial species have a chromid. It has also been found that there is a bias towards co-occurrence of a chromid and a megaplasmid in the same organism. Chromids also appear more frequently in phylogenies than do megaplasmids (in approximately twice as many species), despite megaplasmids being the putative evolutionary source for chromids. This may result in the tendency of organisms to lose their megaplasmids over time, compared with the inherently greater evolutionary stability of chromids.

Replication

Chromids share features of the replication of both chromosomes and plasmids. For one, chromids use the replication system of plasmids. While plasmids do not replicate in coordination with the main chromosome or the cell cycle, chromids do and only replicate once per cell cycle. In the bacterial genus Vibrio, replication of the main chromosome begins before replication of the chromid. The chromid is smaller than the chromosome, and so takes a shorter amount of time to finish replication. For this reason, replication of the chromid is delayed to coordinate replication termination between the chromosome and chromid. Earlier replication of the chromosome compared with the chromid has also been observed in Ensifer meliloti. Bacteria also rely on different replication factors to start replication between the chromosome and the chromid. Replication of the chromosome is initiated upon stimulation of the expression of the protein DnaA, whereas expression of chromid replication

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

requires DnaA but also depends on RctB. This is similar to F1 and P plasmids which also depend on DnaA but still have their replication controlled by other proteins (specifically RepA and RepE). Segregation of the chromid follows different patterns between different genera of bacteria, although it typically takes place after the segregation of the main chromosome.

So far, chromids are known to replicate with one of two types of systems: either with the repABC system or with iterons.

Evolutionary flexibility

Several studies indicate that chromids are less conserved and evolve more rapidly than do chromosomes in bacteria. In a study of many species of the genus Vibrio, it was found that the main, large chromosome had a consistent size range of 3–3.3 Mb, whereas the secondary chromosome flexibly ranged from 0.8 to 2.4 Mb. This considerable variation indicates a greater degree of structural flexibility. Bacteria of the genus Agrobacterium and another genera can have three or more chromids, and these multiple chromids in several strains commonly undergo large-scale rearrangements which can involve the translocation of one sizable portion of one chromid into another. Genes located on chromids are also more prone to evolve and display less purifying selection. Since common species definition for prokaryotes are based on DNA sequence or average nucleotide identity, the greater evolvability of the chromid may result in organisms with chromids having a greater tendency to speciate.

Origins

"Schism" and "plasmid" hypotheses

Several suggestions have been put forwards to explain the origins of chromids. The two main hypotheses are the "schism hypothesis" and the "plasmid hypothesis". According to the schism hypothesis, two separate bacterial chromosomes may arise through the splitting of one larger chromosome, resulting in a main and a secondary chromosome (or a chromid). However, due to the plasmid-type maintenance and replication systems in chromids as well as the uneven distribution of core genes between the main chromosome and the chromid, the plasmid hypothesis suggesting that chromids evolved from megaplasmids which acquired core genes is widely accepted. Once megaplasmids acquire core genes from the main chromosome, combined with the simultaneous loss of those core genes from the main chromosome, the plasmid becomes a stable and required element of the bacterial genome. (Megaplasmids may also acquire duplicate copies of core genes from the main chromosome. The existence of the duplicate core gene may degenerate on the main chromosome, leading to its sole presence on the newly formed chromid. In this case, the chromid is formed through a neutral transition.) This event also stabilizes the other genes located on the new chromid, which may result in a characteristic phenotype for the new lineage. These core genes can transfer to a megaplasmid through several means. One is homologous recombination between the main chromosome and the plasmid. It is also possible that an existing chromid could recombine with a plasmid to gain its replication system. Once a chromid appears in a lineage, it is stable over long evolutionary periods. Several bacteria genera have chromids which are characteristic to each genus. Whereas the chromids found in a single genus may universally share a large number of genes, there are no genes universally found across the chromids of different genera.

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

Plasmids are almost always if not always the source for the origins of chromids, but at least two bacterial strains may have their large replicons derive from the schism of a larger chromosome. In these exceptional cases, the term "secondary chromosome" may be retained to describe them and so, in this sense, differentiate them from "chromids". Identifying a replicon as a "secondary chromosome" may be done on the basis of conserved synteny and random distribution of core genes with the main chromosome.

Proposed adaptive causes

The question of the origins of chromids is tied to the question of why they evolved. One possibility is that chromids are a "frozen accident", where they simply happened to evolve by chance and for no particular reason and so, for this reason alone, are present in the lineage descendant from the organism in which they emerged. In this scenario, core genes end up on the chromid by chance, but the chance fixation of core genes on the secondary replicon through neutral transitions leads to its essentiality to the organism. However, chromids may also bring some advantages which helps the bacterium compete in its environment. It has been observed that bacteria with chromids are capable of growing faster in culture, and also contain fairly more sizable genomes. Chromid-encoding bacteria have a genome with an average size of 5.73 ± 1.66 Mb, whereas bacteria which do not encode chromids have an average genome size of 3.38 ± 1.81 Mb. For this reason, some have concluded that the placement of a number of genes on the chromid instead of the main chromosome allows for genome expansion without compromising replication speed and efficiency. On the other hand, two thirds of bacterial genomes over 6 Mb are not multipartite and only three of the fifty largest genomes are multipartite, and so a larger genome has not yet been causally demonstrated as a reason for the evolutionary origins of a chromid. Chromids can also be frequently found on fast-growing bacteria, suggesting their contribution to replication and division speed, although here too several analyses have raised difficulties with this suggestion as a driving evolutionary force for the emergence of chromids. Instead, it is more likely that genome expansion and faster replication speed may be involved in the maintenance of chromids in lineages but not a causal explanation for their emergence. Chromids may also allow for coordinated expression of niche-specific genes. Random though rare emergence of chromids which happen to have the necessary genes to confer an advantageous lifestyle in a given environment may play an important role in stabilizing that chromid in the organism and leading to a new lineage defined by the presence of the now crucial replicon.

SEX-DETERMINATION SYSTEM

A sex-determination system is a biological system that determines the development of sexual characteristics in an organism. Most organisms that create their offspring using sexual reproduction have two common sexes, males and females, and in other species, there are hermaphrodites, organisms that can function reproductively as either female or male, or both

There are also some species in which only one sex is present, temporarily or permanently. This can be due to parthenogenesis, the act of a female reproducing without fertilization. In some plants or algae the gametophyte stage may reproduce itself, thus producing more individuals of the same sex as the parent.

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

In some species, sex determination is genetic: males and females have different alleles or even different genes that specify their sexual morphology. In animals this is often accompanied by chromosomal differences, generally through combinations of XY, ZW, XO, ZO chromosomes, or haplodiploidy. The sexual differentiation is generally triggered by a main gene (a "sex locus"), with a multitude of other genes following in a domino effect.

In other cases, the sex of a fetus is determined by environmental variables (such as temperature). The details of some sex-determination systems are not yet fully understood.

Some species such as various plants and fish do not have a fixed sex and instead go through life cycles and change sex based on genetic cues during corresponding life stages of their type. This could be due to environmental factors such as seasons and temperature. In some gonochoric species, a few individuals may have conditions that cause a mix of different sex characteristics.

Discovery

Sex determination was discovered in the mealworm by the American geneticist Nettie Stevens in 1903.

- ***In 1694, J.R. Camerarius, conducted early experiments on pollination and reported the existence of male and female characteristics in plants(Maize).***
- ***In 1866, Gregor Mendel published on inheritance of genetic traits. This is known as Mendelian inheritance and it eventually established the modern understanding of inheritance from two gametes.***
- ***In 1902, C.E. McClung identified sex chromosomes in bugs.***
- ***In 1917, C.E. Allen, discovered sex determination mechanisms in plants.***
- ***In 1922, C.B. Bridges, put forth the Genic Balance Theory of sex determination.***
- ***In 1928, Fritz Baltzer first described environmental*** *sex determination.*

Chromosomal systems

Among animals, the most common chromosomal sex determination systems are XY, XO, ZW, ZO, but with numerous exceptions.

According to the Tree of Sex database (as of 2023), the known sex determination systems are:[9]

Sex determination systems in vertebrates, insects and angiosperms

Taxonomic group	XY	XO	ZW	ZO.	Other1	XO/XY ratio	ZO/ZW ratio
1. Vertebrates	722	15	480	3	254	0.02	0.01

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2.	Insects	4415	1857	37	25	156	0.42	0.68
3.	Angiosperms	23	0	1	0	19	0.00	0.00
	Total	5160	1872	518	28	429	0.36	0.05

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1. complex sex chromosomes, homomorphic sex chromosomes, or others

XX/XY sex chromosomes

The XX/XY sex-determination system is the most familiar, as it is found in humans. The XX/XY system is found in most other mammals, as well as some insects. In this system, females have two of the same kind of sex chromosome (XX), while males have two distinct sex chromosomes (XY). The X and Y sex chromosomes are different in shape and size from each other, unlike the rest of the chromosomes (autosomes), and are sometimes called allosomes. In some species, such as humans, organisms remain sex indifferent for a time during development (embryogenesis); in others, however, such as fruit flies, sexual differentiation occurs as soon as the egg is fertilized.

Y-centered sex determination

Some species (including humans) have a gene SRY on the Y chromosome that determines maleness. Members of SRY-reliant species can have uncommon XY chromosomal combinations such as XXY and still live. Human sex is determined by the presence or absence of a Y chromosome with a functional SRY gene. Once the SRY gene is activated, cells create testosterone and anti-müllerian hormone which typically ensures the development of a single, male reproductive system. In typical XX embryos, cells secrete estrogen, which drives the body toward the female pathway.

In Y-centered sex determination, the SRY gene is the main gene in determining male characteristics, but multiple genes are required to develop testes. In XY mice, lack of the gene DAX1 on the X chromosome results in sterility, but in humans it causes adrenal hypoplasia congenita. However, when an extra DAX1 gene is placed on the X chromosome, the result is a female, despite the existence of SRY, since it overrides the effects of SRY. Even when there are normal sex chromosomes in XX females, duplication or expression of SOX9 causes testes to develop. Gradual sex reversal in developed mice can also occur when the gene FOXL2 is removed from females. Even though the gene DMRT1 is used by birds as their sex locus, species who have XY chromosomes also rely upon DMRT1, contained on chromosome 9, for sexual differentiation at some point in their formation.

X-centered sex determination

Some species, such as fruit flies, use the presence of two X chromosomes to determine femaleness. Species that use the number of Xs to determine sex are nonviable with an extra X chromosome.

Other variants of XX/XY sex determination

Some fish have variants of the XY sex-determination system, as well as the regular system. For example, while having an XY format, Xiphophorus nezahualcoyotl and X. milleri also have a second Y chromosome, known as Y', that creates XY' females and YY' males.

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At least one monotreme, the platypus, presents a particular sex determination scheme that in some ways resembles that of the ZW sex chromosomes of birds and lacks the SRY gene. The platypus has sex chromosomes X_1 , X_2 , X_3 , X_4 , X_5 , Y_1 , Y_2 , Y_3 , Y_4 , Y_5 .
The males have $X_1Y_1 / X_2Y_2 / X_3Y_3 / X_4Y_4 / X_5Y_5$.
The females have $X_1X_1 / X_2X_2 / X_3X_3 / X_4X_4 / X_5X_5$.
During meiosis, 5 of X form one chain, and 5 of Y form another chain. Thus, they behave effectively as a typical XY chromosomal system, except each of X and Y is broken into 5 parts, with the effect that recombinations occur very frequently at 4 particular points. One of the X chromosomes is homologous to the human X chromosome, and another is homologous to the bird Z chromosome.

Although it is an XY system, the platypus' sex chromosomes share no homologues with eutherian sex chromosomes. Instead, homologues with eutherian sex chromosomes lie on the platypus chromosome 6, which means that the eutherian sex chromosomes were autosomes at the time that the monotremes diverged from the therian mammals (marsupials and eutherian mammals). However, homologues to the avian DMRT1 gene on platypus sex chromosomes X3 and X5 suggest that it is possible the sex-determining gene for the platypus is the same one that is involved in bird sex-determination. More research must be conducted in order to determine the exact sex determining gene of the platypus.

XX/X0 sex chromosomes

In this variant of the XY system, females have two copies of the sex chromosome (XX) but males have only one (X0). The 0 denotes the absence of a second sex chromosome. Generally in this method, the sex is determined by amount of genes expressed across the two chromosomes. This system is observed in a number of insects, including the grasshoppers and crickets of order Orthoptera and in cockroaches (order Blattodea). A small number of mammals also lack a Y chromosome. These include the Amami spiny rat (Tokudaia osimensis) and the Tokunoshima spiny rat (Tokudaia tokunoshimensis) and Sorex araneus, a shrew species. Transcaucasian mole voles (Ellobius lutescens) also have a form of XO determination, in which both sexes lack a second sex chromosome. The mechanism of sex determination is not yet understood.

The nematode C. elegans is male with one sex chromosome (X0); with a pair of chromosomes (XX) it is a hermaphrodite. Its main sex gene is XOL, which encodes XOL-1 and also controls the expression of the genes TRA-2 and HER-1. These genes reduce male gene activation and increase it, respectively.

ZW/ZZ sex chromosomes

The ZW sex-determination system is found in birds, some reptiles, and some insects and other organisms. The ZW sex-determination system is reversed compared to the XY system: females have two different kinds of chromosomes (ZW), and males have two of the same kind of chromosomes (ZZ). In the chicken, this was found to be dependent on the expression of DMRT1. In birds, the genes FET1 and ASW are found on the W chromosome for females, similar to how the Y chromosome contains SRY. However, not all species depend upon the W for their sex. For example,

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there are moths and butterflies that are ZW, but some have been found female with ZO, as well as female with ZZW. Also, while mammals deactivate one of their extra X chromosomes when female, it appears that in the case of Lepidoptera, the males produce double the normal amount of enzymes, due to having two Z's. Because the use of ZW sex determination is varied, it is still unknown how exactly most species determine their sex. However, reportedly, the silkworm Bombyx mori uses a single female-specific piRNA as the primary determiner of sex. Despite the similarities between the ZW and XY systems, these sex chromosomes evolved separately. In the case of the chicken, their Z chromosome is more similar to humans' autosome 9. The chicken's Z chromosome also seems to be related to the X chromosome of the platypus. When a ZW species, such as the Komodo dragon, reproduces parthenogenetically, usually only males are produced. This is due to the fact that the haploid eggs double their chromosomes, resulting in ZZ or WW. The ZZ become males, but the WW are not viable and are not brought to term.

In both XY and ZW sex determination systems, the sex chromosome carrying the critical factors is often significantly smaller, carrying little more than the genes necessary for triggering the development of a given sex.

ZZ/Z0 sex chromosomes

The ZZ/Z0 sex-determination system is found in some moths. In these insects there is one sex chromosome, Z. Males have two Z chromosomes, whereas females have one Z. Males are ZZ, while females are Z0.

UV sex chromosomes

In some bryophyte and some algae species, the gametophyte stage of the life cycle, rather than being hermaphrodite, occurs as separate male or female individuals that produce male and female gametes respectively. When meiosis occurs in the sporophyte generation of the life cycle, the sex chromosomes known as U and V assort in spores that carry either the U chromosome and give rise to female gametophytes, or the V chromosome and give rise to male gametophytes.

Mating types

The mating type in microorganisms is analogous to sex in multi-cellular organisms, and is sometimes described using those terms, though they are not necessarily correlated with physical body structures. Some species have more than two mating types. Tetrahymena, a type of ciliate, has 7 mating types

Mating types are extensively studied in fungi. Among fungi, mating type is determined by chromosomal regions called mating-type loci. Furthermore, it is not as simple as "two different mating types can mate", but rather, a matter of combinatorics. As a simple example, most basidiomycete have a "tetrapolar heterothallism" mating system: there are two loci, and mating between two individuals is possible if the alleles on both loci are different. For example, if there are 3 alleles per locus, then there would be 9 mating types, each of which can mate with 4 other mating types. By multiplicative combination, it generates a vast number of mating types. For example, Schizophyllum commune, a type of fungus, has $9 \times 32 \times 9 \times 9 = 23328$ *mating types.*

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Haplodiploidy

Haplodiploidy is found in insects belonging to Hymenoptera, such as ants and bees. Sex determination is controlled by the zygosity of a complementary sex determiner (csd) locus. Unfertilized eggs develop into haploid individuals which have a single, hemizygous copy of the csd locus and are therefore males. Fertilized eggs develop into diploid individuals which, due to high variability in the csd locus, are generally heterozygous females. In rare instances diploid individuals may be homozygous, these develop into sterile males. The gene acting as a csd locus has been identified in the honeybee and several candidate genes have been proposed as a csd locus for other Hymenopterans. Most females in the Hymenoptera order can decide the sex of their offspring by holding received sperm in their spermatheca and either releasing it into their oviduct or not. This allows them to create more workers, depending on the status of the colony.

Polygenic sex determination

Polygenic sex determination is when the sex is primarily determined by genes that occur on multiple non-homologous chromosomes. The environment may have a limited, minor influence on sex determination. Examples include African cichlid fish (Metriaclima spp.), lemmings (Myopus schisticolor), green swordtail, medaka, etc. In such systems, there is typically a dominance hierarchy, where one system is dominant over another if in conflict. For example, in some species of cichlid fish from Lake Malawi, if an individual has both the XY locus (on one chromosome pair) and the WZ locus (on another chromosome pair), then the W is dominant and the individual has a female phenotype.

The sex-determination system of zebrafish is polygenic. Juvenile zebrafishes (0–30 days after hatching) have both ovary-like tissue to testis tissue. They then develop into male or female adults, with the determination based on a complex interaction genes on multiple chromosomes, but not affected by environmental variations.

Other chromosomal systems

In systems with two sex chromosomes, they can be heteromorphic or homomorphic. Homomorphic sex chromosomes are almost identical in size and gene content. The two familiar kinds of sex chromosome pairs (XY and ZW) are heteromorphic. Homomorphic sex chromosomes exist among pufferfish, ratite birds, pythons, and European tree frogs. Some are quite old, meaning that there is some evolutionary force that resists their differentiation. For example, three species of European tree frogs have homologous, homomorphic sex chromosomes, and this homomorphism was maintained for at least 5.4 million years by occasional recombination.

The Nematocera, particularly the Simuliids and Chironomus, have sex determination regions that are labile, meaning that one species may have the sex determination region in one chromosome, but a closely related species might have the same region moved to a different non-homologous chromosome. Some species even have the sex determination region different among individuals within the same species (intraspecific variation). In some species, some populations have homomorphic sex chromosomes while other populations have heteromorphic sex chromosomes.

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The New Zealand frog, Leiopelma hochstetteri, uses a supernumerary sex chromosome. With zero of that chromosome, the frog develops into a male. With one or more, the frog develops into a female. One female had as many as 16 of that chromosome.

Different populations of the Japanese frog Rana rugosa uses different systems. Two use homomorphic male heterogamety, one uses XX/XY, one uses ZZ/ZW. Remarkably, the X and Z chromosomes are homologous, and the Y and W as well. Dmrt1 is on autosome 1 and not sex-linked. This means that an XX female individual is genetically similar to a ZZ male individual, and an XY male individual is to a ZW female individual. The mechanism behind this is yet unclear, but it is hypothesized that during its recent evolution, the XY-to-ZW transition occurred twice.

Clarias gariepinus uses both XX/XY and ZW/ZZ system within the species, with some populations using homomorphic XX/XY while others using heteromorphic ZW/ZZ. A population in Thailand appears to use both systems simultaneously, possibly because C. gariepinus were not native to Thailand, and were introduced from different source populations which resulted in a mixture.

Multiple sex chromosomes like those of platypus also occurs in bony fish.[53] Some moths and butterflies have W_1W_2Z ♀ / ZZ ♂ or WZ_1Z_2 ♀ / $Z_1Z_1Z_2Z_2$ ♂

The Southern platyfish has a complex sex determination system involving 3 sex chromosomes and 4 autosomal alleles.

Gastrotheca pseustes has XY_b ♀ / XY_a ♂ , C-banding heteromorphism, meaning that both males and females have XY chromosomes, but their Y chromosomes are different on one or more C-bands. Eleutherodactylus maussi has a $X_1X_1X_2X_2$♀/ X_1X_2Y♂

Origin of sex chromosomes

Sexual chromosome pairs can arise from an autosomal pair that, for various reasons, stopped recombination, allowing for their divergence. The rate at which recombination is suppressed, and therefore the rate of sex chromosome divergence, is very different across clades.

In analogy with geological strata, historical events in the evolution of sex chromosomes are called evolutionary strata. The human Y-chromosome has had about 5 strata since the origin of the X and Y chromosomes about 300 Mya from a pair of autosomes. Each stratum was formed when a pseudoautosomal region (PAR) of the Y chromosome is inverted, stopping it from recombination with the X chromosome. Over time, each inverted region decays, possibly due to Muller's ratchet. Primate Y-chromosome evolution was rapid, with multiple inversions and shifts of the boundary of PAR.

Among many species of the salamanders, the two chromosomes are only distinguished by a pericentric inversion, so that the banding pattern of the X chromosome is the same as that of Y, but with a region near the centromere reversed. (fig 7) In some species, the X is pericentrically inverted and the Y is ancestral. In other species it is the opposite. (p. 15)

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The gene content of the X chromosome is almost identical among placental mammals. This is hypothesized to be because the X inactivation means any change would cause serious disruption, thus subjecting it to strong purifying selection. Similarly, birds have highly conserved Z chromosomes.[51]

Neo-sex chromosomes

Neo-sex chromosomes are currently existing sex chromosomes that formed when an autosome pair fused to the previously existing sex chromosome pair. Following this fusion, the autosomal portion undergoes recombination suppression, allowing them to differentiate. Such systems have been observed in insects, reptiles, birds, and mammals. They are useful to the study of the evolution of Y chromosome degeneration and dosage compensation.

Sex-chromosome turnover

The sex-chromosome turnover is an evolutionary phenomenon where sex chromosomes disappear, or becomes autosomal, and autosomal chromosomes become sexual, repeatedly over evolutionary time. Some lineages have extensive turnover, but others don't. Generally, in an XY system, if the Y chromosome is degenerate, mostly different from the X chromosome, and has X dosage compensation, then turnover is unlikely. In particular, this applies to humans.

The ZW and XY systems can evolve into to each other due to sexual conflict.

Homomorphism and the fountain of youth

It is an evolutionary puzzle why certain sex chromosomes remain homomorphic over millions of years, especially among lineages of fishes, amphibians, and nonavian reptiles. The fountain-of-youth model states that heteromorphy results from recombination suppression, and recombination suppression results from the male phenotype, not the sex chromosomes themselves. Therefore, if some XY sex-reversed females are fertile and adaptive under some circumstances, then the X and Y chromosomes would recombine in these individuals, preventing Y chromosome decay and maintaining long-term homomorphism.

Sex reversal denotes a situation where the phenotypic sex is different from the genotypic sex. While in humans, sex reversal (such as the XX male syndrome) are often infertile, sex-reversed individuals of some species are fertile under some conditions. For example, some XY-individuals in population of Chinook salmon in the Columbia River became fertile females, producing YY sons. Since Chinook salmons have homomorphic sex chromosomes, such YY sons are healthy. When YY males mate with XX females, all their progeny would be XY male if grown under normal conditions.

Support for the hypothesis is found in the common frog, for which XX males and XY males both suppresses sex chromosome recombination, but XX and XY females both recombine at the same rate.

Environmental systems

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

Temperature-dependent

Many other sex-determination systems exist. In some species of reptiles, including alligators, some turtles, and the tuatara, sex is determined by the temperature at which the egg is incubated during a temperature-sensitive period. There are no examples of temperature-dependent sex determination (TSD) in birds. Megapodes had formerly been thought to exhibit this phenomenon, but were found to actually have different temperature-dependent embryo mortality rates for each sex. For some species with TSD, sex determination is achieved by exposure to hotter temperatures resulting in the offspring being one sex and cooler temperatures resulting in the other. This type of TSD is called Pattern I. For others species using TSD, it is exposure to temperatures on both extremes that results in offspring of one sex, and exposure to moderate temperatures that results in offspring of the opposite sex, called Pattern II TSD. The specific temperatures required to produce each sex are known as the female-promoting temperature and the male-promoting temperature. When the temperature stays near the threshold during the temperature sensitive period, the sex ratio is varied between the two sexes. Some species' temperature standards are based on when a particular enzyme is created. These species that rely upon temperature for their sex determination do not have the SRY gene, but have other genes such as DAX1, DMRT1, and SOX9 that are expressed or not expressed depending on the temperature. The sex of some species, such as the Nile tilapia, Australian skink lizard, and Australian dragon lizard, has an initial bias, set by chromosomes, but can later be changed by the temperature of incubation.

It is unknown how exactly temperature-dependent sex determination evolved. It could have evolved through certain sexes being more suited to certain areas that fit the temperature requirements. For example, a warmer area could be more suitable for nesting, so more females are produced to increase the amount that nest next season. In amniotes, environmental sex determination preceded the genetically determined systems of birds and mammals; it is thought that a temperature-dependent amniote was the common ancestor of amniotes with sex chromosomes.

Other environmental systems

There are other environmental sex determination systems including location-dependent determination systems as seen in the marine worm Bonellia viridis – larvae become males if they make physical contact with a female, and females if they end up on the bare sea floor. This is triggered by the presence of a chemical produced by the females, bonellin. Some species, such as some snails, practice sex change: adults start out male, then become female. In tropical clownfish, the dominant individual in a group becomes female while the other ones are male, and bluehead wrasses (Thalassoma bifasciatum) are the reverse.

Clownfish live in colonies of several small undifferentiated fish and two large fish (male and female). The male and female are the only sexually mature fish to reproduce. Clownfish are protandrous hermaphrodites, which means after they mature into males, they eventually can transform into females. They develop undifferentiated until they are needed to fill a certain role in their environment, i.e., if they receive the social and environmental cues to do so.

Some species, however, have no sex-determination system. Hermaphrodite species include the common earthworm and certain species of snails. A few species of fish, reptiles, and insects

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reproduce by parthenogenesis and are female altogether. There are some reptiles, such as the boa constrictor and Komodo dragon that can reproduce both sexually and asexually, depending on whether a mate is available.

Others

There are exceptional sex-determination systems, neither genetic nor environmental.

Cytoplasmic sex determination

The Wolbachia genus of parasitic bacteria lives inside the cytoplasm of its host, and is vertically transmitted from parents to children. They primarily infect arthropods and nematodes. Different Wolbachia can alter the reproductive abilities of its host by a variety of means, including cytoplasmic incompatibility, parthenogenesis, feminization and embryonic male killing.

Mitochondrial male sterility: In many flowering plants, the mitochondria can cause hermaphrodite individuals to be unable to father offspring, effectively turning them into exclusive females. This is a form of mother's curse. It is an evolutionarily adaptive strategy for mitochondria as mitochondria are inherited exclusively from mother to offspring. The first published case of mitochondrial male sterility among metazoans was reported in 2022 in the hermaphroditic snail Physa acuta.

Paternal genome elimination

In some species of insects, springtails and mites, male offspring lose their paternal genome (in whole or in part) during development or in the germline. Males can either be diploid, diploid with missing sex chromosome, functionally haploid or truly haploid, depending on the mechanism of elimination.

Monogeny

In some species of Hymenoptera (ants, bees and wasps), flies and crustaceans, all offspring of a particular individual female are either exclusively male or exclusively female. The underlying mechanisms are diverse and include maternally controlled paternal genome elimination and Mendelian inherited maternal sex-determining factors.

Evolution

Sex determination systems may have evolved from mating type, which is a feature of microorganisms.

Chromosomal sex determination may have evolved early in the history of eukaryotes.[85] But in plants it has been suggested to have evolved recently.

The accepted hypothesis of XY and ZW sex chromosome evolution in amniotes is that they evolved at the same time, in two different branches.

No genes are shared between the avian ZW and mammal XY chromosomes and the chicken Z chromosome is similar to the human autosomal chromosome 9, rather than X or Y. This suggests not that the ZW and XY sex-determination systems share an origin but that the sex chromosomes

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are derived from autosomal chromosomes of the common ancestor of birds and mammals. In the platypus, a monotreme, the X1 chromosome shares homology with therian mammals, while the X5 chromosome contains an avian sex-determination gene, further suggesting an evolutionary link.

However, there is some evidence to suggest that there could have been transitions between ZW and XY, such as in Xiphophorus maculatus, which have both ZW and XY systems in the same population, despite the fact that ZW and XY have different gene locations. A recent theoretical model raises the possibility of both transitions between the XY/XX and ZZ/ZW system and environmental sex determination The platypus' genes also back up the possible evolutionary link between XY and ZW, because they have the DMRT1 gene possessed by birds on their X chromosomes. Regardless, XY and ZW follow a similar route. All sex chromosomes started out as an original autosome of an original amniote that relied upon temperature to determine the sex of offspring. After the mammals separated, the reptile branch further split into Lepidosauria and Archosauromorpha. These two groups both evolved the ZW system separately, as evidenced by the existence of different sex chromosomal locations. In mammals, one of the autosome pair, now Y, mutated its SOX3 gene into the SRY gene, causing that chromosome to designate sex. After this mutation, the SRY-containing chromosome inverted and was no longer completely homologous with its partner. The regions of the X and Y chromosomes that are still homologous to one another are known as the pseudoautosomal region. Once it inverted, the Y chromosome became unable to remedy deleterious mutations, and thus degenerated. There is some concern that the Y chromosome will shrink further and stop functioning in ten million years: but the Y chromosome has been strictly conserved after its initial rapid gene loss.

There are some vertebrate species, such as the medaka fish, that evolved sex chromosomes separately; their Y chromosome never inverted and can still swap genes with the X. These species' sex chromosomes are relatively primitive and unspecialized. Because the Y does not have male-specific genes and can interact with the X, XY and YY females can be formed as well as XX males. Non-inverted Y chromosomes with long histories are found in pythons and emus, each system being more than 120 million years old, suggesting that inversions are not necessarily an eventuality. XO sex determination can evolve from XY sex determination with about 2 million years.

XY SEX-DETERMINATION SYSTEM

The XY sex-determination system is a sex-determination system present in many mammals, including humans, some insects (Drosophila), some snakes, some fish (guppies), and some plants (Ginkgo tree).

In this system, the sex of an individual usually is determined by a pair of sex chromosomes. Typically, females have two of the same kind of sex chromosome (XX), and are called the homogametic sex. Males typically have two different kinds of sex chromosomes (XY), and are called the heterogametic sex. In humans, the presence of the Y chromosome is responsible for triggering male development; in the absence of the Y chromosome, the fetus will undergo female

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development. In most species with XY sex determination, an organism must have at least one X chromosome in order to survive.

The XY system contrasts in several ways with the ZW sex-determination system found in birds, some insects, many reptiles, and various other animals, in which the heterogametic sex is female. A temperature-dependent sex determination system is found in some reptiles and fish.

Mechanisms

All animals have a set of DNA coding for genes present on chromosomes. In humans, most mammals, and some other species, two of the chromosomes, called the X chromosome and Y chromosome, code for sex. In these species, one or more genes are present on their Y chromosome that determine maleness. In this process, an X chromosome and a Y chromosome act to determine the sex of offspring, often due to genes located on the Y chromosome that code for maleness. Offspring have two sex chromosomes: an offspring with two X chromosomes (XX) will develop female characteristics, and an offspring with an X and a Y chromosome (XY) will develop male characteristics, except in various exceptions such as individuals with Swyer syndrome, that have XY chromosomes and a female phenotype, and de la Chapelle Syndrome, that have XX chromosomes and a male phenotype, however these exceptions are rare.

Mammals

In most mammals, sex is determined by presence of the Y chromosome. This makes individuals with XXY and XYY karyotypes males, and individuals with X and XXX karyotypes females.

In the 1930s, Alfred Jost determined that the presence of testosterone was required for Wolffian duct development in the male rabbit.

SRY is a sex-determining gene on the Y chromosome in the therians (placental mammals and marsupials). Non-human mammals use several genes on the Y chromosome.

Not all male-specific genes are located on the Y chromosome. The platypus, a monotreme, use five pairs of different XY chromosomes with six groups of male-linked genes, AMH being the master switch.

Humans

A single gene (SRY) present on the Y chromosome acts as a signal to set the developmental pathway towards maleness. Presence of this gene starts off the process of virilization. This and other factors result in the sex differences in humans. The cells in females, with two X chromosomes, undergo X-inactivation, in which one of the two X chromosomes is inactivated. The inactivated X chromosome remains within a cell as a Barr body.

Other animals

Some species of turtles have convergently evolved XY sex determination systems, specifically those in Chelidae and Staurotypinae.

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Other species (including most Drosophila species) use the presence of two X chromosomes to determine femaleness: one X chromosome gives putative maleness, but the presence of Y chromosome genes is required for normal male development. In the fruit fly individuals with XY are male and individuals with XX are female; however, individuals with XXY or XXX can also be female, and individuals with X can be males.

Plants

Angiosperms

While very few species of dioecious angiosperm have XY sex determination, making up less than 5% of all species, the sheer diversity of angiosperms means that the total number of species with XY sex determination is actually quite high, estimated to be at around 13,000 species. Molecular and evolutionary studies also show that XY sex determination has evolved independently many times in upwards of 175 unique families, with a recent study suggesting its evolution has independently occurred hundreds to thousands of times.

Many economically important crops are known to have an XY system of sex determination, including kiwifruit, asparagus, grapes and date palms.

Gymnosperms

In sharp contrast to angiosperms, approximately 65% of gymnosperms are dioecious. Some families which contain members that are known to have a XY system of sex determination include the cycad families Cycadaceae and Zamiaceae, Ginkgoaceae, Gnetaceae and Podocarpaceae.

Other systems

Sex determination system

Whilst XY sex determination is the most familiar, since it is the system that humans use, there are a range of alternative systems found in nature. The inverse of the XY system (called ZW to distinguish it) is used in birds and many insects, in which it is the females that are heterogametic (ZW), while males are homogametic (ZZ).

Many insects of the order Hymenoptera instead have a haplo-diploid system, where the females are full diploids (with all chromosomes appearing in pairs) but males are haploid (having just one copy of all chromosomes). Some other insects have the X0 sex-determination system, where just the sex-determining chromosome varies in ploidy (XX in females but X in males), while all other chromosomes appear in pairs in both sexes.

Influences

Genetic

In an interview for the Rediscovering Biology website, researcher Eric Vilain described how the paradigm changed since the discovery of the SRY gene:

> *For a long time we thought that SRY would activate a cascade of male genes. It turns out that the sex determination pathway is probably more complicated and SRY may in fact inhibit some anti-male genes.*

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> *The idea is instead of having a simplistic mechanism by which you have pro-male genes going all the way to make a male, in fact there is a solid balance between pro-male genes and anti-male genes and if there is a little too much of anti-male genes, there may be a female born and if there is a little too much of pro-male genes then there will be a male born.*
>
> *We [are] entering this new era in molecular biology of sex determination where it's a more subtle dosage of genes, some pro-males, some pro-females, some anti-males, some anti-females that all interplay with each other rather than a simple linear pathway of genes going one after the other, which makes it very fascinating but very complicated to study.*

In an interview by Scientific American in 2007, Vilian was asked: "It sounds as if you are describing a shift from the prevailing view that female development is a default molecular pathway to active pro-male and antimale pathways. Are there also pro-female and antifemale pathways?" He replied:

> *Modern sex determination started at the end of the 1940s—1947—when the French physiologist Alfred Jost said it's the testis that is determining sex. Having a testis determines maleness, not having a testis determines femaleness. The ovary is not sex-determining. It will not influence the development of the external genitalia. Now in 1959 when the karyotype of Klinefelter [a male who is XXY] and Turner [a female who has one X] syndromes was discovered, it became clear that in humans it was the presence or the absence of the Y chromosome that's sex determining. Because all Klinefelters that have a Y are male, whereas Turners, who have no Y, are females. So it's not a dosage or the number of X's, it's really the presence or absence of the Y. So if you combine those two paradigms, you end up having a molecular basis that's likely to be a factor, a gene, that's a testis-determining factor, and that's the sex-determining gene. So the field based on that is really oriented towards finding testis-determining factors. What we discovered, though, was not just pro-testis determining factors. There are a number of factors that are there, like WNT4, like DAX1, whose function is to counterbalance the male pathway.*

In mammals, including humans, the SRY gene triggers the development of non-differentiated gonads into testes rather than ovaries. However, there are cases in which testes can develop in the absence of an SRY gene (see sex reversal). In these cases, the SOX9 gene, involved in the development of testes, can induce their development without the aid of SRY. In the absence of SRY and SOX9, no testes can develop and the path is clear for the development of ovaries. Even so, the absence of the SRY gene or the silencing of the SOX9 gene are not enough to trigger sexual differentiation of a fetus in the female direction. A recent finding suggests that ovary development and maintenance is an active process, regulated by the expression of a "pro-female" gene, FOXL2. In an interview for the TimesOnline edition, study co-author Robin Lovell-Badge explained the significance of the discovery:

> *We take it for granted that we maintain the sex we are born with, including whether we have testes or ovaries. But this work shows that the activity of a single gene, FOXL2, is all that prevents adult ovary cells turning into cells found in testes.*

Implications

Looking into the genetic determinants of human sex can have wide-ranging consequences. Scientists have been studying different sex determination systems in fruit flies and animal models to attempt an understanding of how the genetics of sexual differentiation can influence biological processes like reproduction, ageing and disease.

Chromosome , Chromosome segregation , Chromomere , Lampbrush chromosome , Minichromosome , Microchromosome , Neochromosome , Parasitic chromosomes , Polytene chromosomes , Secondary chromosome , Sex-determination system , XY sex-determination system , Temperature-dependent sex determination , Environmental sex determination , Sexual Differentiation , Cell Autonomous Sex Identity (CASI)

Maternal

In humans and many other species of animals, the father determines the sex of the child. In the XY sex-determination system, the female-provided ovum contributes an X chromosome and the male-provided sperm contributes either an X chromosome or a Y chromosome, resulting in female (XX) or male (XY) offspring, respectively.

Hormone levels in the male parent affect the sex ratio of sperm in humans. Maternal influences also impact which sperm are more likely to achieve conception.

Human ova, like those of other mammals, are covered with a thick translucent layer called the zona pellucida, which the sperm must penetrate to fertilize the egg. Once viewed simply as an impediment to fertilization, recent research indicates the zona pellucida may instead function as a sophisticated biological security system that chemically controls the entry of the sperm into the egg and protects the fertilized egg from additional sperm.

Recent research indicates that human ova may produce a chemical which appears to attract sperm and influence their swimming motion. However, not all sperm are positively impacted; some appear to remain uninfluenced and some actually move away from the egg.
Maternal influences may also be possible that affect sex determination in such a way as to produce fraternal twins equally weighted between one male and one female.

The time at which insemination occurs during the estrus cycle has been found to affect the sex ratio of the offspring of humans, cattle, hamsters, and other mammals. Hormonal and pH conditions within the female reproductive tract vary with time, and this affects the sex ratio of the sperm that reach the egg.

Sex-specific mortality of embryos also occurs.

History

Ancient ideas on sex determination

Aristotle believed incorrectly that the sex of an infant is determined by how much heat a man's sperm had during insemination. He wrote:

> ***... the semen of the male differs from the corresponding secretion of the female in that it contains a principle within itself of such a kind as to set up movements also in the embryo and to concoct thoroughly the ultimate nourishment, whereas the secretion of the female contains material alone. If, then, the male element prevails it draws the female element into itself, but if it is prevailed over it changes into the opposite or is destroyed.***

Aristotle claimed in error that the male principle was the driver behind sex determination, such that if the male principle was insufficiently expressed during reproduction, the fetus would develop as a female.

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20th century genetics

Nettie Stevens (working with beetles) and Edmund Beecher Wilson (working with hemiptera) are credited with independently discovering, in 1905, the chromosomal XY sex-determination system in insects: the fact that males have XY sex chromosomes and females have XX sex chromosomes. In the early 1920s, Theophilus Painter demonstrated that sex in humans (and other mammals) was also determined by the X and Y chromosomes, and the chromosomes that make this determination are carried by the spermatozoa.

The first clues to the existence of a factor that determines the development of testis in mammals came from experiments carried out by Alfred Jost, who castrated embryonic rabbits in utero and noticed that they all acquired a female phenotype.

In 1959, C. E. Ford and his team, in the wake of Jost's experiments, discovered[34] that the Y chromosome was needed for a fetus to develop as male when they examined patients with Turner's syndrome, who grew up as phenotypic females, and found them to be X0 (hemizygous for X and no Y). At the same time, Jacob & Strong described a case of a patient with Klinefelter syndrome (XXY), which implicated the presence of a Y chromosome in development of maleness.

All these observations led to a consensus that a dominant gene that determines testis development (TDF) must exist on the human Y chromosome. The search for this testis-determining factor (TDF) led to Peter Goodfellow's team of scientists in 1990 to discover a region of the Y chromosome that is necessary for the male sex determination, which was named SRY (sex-determining region of the Y chromosome).

TEMPERATURE-DEPENDENT SEX DETERMINATION

Temperature-dependent sex determination (TSD) is a type of environmental sex determination in which the temperatures experienced during embryonic/larval development determine the sex of the offspring. It is observed in reptiles and teleost fish, with some reports of it occurring in species of shrimp. TSD differs from the chromosomal sex-determination systems common among vertebrates. It is the most studied type of environmental sex determination (ESD). Some other conditions, e.g. density, pH, and environmental background color, are also observed to alter sex ratio, which could be classified either as temperature-dependent sex determination or temperature-dependent sex differentiation, depending on the involved mechanisms. As sex-determining mechanisms, TSD and genetic sex determination (GSD) should be considered in an equivalent manner, which can lead to reconsidering the status of fish species that are claimed to have TSD when submitted to extreme temperatures instead of the temperature experienced during development in the wild, since changes in sex ratio with temperature variation are ecologically and evolutionally relevant.

While TSD has been observed in many reptile and fish species, the genetic differences between sexes and molecular mechanisms of TSD have not been determined. The cortisol-mediated pathway and epigenetic regulatory pathway are thought to be the potential mechanisms involved in TSD.

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The eggs are affected by the temperature at which they are incubated during the middle third of embryonic development. This critical period of incubation is known as the thermosensitive period. The specific time of sex-commitment is known due to several authors resolving histological chronology of sex differentiation in the gonads of turtles with TSD.

Thermosensitive period

The thermosensitive, or temperature-sensitive, period is the period during development when sex is irreversibly determined. It is used in reference to species with temperature-dependent sex determination, such as crocodilians and turtles. The TSP typically spans the middle third of incubation with the endpoints defined by embryonic stage when under constant temperatures. The extent of the TSP varies a little among species, and development within the oviducts must be taken into account in species where the embryo is at a relatively late stage of development on egg laying (e.g. many lizards). Temperature pulses during the thermosensitive period are often sufficient to determine sex, but after the TSP, sex is unresponsive to temperature and sex reversal is impossible.

Types

Within the mechanism, two distinct patterns have been discovered and named Pattern I and Pattern II. Pattern I is further divided into IA and IB.

Pattern IA has a single transition zone, where eggs predominantly hatch males if incubated below this temperature zone, and predominantly hatch females if incubated above it. Pattern IA occurs in most turtles, with the transition between male-producing temperatures and female-producing temperatures occurring over a range of temperatures as little as 1–2°C. Pattern IB also has a single transition zone, but females are produced below it and males above it. Pattern IB occurs in multiple fish species and the tuatara.

Pattern II has two transition zones, with males dominating at intermediate temperatures and females dominating at both extremes. Pattern II occurs in some turtles, lizards, and crocodilians. Mixed sex ratios and (more rarely) intersex individuals have been observed at or near the pivotal temperature of sex determination.

It has been proposed that essentially all modes of TSD are actually Pattern II and those that deviate from the expected female-male-female pattern are species whose viable temperature range does not allow for the extreme temperatures needed to pass the second transition zone.

The distinction between chromosomal sex-determination systems and TSD is often blurred because the sex of some species – such as the three-lined skink Bassiana duperreyi and the central bearded dragon Pogona vitticeps – is determined by sex chromosomes, but this is over-ridden by temperatures that are tolerable but extreme. Also, experiments conducted at the pivotal temperature, where temperature is equivocal in its influence, have demonstrated an underlying genetic predisposition to be one sex or the other.

Examples

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Temperature-dependent sex determination was first described in Agama agama in 1966 by Madeleine Charnier.

A 2015 study found that hot temperatures altered the expression of the sex chromosomes in Australia's bearded dragon lizards. The lizards were female in appearance and were capable of bearing offspring, despite having the ZZ chromosomes usually associated with male lizards

In 2018, a team of Chinese and American researchers showed that the histone H3 lysine 27 (H3K27) demethylase KDM6B (JMJD3), an epigenetic modifier, activates male development in red-eared slider turtles by binding to the promoter of the dominant male gene [DMRT1]. Knocking down the expression of this modifier at 26 °C triggers male-to-female sex reversal in most of the surviving embryos.

Research from 2020 identified the timing of gonadal commitment in the American alligator to understand the effects of estrogen-signaling in TSD. It was determined that a main factor in gonadal fate is the level of testicular genes and estrogen signaling. The study found that critical commitment in testicular development is during stage 24-26, which is later than a known TSP for promoting males in TSD. Additionally, earlier estrogen signaling induced development of parts of the ovary.

Hormones in TSD systems

Synergism between temperature and hormones has also been identified in these systems. Administering estradiol at male-producing temperatures generates females that are physiologically identical to temperature-produced females. The reverse experiment, males produced at female temperatures, only occurs when a nonaromatizable testosterone or an aromatase inhibitor is administered, indicating that the enzyme responsible for conversion of testosterone to estradiol, aromatase, plays a role in female development. Nonetheless, the mechanisms for TSD are still relatively unknown, but in some ways, TSD resembles genetic sex determination (GSD), particularly in regards to the effects of aromatase in each process. In some fish species, aromatase is in both the ovaries of female organisms who underwent TSD and those who underwent GSD, with no less than 85% of the coding sequences of each aromatase being identical, showing that aromatase is not unique to TSD and suggesting that there must be another factor in addition to it that is also affecting TSD.

Hormones and temperature show signs of acting in the same pathway, in that less hormone is required to produce a sexual shift as the incubation conditions near the pivotal temperature. It has been proposed that temperature acts on genes coding for such steroidogenic enzymes, and testing of homologous GSD pathways has provided a genic starting point. Yet, the genetic sexual determination pathway in TSD turtles is poorly understood and the controlling mechanism for male or female commitment has not been identified.

While sex hormones have been observed to be influenced by temperature, thus potentially altering sexual phenotypes, specific genes in the gonadal differentiation pathway display temperature influenced expression. In some species, such important sex-determining genes as DMRT1[30] and

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those involved in the Wnt signalling pathway could potentially be implicated as genes which provide a mechanism (opening the door for selective forces) for the evolutionary development of TSD. Aromatase has also been shown to play a role in certain tumor development.[31]

Adaptive significance

The adaptive significance of TSD is currently not well understood. One possible explanation that TSD is common in amniotes is phylogenetic inertia – TSD is the ancestral condition in this clade and is simply maintained in extant lineages because it is currently adaptively neutral or nearly so. Indeed, recent phylogenetic comparative analyses imply a single origin for TSD in most amniotes around 300 million years, with the re-evolution of TSD in squamates and turtles after they had independently developed GSD. Consequently, the adaptive significance of TSD in all but the most recent origins of TSD may have been obscured by the passage of deep time, with TSD potentially being maintained in many amniote clades simply because it works 'well enough' (i.e. has no overall fitness costs along the lines of the phylogenetic inertia explanation).

Other work centers on a 1977 theoretical model (the Charnov–Bull model), predicted that selection should favour TSD over chromosome-based systems when "the developmental environment differentially influences male versus female fitness"; this theoretical model was empirically validated thirty years later but the generality of this hypothesis in reptiles is questioned. This hypothesis is supported by the persistence of TSD in certain populations of spotted skink (Niveoscincus ocellatus), a small lizard in Tasmania, where it is advantageous to have females early in the season. The warmth early in the season ensures female-biased broods that then have more time to grow and reach maturity and possibly reproduce before they experience their first winter, thereby increasing fitness of the individual.

In support of the Charnov and Bull hypothesis, Warner and Shine (2008) showed confidently that incubation temperature influences males' reproductive success differently than females in Jacky Dragon lizards (Amphibolurus muricatus) by treating the eggs with chemicals that interfere with steroid hormone biosynthesis. These chemicals block the conversion of testosterone to estradiol during development so each sex offspring can be produced at all temperatures. They found that hatching temperatures that naturally produce each sex maximized fitness of each sex, which provides the substantial empirical evidence in support of the Charnov & Bull model for reptiles.

Spencer and Janzen (2014) found further support for the Charnov-Bull model by incubating painted turtles (Chrysemys picta) at different temperatures and measuring various characteristics indicative of fitness. The turtles were incubated at temperatures that produce solely males, both sexes, and solely females. Spencer and Janzen (2014) found that hatchlings from mixed-sex nests were less energy efficient and grew less than their same-sex counterparts incubated in single-sex producing temperatures. Hatchlings from single-sex producing temperatures also had higher first-year survivorship than the hatchlings from the temperature that produces both sexes. TSD may be advantageous and selected for in turtles, as embryo energy efficiency and hatchling size are optimized for each sex at single-sex incubation temperatures and are indicative of first-year survivorship. This suggests that natural selection would favor TSD, as TSD may enhance the fitness of offspring.

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An alternative hypothesis of adaptive significance was proposed by Bulmer and Bull in 1982 and supported by the work of Pen et al. (2010). They conjectured that disruptive selection produced by variation in the environment could result in an evolutionary transition from ESD to GSD. Pen et al. (2010) addresses evolutionary divergence in SDMs via natural selection on sex ratios. Studying the spotted skink, they observed that the highland population was not affected by temperature, yet, there was a negative correlation between annual temperature and cohort sex ratios in the lowlands. The highlands are colder with a higher magnitude of annual temperature fluctuation and a shorter activity season, delaying maturity, thus GSD is favored so sex ratios are not skewed. However, in the lowlands, temperatures are more constant and a longer activity season allows for favorable conditions for TSD. They concluded that this differentiation in climate causes divergent selection on regulatory elements in the sex-determining network allowing for the emergence of sex chromosomes in the highlands.

Climate change effects

Climate change presents a unique threat in species influenced by temperature-dependent sex determination by skewing sex ratios and population decline. The warming of the habitats of species exhibiting TSD are beginning to affect their behavior and may soon start affecting their physiology. Many species (with Pattern IA and II) have begun to nest earlier and earlier in the year to preserve the sex ratio. The three traits of pivotal temperature (the temperature at which the sex ratio is 50%), maternal nest-site choice, and nesting phenology have been identified as the key traits of TSD that can change, and of these, only the pivotal temperature is significantly heritable, this would have to increase by 27 standard deviations to compensate for a 4 °C temperature increase. It is likely that climate change will outpace the ability of many TSD animals to adapt, and many will likely go extinct. However, there is evidence that during climatic extremes, changes in the sex determining mechanism itself (to GSD) are selected for, particularly in the highly-mutable turtles. It has also been proposed that sea turtles may be able to use TSD to their advantage in a warming climate. When the offspring viability is decreased due to increased temperatures, they are able to use the coadaptation between sex ratio and survivability to increase the production of female offspring. This allows sea turtles to maintain populations and could increase their resiliency to climate change.

ENVIRONMENTAL SEX DETERMINATION

Environmental sex determination is the establishment of sex by a non-genetic cue, such as nutrient availability, experienced within a discrete period after fertilization. Environmental factors which often influence sex determination during development or sexual maturation include light intensity and photoperiod, temperature, nutrient availability, and pheromones emitted by surrounding plants or animals. This is in contrast to genotypic sex determination, which establishes sex at fertilization by genetic factors such as sex chromosomes. Under true environmental sex determination, once sex is determined, it is fixed and cannot be switched again. Environmental sex determination is

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different from some forms of sequential hermaphroditism in which the sex is determined flexibly after fertilization throughout the organism's life.

Adaptive significance

Environmental sex determination is similar to certain forms[vague] of sexual selection in that there are oftentimes different and opposing selective pressures on males and females because of the costs of reproduction. Sexual selection is common throughout the tree of life (most known in birds); often resulting in sexual dimorphism, or size and appearance differences between sexes in the same species. In environmental sex determination, selective pressures over evolutionary time have selected for flexibility in sex determination to optimize fitness in a heterogenous environment because of the different costs of sex in males and females. Certain environmental conditions differentially affect each sex such that it would be beneficial to become one sex and not the other. This is especially pertinent for sessile organisms that cannot move to a different environment. In plants, for example, female sexual function is often more energetically expensive because once fertilized they must use significant stored energy to produce fruits, seeds, or sporophytes whereas males must only produce sperm (and sperm-containing structure; antheridium in seedless plants, and pollen in seed plants).

Mechanisms

Lacking genetic information coding for separate sexes such as sex chromosomes, individuals that exhibit environmental sex determination contain genetic information coding for both sexes on autosomes. In general, once exposed to certain environmental cues, epigenetic changes cause developing individuals to become either male or female. Environmental cues that often trigger the development of males or females include temperature, nutrient (or food in the case of animals) and water availability, photoperiod, competitive stress, and pheromones from conspecific individuals. Specific mechanisms and cues vary between species.

Taxonomic range

Crustaceans

The amphipod crustacean Gammarus duebeni produces males early in the mating season, and females later, in response to the length of daylight, the photoperiod. Because male fitness improves more than female fitness with increased size, environmental sex determination is adaptive in this system by permitting males to experience a longer growing season than females.

The branchiopod crustacean Daphnia magna parthenogenetically produces male progeny in response to a combination of three environmental factors, namely a reduced photoperiod in autumn, shortage of food and raised population density.

Annelids

Bonellia viridis, a marine worm, has location-dependent sex determination; sex depends on where the larvae land.

Vertebrates

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The sex of most amniote vertebrates, such as mammals and birds, is determined genetically. However, some reptiles have temperature-dependent sex determination, where sex is permanently determined by thermal conditions experienced during the middle third of embryonic development. The sex of crocodilians and sphenodontians is exclusively determined by temperature. In contrast, squamates (lizards and snakes) and turtles exhibit both genotypic sex determination and temperature-dependent sex determination, although temperature dependence is much more common in turtles than in squamates.

Ferns

Most fern species (with a few exceptions, namely the Salvineales) are homosporous and lack sex chromosomes. Lacking genetic information coding for separate sexes, every fern spore has the capacity to become a male, female, or hermaphroditic gametophyte depending on the environment. In many fern species, including Ceratopteris richardii, environmental sex determination is linked to breeding systems. Fern gametophytes exhibit a wide variety of breed systems which can be divided into outcrossing and inbreeding. To promote outcrossing, female gametophytes release a chemical pheromone known as Antheridiogen which controls the sex of nearby developing gametophytes. Antheridiogen secreted by females promotes the development of nearby asexual gametophytes into males. This is adaptive because inducing maleness increases the probability of outcrossing as males provide sperm for the females rather than the females becoming hermaphroditic (or bisexual) and self-fertilizing. However, if no fertilization occurs, the female gametophyte can still become hermaphroditic and self-fertilize if the conditions are conducive to growth, ultimately resulting in inbreeding depression.

Additionally, similar to crocodilians, homosporous fern gametophyte sex is determined by the abiotic environment in accordance with the size-advantage model. In stressful environments (crowding or nutrient stress), gametophytes are smaller and develop into males. While in more favorable growing conditions, gametophytes are larger and develop into females.

Moss

Moss gametophytes can be either asexual, female, male, or hermaphroditic like ferns. Unlike homosporous ferns, moss gametophytes can be either monoicous or dioicous (similar to monoecious and dioecious in vascular plants), with most studied dioicous species exhibiting genetic sex determination via the UV sex chromosome sex determination system. Some monoicous moss species such as Splachnum ampullaceum exhibit environmental sex determination during early development, with low light, low pH, and low nutrient availability all promoting male development. In the presence of auxin, a widespread plant hormone, or gibberellins, compounds similar to Antheridiogen in ferns, both female and male individuals invest more in sexual structures (antheridia and archegonia). Environmental sex determination in moss is fundamentally different from the spatial segregation of sexes, the occurrence of environmentally mediated sex ratios in moss patches, observed in sexually static moss species. Spatial segregation of the sexes in mosses is caused by differential survival rates between sexes as a result of the competitive advantage of female moss. This leads to female dominated populations maintained by asexual reproduction and minimal sexual reproduction. In contrast, environmental sex determination is the dynamic development of females or males in different environmental conditions.

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Angiosperms

Many angiosperms exhibit sequential hermaphroditism, meaning that they can switch sexes continually throughout their life based on the current conditions and resource availability to optimize fitness each flowering season. But sequential hermaphroditism and environmental sex determination are not mutually exclusive. For example, Catasetum viridiflavum, an epiphyte (plant that grows on another plant) in the Orchidaceae family exhibits sequential hermaphroditism where the younger, smaller individuals have male inflorescences and the older, larger individuals have female inflorescences, but sex expression is also strongly influenced by light intensity. Individuals in high light are more often female and individuals in the low light are more often male, regardless of size. In higher light, individuals produce more ethylene, a common plant hormone, which promotes the formation of female flowers.

Sexual Differentiation

Sexual differentiation is the process of development of the sex differences between males and females from an undifferentiated zygote. Sex differentiation is usually distinct from sex determination; sex determination is the designation of the development stage towards either male or female, while sex differentiation is the pathway towards the development of the phenotype.

In many species, testicular or ovarian differentiation begins with appearance of Sertoli cells in males and granulosa cells in females.

As embryos develop into mature adults, sex differences develop at many levels, including chromosomes, gonads, hormones, and anatomy. Beginning with determination of sex by genetic and/or environmental factors, humans and other organisms proceed towards different pathways of differentiation as they grow and develop.

Sex determination systems

Humans, many mammals, and some insects and other animals have an XY sex-determination system. Humans have forty-six chromosomes, including two sex chromosomes, XX in females and XY in males. The Y chromosome must carry at least one essential gene which determines testicular formation (originally termed TDF). In transgenic XX mice (and some human XX males), SRY[expand acronym] alone is sufficient to induce male differentiation.

Other chromosomal systems exist in other taxa, such as the ZW sex-determination system in birds and the XO system in insects.

Environmental sex determination refers to the determination (and then differentiation) of sex via non-genetic cues like social factors, temperature, and available nutrients. In some species, such as clownfish (known to be universally hermaphroditic), sex differentiation can occur more than once

as a response to different environmental cues, offering an example of how sex differentiation does not always follow a linear path.

There have been multiple transitions between environmental and genetic sex determination systems in reptiles over time, and recent studies have shown that temperature can sometimes override sex determination via chromosomes.

Humans

The early stages of human differentiation appear to be quite similar to the same biological processes in other mammals—and the interaction of genes, hormones and body structures is fairly well understood. In the first weeks of gestation, a fetus is anatomically indistinguishable as male or female and lacks production of any particular sex hormones. Only a karyotype distinguishes male from female. Specific genes induce gonadal differences, which produce hormonal differences, which cause anatomic differences, leading to psychological and behavioral differences, some of which are innate and some induced by the social environment.

Various processes are involved in the development of sex differences in humans. Sexual differentiation in humans includes development of different genitalia—and the internal genital tracts, breasts, and body hair—and plays a role in gender identification.

The development of sexual differences begins with the XY sex-determination system that is present in humans, and complex mechanisms are responsible for the development of the phenotypic differences between male and female humans from an undifferentiated zygote. Atypical sexual development, and ambiguous genitalia, can be a result of genetic and hormonal factors.

The differentiation of other parts of the body than the sex organ creates the secondary sex characteristics. Sexual dimorphism of skeletal structure develops during childhood, and becomes more pronounced at adolescence.

Other animals

The first genes involved in the cascade of differentiation can differ between taxa and even between closely related species. For example: in zebrafish the first known gene to induce male differentiation is the amh gene, in tilapia it is tDmrt1, and in southern catfish it is foxl2.

In fish, due to the fact that modes of reproduction range from gonochorism (distinct sexes) to self-fertilizing hermaphroditism (where one organism has functioning gonadal features of multiple sexes), sexual differentiation is complex. Two major pathways in gonochores exist: one with a nonfunctional, undifferentiated phase leading to delayed differentiation (secondary), and one without (primary), where differences between the sexes can be noted prior to hatching. Secondary gonochorists remain in the bipotential phase until a biotic or abiotic cue directs development down one pathway. Primary gonochorism, without an intersex phase, follows classical pathways of genetic sex determination, but can still be later influenced by the environment. Differentiation pathways progress, and secondary sex characteristics such as anal fin bifurcation and ornamentation typically arise at puberty.

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In birds, research on Gallus gallus domesticus, has shown that determination of sex is likely cell-autonomous, i.e. that sex is determined in each somatic cell independently of, or in conjunction with, the hormone signaling that occurs in other species. Studies on gynandromorph chickens showed that the mosaicism could not be explained by hormones alone, pointing to direct genetic factors, possibly one or a few Z-specific genes such as double-sex or DMRT1.

Flexibility

The most intensively studied species, such as fruit flies, nematodes, and mice, reveal that evolutionarily, sex determination/differentiation systems are not wholly conserved and have evolved over time. Beyond the presence or absence of chromosomes or social/environmental factors, sexual differentiation can be regulated in part by complex systems like the ratio of genes on X chromosomes and autosomes, protein production and transcription, and specific mRNA splicing.

Differentiation pathways can be altered at many stages of the process. Sex reversal, where the development of a sexual phenotype is redirected during embryonic development, happens in the initiation phase of gonadal sex differentiation. Even in species where there is a well-documented master regulator gene, its effects can be overridden by a downstream gene.

Furthermore, hermaphrodites serve as examples of the flexibility of sexual differentiation systems. Sequential hermaphrodites are organisms that possess reproductive capabilities of one sex, and then that sex changes. Differentiated gonadal tissue of the organism's former sex degenerates, and new sex gonadal tissue grows and differentiates. Organisms that have the physiological capability to reproduce as a male and as a female at the same time are known as simultaneous hermaphrodites. Some simultaneous hermaphroditic organisms, like certain species of goby, have distinctive male and female phases of reproduction and can flip back and forth, or "sex reverse", between the two.

Socially-determined

In some species, such as sequentially hermaphroditic clownfish, changes in social environment can lead to sexual differentiation or sex reversal, i.e. differentiation in the opposite direction. In clownfish, females are larger than males, and in social groups, there is typically one large female, multiple smaller males, and undifferentiated juveniles. If the female is removed from the group, the largest male changes sex, i.e. the former gonad tissue degenerates and new gonad tissue grows. Furthermore, the pathway of differentiation in activated in the largest juvenile, which becomes male.[10]

Alternative morphs

Polymorphism (biology)

Sexual differentiation in a species does not have to produce one recognizable female type and one recognizable male type. In some species alternative morphs, or morphotypes, within one sex exist, such as flanged (larger than females, with large flap-like cheek-pads) and unflanged (about the same size as females, no cheek-pads) male orangutans, and sometimes differences between male morphs can be more noticeable than differences between a male and a female within such species.

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Furthermore, sexual selection can be involved in the development of different types of males with alternative reproductive strategies, such as sneaker and territorial males in dung beetles or haremic males and pair-bonding males in the Nigerian cichlid fish P. pulcher. Sometimes alternative morphs are produced by genetic differences, and in other cases, the environment can be involved, demonstrating some degree of phenotypic plasticity.

Brain differentiation

Neuroscience of sex differences

In many animals, differences in the exposure of a fetal brain to sex hormones are correlated with significant differences of brain structure and function, which correlate with adult reproductive behavior. The causes of differences between the sexes are only understood in some species. Fetal sex differences in human brains coupled with early differences in experience may be responsible for sex differences observed in children between 4 years old and adolescence.

Many individual studies in humans and other primates have found statistically significant sex differences in specific brain structures; however, some studies have found no sex differences, and some meta-analyses have called into question the over-generalization that women and men's brains function differently. Males and females statistically differ in some aspects of their brains, but there are areas of the brain which appear not to be sexually differentiated at all. Some scholars describe human brain variation not as two distinct categories, and not even a maleness-femaleness continuum, but as mosaics.

In birds, hypotheses of male-female brain sex differences have been challenged by recent findings that differences between groups can be at least partially explained by the individual's dominance rank. Furthermore, the behavioral causes of brain sex differences have been enumerated in studies of sex differences between different mating systems. For example, males of a polygynous vole species with intrasexual male competition have better spatial learning and memory than the females of their own species, but also better spatial learning and memory than all sexes of other closely related species that are monogamous; thus the brain differences commonly seen as "sex differences" have been instead linked to competition. Sexual selection does play a role in some species, though, as males who display more song behaviors are selected for by females—so some sex differences in bird song brain regions seem to have been evolutionarily selected for over time.

CELL AUTONOMOUS SEX IDENTITY (CASI)

CELL AUTONOMOUS SEX IDENTITY (CASI) *refers to the intrinsic determination of a cell's sex-specific characteristics based on its genetic and epigenetic makeup, independent of external hormonal influences. Unlike traditional models of sex differentiation, which emphasize the role of gonadal hormones in directing cellular and tissue-level sexual traits, CASI highlights the ability of individual cells to express their sexual identity autonomously. This concept has significant implications for understanding sexual dimorphism, development, and the evolutionary diversity of sex determination mechanisms across species.*

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CASI has been observed in various organisms, including birds, insects, and fish, and challenges the long-held view that hormonal signaling is the primary determinant of sex-specific traits. In certain species, CASI plays a critical role in development, with sex chromosomes directly influencing cellular function and morphology. The study of CASI provides new insights into how genetic and epigenetic factors contribute to the differentiation of cells and tissues and has potential applications in understanding human biology, reproductive health, and disorders of sexual development.

Historical Background

The concept of cell autonomous sex identity (CASI) emerged as a challenge to the traditional understanding of sexual differentiation, which largely centered around the role of gonadal hormones in directing the development of sex-specific traits. Early research on sex determination systems focused heavily on the influence of hormonal signaling, particularly in mammals, where the testes and ovaries are known to orchestrate a cascade of changes in both primary and secondary sexual characteristics.

The first indications that sex identity could be cell-autonomous rather than entirely hormone-driven arose from studies in non-mammalian species, particularly birds and insects. In the mid-20th century, researchers investigating sexual dimorphism in avian species observed that male and female cells could exhibit distinct characteristics even when exposed to the same hormonal environment. This led to the hypothesis that sex determination might occur at the cellular level in some cases, independent of systemic hormonal control.

The field gained significant traction in the 21st century with advancements in genetic and molecular biology. Landmark studies in chickens demonstrated that individual cells in somatic tissues could retain their sex identity regardless of the hormonal milieu, providing compelling evidence for CASI. This finding contrasted sharply with mammalian models, where hormonal influences were thought to dominate sexual differentiation.

Further research expanded the scope of CASI to other species, such as insects and fish, revealing diverse mechanisms by which sex chromosomes and gene expression patterns could directly influence cellular phenotypes. These discoveries underscored the evolutionary diversity in sex determination processes and highlighted the importance of CASI in understanding sexual dimorphism across the animal kingdom.

On-going research into exploring the implications of CASI for evolution, health and disease continue. The historical shift from hormone-centric models to a more nuanced understanding that includes cell-autonomous mechanisms marks a significant paradigm change in the study of sexual differentiation.

Mechanisms of Cell Autonomous Sex Identity

Cell autonomous sex identity arises from the intrinsic properties of individual cells, determined by genetic and epigenetic factors encoded by their sex chromosomes. Unlike hormone-driven sex differentiation, where external chemical signals guide the development of sexual traits, CASI relies

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on the direct expression of genes and regulatory networks that are inherently linked to a cell's chromosomal sex.

At the core of CASI is the differential expression of genes located on the sex chromosomes (e.g., Z and W in birds, X and Y in mammals). In organisms where CASI has been observed, the presence of these sex chromosomes directly influences the transcriptional landscape of individual cells, leading to sex-specific cellular characteristics. For example, in birds, studies have shown that male (ZZ) and female (ZW) cells exhibit distinct gene expression profiles even when exposed to identical hormonal environments.

Key Components of Cell Autonomous Sex Identity Mechanisms
Sex Chromosome-Linked Gene Expression
Genes located on sex chromosomes, such as DMRT1 in birds and TRA-1 in some insects, play crucial roles in establishing cell-autonomous sex identity. These genes are often expressed in a sex-specific manner, driving divergent developmental pathways at the cellular level.

Epigenetic Regulation
Epigenetic modifications, such as DNA methylation and histone modifications, contribute to the regulation of sex-specific gene expression. In some cases, these modifications help maintain the cellular memory of sex identity throughout an organism's life.

Non-Hormonal Signaling Pathways. :- Intrinsic signaling pathways within the cell can reinforce sex-specific gene expression and cellular phenotypes. These pathways act independently of systemic hormonal influences, highlighting the autonomy of CASI.

Interactions with Autosomal Genes
While CASI primarily relies on sex chromosome-linked factors, interactions with autosomal genes also contribute to the establishment and maintenance of sex-specific traits. For example, some autosomal genes are regulated by sex-specific transcription factors encoded on the sex chromosomes.

Examples of Cell Autonomous Sex Identity in Action

1. *Avian Somatic Cells: Studies in birds, such as chickens, have demonstrated that male and female somatic cells can maintain their sexual identity in mixed-sex chimeras, providing direct evidence of CASI.*
2. *Drosophila (Fruit Flies): Insects like fruit flies exhibit CASI in the differentiation of somatic tissues, where sex-specific transcription factors directly influence cellular development.*
3. *Fish Gonads: CASI has also been observed in fish species where gonadal cells retain their sex identity independent of external hormonal cues.*

The mechanisms underlying CASI highlight the diversity and complexity of sex determination processes across species. These insights challenge the traditional hormone-centric view of sexual
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differentiation and emphasize the importance of understanding cell-intrinsic factors in shaping sex-specific development.

Cell Autonomous Sex Identity in Model Organisms

Research on cell autonomous sex identity has leveraged various model organisms to uncover the genetic, cellular, and developmental mechanisms underlying sex-specific traits. These studies have provided valuable insights into how CASI operates across different taxa and contributed to a broader understanding of sex determination and differentiation.

Birds

Birds, particularly chickens (Gallus gallus), have been instrumental in studying CASI. Unlike mammals, where gonadal hormones dominate sex differentiation, avian somatic cells exhibit intrinsic sex identity. Studies using mixed-sex chimeric chickens demonstrated that male (ZZ) and female (ZW) cells maintain their distinct sexual identity even when transplanted into tissues of the opposite sex. The DMRT1 gene, located on the Z chromosome, has been identified as a key regulator of CASI in birds. Its dosage-dependent expression in males plays a critical role in driving male-specific development.

Drosophila (Fruit Flies)

In the fruit fly (Drosophila melanogaster), CASI is evident in the development of sex-specific somatic tissues, such as bristles and reproductive structures. The sex determination pathway in Drosophila is governed by the Sex-lethal (Sxl) gene, which initiates a cascade of transcriptional events leading to sex-specific alternative splicing of downstream genes like doublesex (dsx). This pathway operates independently in each cell, demonstrating the cell-autonomous nature of sex determination in this species.

Zebrafish

Zebrafish (Danio rerio), a widely used vertebrate model, have also been studied for CASI, particularly in the context of gonadal development. While zebrafish lack sex chromosomes, sex-specific gene expression patterns in gonadal cells are largely autonomous. This has provided a unique perspective on CASI in species without traditional chromosomal sex determination systems.

Mammals

Although CASI is less prominent in mammals due to the dominant role of gonadal hormones, evidence of cell-autonomous sex differences exists. For example, studies in murine models have shown that the presence of XX or XY chromosomes in brain cells can lead to sex-specific differences in neuronal development and function, independent of gonadal hormone influence.

C. elegans (Roundworms)

The nematode Caenorhabditis elegans has provided key insights into CASI in hermaphroditic and male individuals. Sex determination in C. elegans is controlled by the X:A ratio (the number of X chromosomes relative to autosomes), which regulates a cascade of sex-specific gene expression. Each cell independently interprets this ratio, leading to cell-autonomous decisions about sexual differentiation.

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Butterflies and Moths (Lepidoptera)

In Lepidoptera, sex determination involves a WZ/ZZ system, similar to birds. Studies have shown that the sex of individual cells is influenced by chromosomal composition, with evidence of CASI playing a significant role in the development of sex-specific traits, such as wing patterns and pheromone production.

Implications of Cell Autonomous Sex Identity

The discovery and study of cell autonomous sex identity have far-reaching implications across various fields of biology, medicine, and evolution. By highlighting the intrinsic properties of cells in determining sex-specific traits, CASI has challenged traditional hormone-centric models of sexual differentiation and opened new avenues of research and application.

Evolutionary Biology

CASI provides critical insights into the evolution of sex determination systems. The existence of cell-autonomous mechanisms suggests that sex-specific traits can evolve independently of hormonal influences, potentially allowing for greater plasticity in evolutionary pathways. This understanding helps explain the diversity of sex determination strategies observed across taxa, from chromosomal to environmental systems.

Developmental Biology

CASI has redefined our understanding of sexual development by emphasizing the role of intrinsic cellular mechanisms. This has implications for studying developmental disorders related to sexual differentiation, such as androgen insensitivity syndrome and Turner syndrome, as it highlights the interplay between genetic, epigenetic, and cellular factors.

Comparative Physiology

By exploring CASI across different species, researchers can identify universal and species-specific mechanisms of sexual differentiation. This comparative approach enhances our understanding of how sex-specific traits are regulated in diverse environmental and ecological contexts.

Neuroscience and Behavior

In mammals, evidence of CASI in brain cells has implications for understanding sex differences in neural development, cognition, and behavior. CASI may contribute to innate sex-specific behaviors and provide new perspectives on the biological basis of neurodevelopmental disorders that exhibit sex-biased prevalence, such as autism spectrum disorder.

Biomedical Research

CASI highlights the importance of considering sex as a biological variable in research. Intrinsic differences between male and female cells could influence disease progression, drug responses, and therapeutic outcomes. This understanding emphasizes the need for sex-specific approaches in clinical trials and personalized medicine.

Implications for Agriculture and Conservation

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CASI research can also benefit applied fields like agriculture and wildlife conservation. In poultry farming, for example, understanding CASI may allow for the development of sex-specific growth strategies or improve breeding programs. Similarly, in conservation, insights into CASI could inform efforts to manage populations with skewed sex ratios or develop strategies for assisted reproduction in endangered species.

Cell Autonomous Sex Identity and Hormonal Influence

While cell autonomous sex identity emphasizes the intrinsic sex-specific properties of individual cells, the interplay between CASI and hormonal influences plays a critical role in shaping an organism's overall sexual phenotype. CASI and hormones are not mutually exclusive but instead represent complementary mechanisms of sexual differentiation.

Independence of Cell Autonomous Sex Identity from Hormonal Cues

CASI operates independently of systemic hormonal signals, as demonstrated in studies where individual cells maintain their sexual identity regardless of the hormonal environment. For example, in avian chimeras, male (ZZ) and female (ZW) cells retain their respective gene expression profiles even when transplanted into opposite-sex tissues. This underscores the cell-intrinsic nature of CASI and its role in establishing baseline sex identity at the cellular level.

Hormonal Modulation of Cell Autonomous Sex Identity Traits

While CASI establishes the foundational sex identity of a cell, hormones can modulate the expression of CASI-driven traits. For instance, in birds, male and female somatic cells may exhibit intrinsic differences due to CASI, but the extent to which these differences manifest in tissues can be influenced by circulating hormones such as estrogen and testosterone. Hormones act as amplifiers, enhancing or suppressing sex-specific characteristics that are intrinsically determined by CASI.

Interactions Between Cell Autonomous Sex Identity and Hormones

CASI and hormonal influences interact dynamically during development and adulthood:

- *Developmental Coordination: In many species, CASI establishes cellular sex identity early in development, which is later reinforced or fine-tuned by hormonal signals. For example, in mammals, the SRY gene on the Y chromosome initiates testis development, but subsequent male sexual differentiation heavily relies on androgens.*
- *Sexual Dimorphism: The combined effects of CASI and hormones contribute to the development of sexually dimorphic traits. In some cases, CASI may dictate cellular predispositions, while hormones ensure the coordinated expression of these traits across tissues and organs.*

Contexts of Cell Autonomous Sex Identity-Hormonal Conflict

Instances where CASI and hormonal influences diverge provide unique insights into their interplay. For example:

- ***Chimeric Studies**: In mixed-sex chimeras, cells maintain CASI-determined sexual identity even when exposed to conflicting hormonal environments.*
    - ***Hormone Insensitivity Syndromes**: Disorders like androgen insensitivity syndrome (AIS) reveal the limitations of hormonal influence when CASI-driven traits dominate cellular responses. In AIS, individuals with XY chromosomes (CASI-determined male identity) develop phenotypically female characteristics due to a lack of response to androgens.*

Implications for Research and Medicine

Understanding the interaction between CASI and hormonal influences has profound implications:

1. ***Endocrinology**: Investigating how CASI interacts with hormone-driven processes can provide deeper insights into endocrine disorders.*
2. ***Regenerative Medicine**: Incorporating both CASI and hormonal influences in tissue engineering could improve outcomes for sex-specific therapies.*
3. ***Sex Differences in Disease**: CASI may explain intrinsic cellular differences between males and females that persist even when hormonal effects are absent or minimized*

Evolutionary Perspective

The study of cell autonomous sex identity offers profound insights into the evolution of sex determination and differentiation across species. CASI reveals an evolutionary framework that integrates cell-intrinsic mechanisms with broader hormonal systems, providing adaptability and resilience in diverse ecological and environmental contexts.

Cell Autonomous Sex Identity as an Evolutionary Foundation

CASI represents an ancient and conserved mechanism for sex determination that predates the evolution of complex hormonal systems. The ability of individual cells to autonomously interpret genetic cues and establish their sexual identity is evident across a wide range of taxa, from simple invertebrates like Drosophila to more complex vertebrates such as birds. This suggests that CASI is a fundamental evolutionary strategy, ensuring sex-specific cellular function at the earliest stages of multicellular organismal development.

Divergence of Hormonal Regulation

As organisms evolved, systemic hormonal systems likely arose to coordinate sex-specific traits across tissues and organs, supplementing the intrinsic mechanisms provided by CASI. This dual system allowed for more complex sexual dimorphisms and greater adaptability to environmental pressures, such as mate competition and reproductive success. The divergence of hormonal regulation in mammals (testosterone and estrogen dominance) and birds (estradiol-driven mechanisms) reflects evolutionary fine-tuning built upon the foundation of CASI.

Role in Sex Chromosome Evolution

CASI has implications for understanding the evolution of sex chromosomes. The ability of cells to interpret sex chromosome composition autonomously may have driven the specialization of sex

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chromosomes, such as the differentiation of X and Y in mammals and Z and W in birds. In species where chromosomal sex determination is absent or secondary, as in zebrafish or certain reptiles, CASI may provide insights into how sex identity is maintained in the absence of clear chromosomal cues.

Evolutionary Advantages of Cell Autonomous Sex Identity

The cell-autonomous nature of CASI offers several evolutionary advantages:

1. *Resilience to Environmental Fluctuations: CASI ensures intrinsic sex determination at the cellular level, which may be less susceptible to environmental perturbations than hormonal systems.*
2. *Tissue-Specific Adaptation: CASI allows for the independent evolution of sex-specific traits in different tissues, enabling specialized functions that enhance reproductive success and survival.*
3. *Flexibility in Evolutionary Pathways: CASI provides a substrate for the evolution of diverse sex determination systems, allowing species to adapt sex determination strategies to ecological niches or environmental constraints.*

Comparative Evolutionary Insights

Studies of CASI across taxa reveal evolutionary trade-offs between cell-autonomous mechanisms and hormonal regulation. For example:

- *Birds and Mammals: The prominence of CASI in birds contrasts with the hormone-dominated systems of mammals, highlighting different evolutionary pressures shaping sex determination.*
- *Invertebrates and Vertebrates: The conservation of CASI in invertebrates, such as Drosophila, and its adaptation in vertebrates illustrates how intrinsic sex determination mechanisms have been modified across evolutionary time scales.*

Broader Evolutionary Implications

CASI underscores the importance of considering multiple levels of biological organization in evolution. While hormones allow for organism-wide coordination, CASI demonstrates cellular-level autonomy in driving evolutionary change. This duality provides a robust framework for the emergence and maintenance of sex-specific traits across a wide variety of life forms.

Cell Autonomous Sex Identity and Human Biology

The study of cell autonomous sex identity in humans is an emerging field that offers new insights into sex differentiation, disorders of sexual development (DSDs), and broader aspects of human biology. While hormonal signals are well-known to play a key role in sexual differentiation, CASI presents a crucial layer of regulation that operates at the cellular level, influencing how human cells "decide" their sex identity independent of external hormonal cues. This section explores the implications of CASI for human biology, from sexual development to disease and beyond.

Cell Autonomous Sex Identity and Sexual Differentiation in Humans

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CASI plays a foundational role in early sexual differentiation in humans, particularly during embryonic development. In XY embryos, the SRY gene on the Y chromosome activates a cascade of signals that trigger testis development, while in XX embryos, the absence of SRY leads to ovarian development. While hormones such as testosterone and estrogen play major roles in furthering sexual development and secondary sexual characteristics, CASI ensures that each cell reflects its genetic sex, whether male (XY) or female (XX), from the very beginning.

Research has shown that cells, particularly in the gonads, brain, and other tissues, retain their cellular sex identity even in conditions where hormonal signals might be disrupted or absent. This independent cellular identity suggests that CASI might be at work throughout human development, regulating key processes such as the differentiation of gonads and the central nervous system.

Disorders of Sexual Development and Cell Autonomous Sex Identity

Understanding CASI is crucial for interpreting certain disorders of sexual development (DSDs), in which an individual's chromosomal sex and phenotypic sex do not align as expected. These conditions can be classified into several categories, including conditions where individuals with XY chromosomes develop female characteristics (e.g., androgen insensitivity syndrome) or individuals with XX chromosomes develop male characteristics (e.g., congenital adrenal hyperplasia).

In cases such as androgen insensitivity syndrome (AIS), cells that would typically be influenced by testosterone fail to respond to the hormone, resulting in the development of female external genitalia despite the presence of a Y chromosome. However, the intrinsic cellular identity of the individual's cells, as determined by their chromosomal sex (XX or XY), remains intact at the cellular level, which aligns with CASI. This suggests that CASI can influence the phenotypic sex independently of hormonal signaling.

Cell Autonomous Sex Identity and Brain Development

CASI's role in human brain development is another important aspect of its contribution to human biology. There is increasing evidence that CASI may contribute to sex differences in brain structures and functions, potentially influencing cognition, behavior, and neurological conditions. Research in humans and animal models has suggested that sexual differentiation in the brain begins early in development, and that certain brain cells might maintain their intrinsic sex identity, even in the absence of external hormonal signaling.

For example, while hormones such as estrogen and testosterone are known to influence brain sexual differentiation in typical sexual development, there may also be cellular mechanisms driven by CASI that set the foundation for sexually dimorphic traits in the brain, including differences in regions responsible for motor control, spatial ability, and emotional regulation. These findings could be important for understanding sex-based differences in neurodevelopmental disorders, such as autism spectrum disorder (ASD), which shows a higher prevalence in males.

Cell Autonomous Sex Identity and Human Disease

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The implications of CASI extend to human health, especially in relation to sex-specific diseases. While hormonal influences have long been studied in diseases such as cancer (e.g., prostate cancer, ovarian cancer), CASI suggests that the cellular sex identity may also contribute to disease susceptibility and progression.

For example, in certain types of cancers, such as breast cancer or ovarian cancer, the intrinsic sex identity of cells could affect their behavior, such as their response to treatment, their rate of growth, and their metastatic potential. Investigating CASI could help elucidate why some diseases manifest differently in males and females and why certain diseases are sex biased.

Tab 2

Comparative Genomic Architecture: A Comprehensive Analysis of Eukaryotic, Prokaryotic, and Aberrant Chromosome Systems

Primary Eukaryotic Chromosome Systems: Human Cytogenetics and Pathologies

Eukaryotic genomes are packaged into highly organized nucleoprotein complexes known as chromatin, which undergo dynamic remodeling to facilitate transcription, replication, and segregation. Within this architecture, the double-stranded DNA helix winds around an octamer of core histone proteins—specifically histones H2A , H2B , H3 , and H4 —to form the fundamental nucleosomal subunit. Aided by chaperone proteins and structural maintenance of chromosomes (SMC) complexes, this chromatin fiber is organized into distinct topological domains.

These domains are classified into transcriptionally active, loosely packaged euchromatin and highly condensed, transcriptionally silent heterochromatin. Heterochromatin is further divided into constitutive heterochromatin—which remains permanently condensed, contains repetitive sequences, and is located primarily near centromeres and telomeres—and facultative heterochromatin, which undergoes transcription-dependent condensation or decondensation.

The diploid human genome consists of 23 distinct pairs of chromosomes, totaling 46 chromosomes per somatic cell. This complement comprises 22 pairs of autosomes and one pair of sex chromosomes, or allosomes, which dictate biological sex. Physical mapping of these chromosomes reveals a clear correlation between physical size, gene density, and the clinical phenotypes that result from structural or numerical aberrations.

Chromosome	***Physical Size (bp)***	***Protein-Coding Genes***	***Key Gene Classifications***	***Associated Pathological Deficiency Diseases***	***General Therapeutic Approaches and Clinical Management***

★ | ***Chromosome 1*** | *248,956,422* | *2,047* | *Actin skeletal muscle alpha, Pancreatic Amylase, GBA, LMNA, MTHFR, KIF1B, MFN2, GLC1A* | *Gaucher disease, **1 p 36** deletion syndrome, Multiple Myeloma (**1 q 21 gain**), TAR syndrome **(1 q 21.1 microdeletion)*** | *Enzyme replacement therapy for Gaucher; proteasome inhibitors, monoclonal antibodies, and autologous stem cell transplantation for Multiple Myeloma.* |

★ | ***Chromosome 4*** | *190,214,555* | *753* | *Huntingtin (HTT), FGFR3, MN blood group* | *Huntington disease, Achondroplasia, Wolf-Hirschhorn syndrome (**4 p** deletion)* | *Symptomatic management, supportive orthopedic surgery, genetic counseling, and developmental therapies for chromosomal deletions.* |

★ | ***Chromosome 5*** | *181,538,259* | *881* | *Survival Motor Neuron 1 (SMN1), Acidic Fibroblast Growth Factor* | *Spinal Muscular Atrophy (SMA), Cri du chat syndrome (**5 p** deletion)* | *Antisense oligonucleotide therapies (e.g., Nusinersen) or gene replacement therapy for SMA; early developmental interventions.* |

★ | ***Chromosome 11*** | *135,086,622* | *1,312* | *Beta-globin (HBB), Insulin (INS), Catalase* | *Sickle cell anemia, Beta-thalassemia, Jacobsen syndrome (11 q terminal deletion)* | *Blood transfusions, bone marrow transplantation, hydroxyurea, and gene-editing therapies (CRISPR-based).* |

★ | ***Chromosome 15*** | *101,991,189* | *613* | *Hexosaminidase A (HEXA), Prader-Willi/Angelman critical region genes* | *Tay-Sachs disease, Prader-Willi syndrome, Angelman syndrome* | *Supportive and palliative care for Tay-Sachs; growth hormone therapy, behavioral and dietary management for Prader-Willi.* |

- ★ | ***Chromosome 17*** | *83,257,441 | 1,185 | BRCA1, Growth Hormone 1 (GH1), Peripheral Myelin Protein 22 (PMP22) | Hereditary Breast/Ovarian Cancer susceptibility, Charcot-Marie-Tooth type 1A (CMT1A), Canavan disease | Prophylactic surgeries and PARP inhibitors for BRCA1 mutations; recombinant growth hormone; physical therapy and orthotics for CMT1A.* |

- ★ | ***Chromosome 21*** | *46,709,983 | 231 | Amyloid Precursor Protein (APP), Superoxide Dismutase 1 (SOD1) | Down syndrome (Trisomy 21), Familial Alzheimer disease | Early intervention programs, cardiac evaluations, thyroid screening, and targeted symptomatic treatment.* |

- ★ | ***Chromosome 22*** | *50,818,468 | 492 | Myoglobin, Catechol-O-Methyltransferase (COMT), BCR-ABL fusion (translocation) | DiGeorge syndrome (22 q 11.2 deletion), Chronic Myeloid Leukemia (t(9;22) translocation) | Tyrosine kinase inhibitors (e.g., Imatinib) for CML; immune monitoring, calcium supplementation, and speech therapy for DiGeorge.* |

- ★ | ***Chromosome X*** | *156,040,895 | 843 | Coagulation Factor VIII (F8), Factor IX (F9), Dystrophin (DMD), FMR1 | Hemophilia A/B, Duchenne/Becker muscular dystrophy, Turner syndrome (45, X), Fragile X syndrome | Recombinant clotting factors; corticosteroids for DMD; growth hormone and estrogen replacement therapy for Turner syndrome.* |

- ★ | ***Chromosome Y*** | *57,227,415 | 63 | Sex-Determining Region Y (SRY/TDF), AZF region genes | Azoospermia (male infertility), Swyer syndrome (46, XY complete gonadal dysgenesis) | Assisted reproductive technologies (e.g., ICSI) for azoospermia; hormone replacement and gonadectomy for Swyer syndrome.* |

Chromosomal abnormalities *are divided into numerical anomalies, such as aneuploidies, and structural anomalies, including microdeletions, duplications, and translocations. Aneuploidies are primarily caused by meiotic nondisjunction, where homologous chromosomes or sister chromatids fail to segregate during gametogenesis. Trisomy 21 is the most common viable autosomal trisomy.*

Other autosomal trisomies, such as Trisomy 18 (Edwards syndrome) and Trisomy 13 (Patau syndrome), present with more severe multi-system phenotypes and high infantile mortality rates. Sex chromosome aneuploidies, such as Klinefelter syndrome (47, XXY), Triple-X syndrome (47, XXX), XYY syndrome (47, XYY), and Turner syndrome (45, X), are generally less severe due to the biological mechanisms of dosage compensation, ***specifically*** *X-chromosome inactivation, and the low gene density of the Y chromosome.*

Microdeletion and microduplication syndromes are structural anomalies that typically occur via non-allelic homologous recombination mediated by low-copy repeats during meiosis. These syndromes, such as the ***1 p 36*** *deletion syndrome or the distal* ***22 q 11.2*** *microdeletion, disrupt key gene dosages, leading to distinct neurodevelopmental, cardiac, and craniofacial phenotypes.*

Historically*, cytogenetic diagnostics relied on G-banded karyotyping to detect large numerical and structural aberrations. Modern diagnostics have transitioned to molecular cytogenetics and genomics, including Fluorescence In Situ Hybridization (FISH), Chromosomal Microarray (CMA), and Next-Generation Sequencing (NGS). These technologies enable high-resolution detection of copy number variants and microdeletions down to the single-nucleotide level.*

Therapeutics for chromosomal disorders are largely supportive, focusing on symptomatic management, developmental therapies, and protein or hormone replacement. ***However****, advances in gene editing, antisense oligonucleotides, and mRNA-based therapies are opening new avenues for targeting the underlying genetic defects directly.*

Mitotic and Meiotic Chromosome Segregation Mechanics across Phylogeny

The faithful transmission of genetic information across generations requires precise chromosome segregation during mitosis and meiosis. Centromeres serve as the primary constriction on mitotic chromosomes and function as the assembly site for the kinetochore, a multi-protein complex that binds spindle microtubules. These localized centromeres are typical of monocentric chromosomes, which are found in most eukaryotes.

***Conversely**, some species possess holocentric chromosomes, which lack a single primary constriction. Instead, their kinetochores are diffuse and assemble along the entire length of the chromosome. During mitotic anaphase, holocentric sister chromatids segregate as linear bars parallel to the spindle pole, rather than forming the classical V-shaped structures seen in monocentric chromosomes.*

*This structural difference has significant evolutionary implications, particularly regarding tolerance to double-strand DNA breaks. In monocentric organisms, a chromosome break produces an acentric fragment that lacks a centromere and is typically lost during cell division, leading to aneuploidy and cell death. In holocentric organisms, broken chromosome fragments retain kinetic activity because microtubule-binding sites are distributed along their entire length. **Consequently**, these fragments can segregate properly and be stably inherited.*

*The nematode **Caenorhabditis elegans** is a primary model for studying holocentric chromosome segregation. In **C. elegans** mitotic cells, CENP-A (a specialized histone \text{H3} variant) and its chaperone proteins organize centromeric chromatin across the entire outer face of the chromosome to direct kinetochore assembly. This holocentric structure is hypothesized to have evolved as an adaptive defense mechanism in phytophagous insects and soil-dwelling nematodes, protecting their genomes against clastogenic chemicals produced by plants or high levels of environmental UV radiation.*

While holocentricity provides stability to chromosomal fragments, it introduces unique challenges during meiosis. In canonical, monocentric meiosis, reciprocal crossovers (chiasmata) link homologous chromosomes.

Cohesion along the chromosome arms is cleaved during meiosis I, allowing homologous centromeres to segregate to opposite poles. Centromeric cohesion is protected until meiosis II, when it is cleaved to allow sister chromatids to segregate.

In a holocentric system, the presence of diffuse kinetochores along the entire length of recombined homologous chromosomes would cause microtubules to pull them toward both spindle poles simultaneously, resulting in chromosome breakage. To prevent this, holocentric organisms have evolved alternative meiotic segregation strategies:

- ***Chromosomal Remodeling (*C. elegans*):** During meiotic prophase in **C. elegans** oocytes, the single crossover event divides the bivalent chromosome into a long arm and a short arm. This crossover site acts as a functional landmark to restrict the recruitment of outer-kinetochore proteins to the short arm (forming a cup-like structure) while protecting cohesin along the long arm. This remodeling effectively converts the holocentric chromosome into a functional monocentric chromosome during meiosis. **Notably**, this meiotic segregation is completely independent of CENP-A and CENP-C, demonstrating a functional uncoupling of meiotic kinetochore assembly from mitotic centromeric chromatin.*

***Inverted Meiosis (Plants and Insects):** In several holocentric plant lineages (such as **Rhynchospora** and **Luzula** species) and insects (such as **Leptidea** butterflies), the canonical order of meiotic divisions is reversed. Sister chromatids segregate during meiosis I (an equational division), whereas homologous chromosomes remain terminally associated by chromatin threads and segregate during meiosis II (a reductional division).*

These chromatin threads are often heterochromatic and enriched with satellite DNA. Inverted meiosis reduces the risk of aneuploidy in hybrids between species with different chromosome numbers, allowing chromosomal rearrangements to persist and potentially driving chromosomal speciation.

*Understanding chromosome dynamics also requires analyzing non-homologous spatial interactions. Historically documented by cytogeneticists in polyploid species such as **Dahlia Merckii** (2n=36), **D. coccinea** (2n=32), and **D. variabilis** (2n=64), chromosome pairing is divided into primary and secondary associations:*

- ***Primary Association:** This process arises from sequence-specific pairing at zygotene and is stabilized by chiasmata formed at pachytene. These physical connections are maintained through diakinesis, determining the regular segregation of bivalents or multivalents at metaphase I.*

- ***Secondary Association:** This non-random spatial clustering occurs at pro-metaphase and is driven by a general biochemical affinity between homoeologous chromosomes in polyploids. While secondary association does not affect meiotic segregation or chiasma maintenance, it serves as an indicator of ancestral genomic homologies and evolutionary polyploidization events.*

Specialized Giant Chromosomes: Structural and Functional Adaptations

To support specialized developmental programs and high levels of transcription, some eukaryotic cells develop unique, giant chromosome structures. These specialized chromosomes differ significantly from the standard mitotic and meiotic chromosome templates.

Chromomeres

Chromomeres are bead-like structural units of condensed chromatin distributed linearly along the chromosome axis. They represent localized domains of tightly packaged DNA and histones.
In lampbrush chromosomes, chromomeres are connected by inter-chromomere fibers and serve as the structural anchor from which lateral loops of transcriptionally active DNA emerge.

Lampbrush Chromosomes

***First observed in amphibian** oocytes, lampbrush chromosomes are large, extended chromosomes found during the diplotene stage of meiotic prophase I in most animals (excluding mammals) and in the giant nucleus of some unicellular algae, such as **Acetabularia**. They consist of two homologous chromosomes held together by chiasmata, with each chromosome containing a pair of sister chromatids that form the main axis. Symmetrical lateral loops of decondensed chromatin project from the chromomeres along this axis.*

These lateral loops are coated with an asymmetrical matrix of nascent RNA transcripts and RNA-binding proteins, with transcription progressing from a thin end to a thick end. The primary function of lampbrush chromosomes is the rapid, high-volume synthesis of maternal mRNAs and proteins required for early embryonic development and yolk deposition. This highly extended loop structure allows RNA polymerase II to access the DNA template at rates far exceeding those of somatic cells.

Polytene Chromosomes

Discovered by Édouard-Gérard Balbiani in dipteran larval salivary glands, polytene chromosomes are giant, multi-stranded chromosomes formed through repeated rounds of DNA replication without sister chromatid separation or nuclear division (a process known as endoreplication or endomitosis). This endoreplication aligns thousands of sister chromatids in parallel, resulting in a thick, highly visible chromosome under light microscopy.

Polytene chromosomes display alternating dark bands and light interbands:

- ***Dark Bands:*** *Tightly packed, highly condensed heterochromatic regions that contain approximately 95 % of the chromosomal DNA.*

- ***Light Interbands****: Less condensed euchromatic regions with higher RNA concentrations.*

Under developmental and physiological cues, specific bands decondense and expand into localized swellings called ***chromosome puffs,*** *or larger structures known as* ***Balbiani rings****.*

These puffs represent uncoiled, transcriptionally active DNA loops undergoing intensive mRNA synthesis. Polyteny provides a metabolic advantage by increasing gene copy numbers, enabling high-volume protein synthesis in specialized larval tissues.

Evolutionary Diversification: Minichromosomes, *Microchromosomes, and Chromids*
Chromosomal evolution across diverse animal and bacterial lineages has yielded non-canonical chromosomal classifications that challenge standard definitions of scale and function.

Minichromosomes
The term "minichromosome" is historically applied to small, functional chromosomes in eukaryotic cells or to engineered circular plasmids designed to replicate at low copy numbers in bacterial cells. In prokaryotes, naturally occurring circular or linear replicons that are smaller than the primary chromosome but contain essential genes are often classified as minichromosomes, megaplasmids, or, more formally, chromids.

Microchromosomes
Microchromosomes are small, gene-dense chromosomes typically measuring less than 1.5 μm in length during metaphase. They are characteristic of avian karyotypes, some reptiles, fish, amphibians, and monotremes. In a typical avian karyotype, such as that of the chicken ***(Gallus gallus, 2n = 78),*** *the genome is split into 9 pairs of macrochromosomes, the Z and W sex chromosomes, and approximately 30 pairs of morphologically indistinguishable microchromosomes.*

Comparative genomic analysis reveals distinct structural and genetic properties that separate macrochromosomes and microchromosomes. While macrochromosomes are typically larger than 20 Mb} and have low to moderate gene density, microchromosomes are typically smaller than 20 Mb (down to 0.5 μm in length) but are highly gene-dense and rich in coding sequences. Microchromosomes feature a high GC content and a lower repetitive DNA footprint, which allows them to replicate early in the S phase and undergo higher recombination rates. ***Structurally****, they are often acrocentric, with centromeres that are difficult to localize.*

Comparative genomic studies *indicate that microchromosomes are stable chromosomal elements. Synteny analysis between the Florida lancelet (Branchiostoma floridae, an invertebrate chordate) and vertebrates suggests that the ancestral vertebrate genome was composed entirely of microchromosomes. Consequently, the preservation of microchromosomes in birds, reptiles, and amphibians represents the ancestral vertebrate state, whereas the lack of microchromosomes in mammals is the evolutionary outlier, resulting from extensive chromosomal fusions that formed macrochromosomes. The high gene density and elevated recombination rates of microchromosomes may help minimize repetitive DNA elements, keeping avian genomes compact to support a high metabolic rate and flight.*

Secondary Chromosomes and Bacterial Chromids
The discovery of multi-replicon systems in approximately 10\% of bacterial strains has shifted the historical paradigm that bacterial genomes consist of a single circular chromosome. While the largest replicon is the primary chromosome, additional large, essential replicons are classified as secondary chromosomes or chromids.

A replicon must meet three criteria to be classified as a chromid:

1. It uses a plasmid-type replication and partition system.

2. Its nucleotide composition (GC content and codon usage bias) is close to that of the primary chromosome.

3. It carries core, essential genes that are typically found on the primary chromosome in related species.

Chromids differ from standard plasmids, which carry non-essential accessory genes, and from true chromosomes, which use DnaA-mediated replication initiation.

*In **Vibrio cholerae**, the causative agent of cholera, the genome is split into a 3.0 Mbp primary chromosome **(Chr1)** and a 1.0 Mbp secondary chromosome **(Chr2)**. **Chr1** initiates replication at an **oriC** -like origin **(ori1)** mediated by the DnaA initiator protein. In contrast, **Chr2** initiates replication at a plasmid-like origin **(ori2)** regulated by a Vibrio-specific initiator protein called RctB. RctB binds to distinct regulatory loci, acting as an initiator at iteron sites (12-mers) and as a repressor at 39-mer inhibitory sites.*

*To maintain chromosomal stability, **Chr1** and **Chr2** coordinate their replication so that both cycles terminate synchronously before cell division. This synchronization is regulated by a **150 -bp** locus on **Chr1** called **crtS** (chromosomal replication trigger site). Replication of the **crtS** site on **Ch[span$_2$42](start$_s$pan)[span$_2$42](end$_s$pan)[span$_2$46](start$_s$pan)[span$_2$46](end$_s$pan)r1** triggers the initiation of **Chr2** replication by binding to RctB. The **crtS** locus acts as an anti-inhibitory site, preventing the inhibitory 39-mer sites on **Chr2** from suppressing RctB activity. This mechanism ensures that **Chr2** replicates only once per cell cycle, at a specific window linked to the progression of **Chr1** replication.*

*From an evolutionary perspective, bacterial secondary chromosomes are less conserved and evolve more rapidly than primary chromosomes. Selection analysis in **Vibrio** and **Burkholderia** species reveals that genes located on secondary chromosomes exhibit faster substitution rates **(d_N / d_S)** and weaker codon usage bias than their orthologs on primary chromosomes. This faster evolutionary rate is driven by two main factors:*

- ***Gene Dosage and Replication Timing:** Because secondary chromosomes initiate replication later in the cell cycle, they have a lower average gene copy number (dosage) in rapidly growing cells, which reduces their overall expression levels.*
- ***Accessory Genomes for Ecological Niches**: Secondary chromosomes often serve as "evolutionary test beds". They are enriched with genes for the transport and metabolism of carbohydrates and inorganic ions, as well as specialized biosynthetic gene clusters (such as spore pigments and surfactants in the Actinobacterium **Embleya**). This evolutionary plasticity allows secondary chromosomes to acquire, duplicate, and diversify genes, helping the host adapt to fluctuating environmental conditions or host-pathogen interactions.*

Selfish, Parasitic, and Aberrant Chromosomal Elements

Genomes can host atypical chromosomes that do not follow standard rules of replication, segregation, or host adaptation. These elements range from cancer-driving chromosomal rearrangements to parasitic, supernumerary chromosomes.

Neochromosomes

Neochromosomes are giant, structurally abnormal marker chromosomes found in approximately 3 % of all human cancers. They are highly prevalent in well-differentiated and de-differentiated liposarcomas (WD/DD-LPS), occurring in up to 90\% of cases, as well as in parosteal osteosarcomas. Neochromosomes can exceed 600 Mb in size and contain hundreds of amplified DNA fragments from multiple chromosomes stitched together randomly.

Biophysical and sequencing analyses have resolved the multi-stage life history of cancer-associated neochromosomes:

1. Initiation via Chromothripsis: *A localized catastrophic shattering event, typically involving chromosome 12* ***(12q13 - q15),*** *produces dozens of double-stranded DNA fragments. These fragments are repaired by non-homologous end-joining to form a circular ring chromosome or episome.*

2. Amplification via Breakage-Fusion-Bridge (BFB) Cycles: *Lacking telomeres, the circular structures undergo DNA replication and unequal sister chromatid crossovers, generating dicentric rings. During cell division, spindle forces pull the dicentric rings to opposite poles, forming anaphase bridges that tear the DNA apart. This circular BFB cycle repeats hundreds of times, driving random genomic amplification.*

3. Oncogenic Selection: *The BFB cycles generate massive copy-number gains (30 to 60 copies) of key oncogenes on chromosome 12, such as* ***MDM2*** *(which inhibits p53) and* ***CDK4*** *(which inhibits RB1). Co-amplified passenger genes that do not provide a survival benefit are frequently silenced epigenetically.*

4. Capture of Foreign Genomic Material: *During ongoing division, the neochromosome captures additional donor DNA fragments from other chromosomes via punctuated chromothriptic events, integrating extra-chromosomal DNA (ecDNA) and other oncogenic loci.*

5. Karyotypic Stabilization: *Prolonged BFB cycles erode the neochromosome's centromere, leading to mitotic instability and crisis. This crisis is resolved through neocentromere formation or the capture of a native centromere from a donor chromosome. Finally, the neochromosome is stabilized into a linear structure by capturing telomeric caps, terminating the BFB cycle and fixing the oncogenic marker chromosome within the cancer cell lineage.*

Parasitic B Chromosomes

B chromosomes, or supernumerary chromosomes, are dispensable, non-essential chromosomes found in thousands of plant, animal, and fungal species. They exist alongside the standard autosome and allosome complement (the A chromosomes) but do not pair or recombine with them during meiosis. Historically viewed as genomic parasites, B chromosomes are maintained in populations because they undergo biased, non-Mendelian transmission (known as chromosome drive). This drive allows them to accumulate in offspring at rates higher than Mendelian ratios, offsetting the physiological and reproductive fitness costs they impose on the host.

B chromosomes originate from standard A chromosomes via unequal segregation, chromosomal rearrangements, or duplication events, followed by the accumulation of repetitive elements, transposable elements, and organellar DNA. Over evolutionary time, B chromosomes can engage in "arms races" with the host genome, where drive mechanisms on B chromosomes promote their transmission while suppressors on the A chromosomes evolve to limit their accumulation.

In some lineages, B chromosomes have been domesticated to perform adaptive biological functions:

- ***Paternal Sex Ratio (PSR) Chromosome in Wasps:*** *In the haplodiploid jewel wasp Nasonia vitripennis, males develop as haploids from unfertilized eggs, while females develop as diploids from fertilized eggs. The PSR chromosome is a selfish B chromosome transmitted via*

paternal sperm. Upon fertilization, the PSR chromosome triggers the complete condensation and elimination of the paternal autosomes (excluding itself), converting the diploid zygote (destined to be female) into a haploid male that carries the PSR.

This sex-ratio distortion ensures the transmission of the PSR chromosome, which is restricted to the male lineage.

Feminizing B Chromosomes in Cichlid Fish: *In several cichlid fish species from Lake Victoria and Lake Malawi (such as* ***Astatotilapia latifasciata*** *and* ***Pundamilia nyererei****), B chromosomes have been linked to female sex determination. High-throughput sequencing of cichlid B chromosomes has revealed transcriptionally active genes involved in microtubule organization, cell cycle regulation, and sex determination. In these cichlids, the B chromosome carries a dominant female-determining locus that is epistatically dominant over the standard XY sex-determination system. This feminizing effect enhances the transmission of the B chromosome by driving its segregation through female meiotic divisions, which are less prone to drive-associated drag than male spermatogenesis. This represents an evolutionary transition where a parasitic B chromosome can domesticate into a novel sex chromosome.*

Sex-Determination Networks and Environmental Epigenetic Plasticity

Organisms use diverse genetic and environmental systems to determine biological sex, demonstrating the evolutionary flexibility of sex-determination pathways.

Genotypic Sex Determination (GSD)

Under GSD, biological sex is fixed at fertilization by genetic factors, typically sex chromosomes. The most common GSD mechanisms are male heterogamety (XX/XY, as in humans and other mammals) and female heterogamety (ZZ/ZW, as in birds and some reptiles). In the human XX/XY system, the presence of the ***SRY*** *The gene on the Y chromosome acts as the primary genetic switch, triggering a transcriptional cascade that directs the bipotential gonad to differentiate into testes.*

Environmental Sex Determination (ESD)

Under ESD, sex is established after fertilization by non-genetic environmental cues experienced during a critical developmental window. Cues that trigger ESD include nutrient availability, photoperiod, social hierarchy, and chemical gradients.

- ***Photoperiod-Dependent ESD:*** *The amphipod crustacean* ***Gammarus duebeni*** *produces males early in the mating season (during long photoperiods) and females later (during short photoperiods). This is adaptive because males have a longer growing season, helping them achieve a larger body size, which directly correlates with male reproductive success.*

- ***Location-Dependent ESD:*** *In the marine echiuroid worm* ***Bonellia viridis****, sex is determined by where the planktonic larva settles. If a larva lands on the open ocean floor, it develops into a large, free-living female. If the larva lands on or near an established female's proboscis, it is exposed to chemical masculinizing pheromones. The larva then migrates into the female's body and differentiates into a microscopic, parasitic male that functions as a sperm-producing symbiont.*

- ***Social and Position-Dependent ESD:*** *In the marine slipper snail* ***Crepidula fornicata*** *individuals stack on top of one another to form a mating mound. All young individuals develop initially as males. As the stack grows, the physical position of a snail determines its sexual fate. If a male is attached to a female at the base of the mound, it remains male. If the female dies or is removed, the male undergoes a transitional phase, degenerating its male reproductive tract and developing into a female to support the stack.*

Temperature-Dependent Sex Determination (TSD)

TSD is a common form of ESD observed in reptiles (including all crocodilians, most turtles, tuataras, and some lizards) and teleost fish. In TSD species, biological sex is determined irreversibly by the ambient incubation temperature during the middle third of embryonic development, known as the Thermosensitive Period (TSP). Reptilian TSD is categorized into three distinct thermal patterns:

TSD Ia (Male-to-Female / MF): *Low incubation temperatures produce 100\% male offspring, while high temperatures produce 100\% female offspring. This pattern is common in turtles, such as the red-eared slider (**Trachemys scripta**).*

TSD Ib (Female-to-Male / FM): *Low incubation temperatures produce **100 %[span$_1$0](start$_s$pan)[span$_1$0](end$_s$pan)[span$_1$2](start$_s$pan)[span$_1$2](end$_s$pan)** female offspring, while high temperatures produce 100 % male offspring. This pattern is observed in tuataras and some lizards.*

- ***TSD II (Female-Male-Female / FMF):*** *Extreme temperatures (both low and high) produce female offspring, whereas intermediate temperatures produce male offspring. This pattern is typical of crocodilians, such as the American alligator (**Alligator mississippiensis**), and some lizards and turtles.*

The Charnov-Bull model explains the evolutionary adaptive significance of TSD, proposing that selection favors TSD when the incubation temperature differentially affects the lifetime reproductive fitness of males versus females. For example, in species where large adult size provides a greater fitness advantage to females (e.g., to support egg production), temperatures that promote faster embryonic growth and larger hatchling size are linked to female development.

At the molecular level, TSD is regulated by temperature-sensitive transcription factors and epigenetic modifications that control steroidogenesis. The key molecular components of this transduction pathway include:

The Aromatase Enzyme Pathway: *Aromatase, encoded by the **CYP19A1** gene, converts male androgens (testosterone) into female estrogens (estradiol). In TSD species, estrogen is essential for ovarian differentiation. At female-producing temperatures, aromatase expression is highly upregulated during the TSP, converting local androgens to estrogens and directing the bipotential gonad to develop as an ovary. At male-producing temperatures, aromatase expression remains low, and the lack of estrogen leads to testicular development. This pathway can be overridden experimentally:*
administering exogenous estrogens or aromatase inhibitors during the TSP can force sex reversal regardless of the incubation temperature.

Transcriptional and Epigenetic Regulators: *The temperature signal is converted into stable transcriptional profiles via epigenetic modifications. Key genes involved include **Dmrt1** (Doublesex mab-3-related transcription factor 1), which promotes testicular development, and **FoxL2** (Forkhead box protein L2), which promotes ovarian development. During the TSP, incubation temperatures alter DNA methylation patterns and histone modifications in the promoter regions of **Dmrt1** and **FoxL2**. For example, male-producing temperatures cause demethylation of the **Dmrt1** promoter, upregulating its expression and driving testicular differentiation, while female-producing temperatures silence **Dmrt1** and activate **FoxL2** and **CYP19A1** to establish the ovarian pathway.*

*The evolutionary transition from ESD to GSD can occur through simple genetic changes. In the microcrustacean **Daphnia pulex**, which typically relies on environmental cues to determine sex, specific genetic variants have lost their environmental responsiveness. Structural rearrangements and recombination suppression on Chromosome I have isolated a sex-determining locus called **Dfh**. This suppression prevents recombination between haplotypes, allowing antagonistic traits to accumulate and driving the emergence of a mixed-mating system where sex determination is regulated by both*

*genetic and environmental factors. This genetic transition in **Daphnia** mirrors the early stages of proto-sex chromosome evolution, illustrating how stable genetic networks can override environmental plasticity to transition a species from environmental to genotypic sex determination.*

Comparative Cross-Species Genomic Matrix

To contextualize the human chromosomal paradigm within a broader phylogenetic framework, the table below compares human chromosomes with corresponding genetic, functional, and pathological parameters across diverse species.

| Organism Class & Species | Chromosome Type & Architecture | Key Residing Genes & Respective Classifications | Pathological Deficiency Defects or Mutational Manifestations | Direct Therapeutic or Biological Management |

|---|---|---|---|---|

- *| **Homo sapiens (Human)** | Diploid, linear, monocentric autosomes and sex chromosomes (2n=46) | **HTT** (neurological maintenance), **SMN1** (motor neuron survival), **HBB** (oxygen transport), **BRCA1** (DNA repair) | Down syndrome, Spinal Muscular Atrophy, **1p36** deletion syndrome, Sickle cell anemia, Beta-thalassemia | Recombinant hormones; proteasome inhibitors, dexamethasone, and monoclonal antibodies; antisense oligonucleotides. |*

- *| **Gallus gallus (Chicken)** | Haploid-diploid linear macro- and microchromosomes (2n=78) | Fatty Acid Synthase (metabolism), Major Histocompatibility Complex (immunological surveillance) | Severe immunodeficiency (susceptibility to viral pathogens like Marek's disease), metabolic arrest | Marker-assisted genomic selection; viral vaccination programs; targeted environmental biosecurity controls. |*

- *| **Caenorhabditis elegans** (Nematode) | Linear, holocentric autosomes and sex chromosome (2n=12 hermaphrodites, 11 males) | **him-3, htp-1, htp-2, htp-3** (axial elements), CENP-A, CENP-C (kinetochore assembly) | High Incidence of Males (HIM phenotype) due to meiotic nondisjunction; embryonic lethality and meiotic arrest | RNA-interference (RNAi) knockdown studies; rescue via extrachromosomal DNA arrays; temperature-sensitive mutant profiling. |*

- *| **Vibrio cholerae (Bacterium)** | **Circular, multi-replicon** chromosomes (Chr1, Chr2/chromid) | dnaA (primary initiator), **rctB** (secondary initiator), **crtS** (replication trigger), **parS2** (partitioning) | Lethal cell-cycle arrest upon **crtS** deletion; loss of essential metabolic and transcription pathways located on Chr2 | Antibiotic therapies (e.g., fluoroquinolones); experimental targeting of RctB-DNA bindings to disrupt Chr2 replication. |*

- *| **Nasonia vitripennis (Jewel Wasp)** | Haplo-diploid monocentric chromosomes with parasitic B-chromosomes | Paternal Sex Ratio (PSR) specific chromatin-modifying locus | Complete destruction of paternal genome in fertilized eggs, causing extreme male-biased sex ratio and colony collapse | Biological population modeling; maternal genetic suppression modifiers to neutralize the PSR drive mechanism. |*

- *| **Astatotilapia latifasciata (Cichlid Fish)** | Monocentric A-chromosomes with transcriptionally active B-chromosomes | Duplicated cell-cycle and microtubule organization genes, brain aromatase **(cyp19a1b)**, **amh** duplications | Skewed, heavily male-biased sex ratios and decreased species survival under fluctuating ecological conditions | Controlled hybridization programs; thermal and hormonal therapies to correct sex-ratio skewing. |*

- *| **Embleya australiensis** (Actinobacterium) | Linear primary chromosome (7.1 Mb) and linear chromid EEC1 (4.2 Mb) | Spore pigment Biosynthetic Gene Clusters (BGC), surfactant peptide SapB BGCs | Structural arrest of the life cycle (complete lack of aerial hyphae*

formation and spore pigmentation) | Plasmid-mediated heterologous gene expression of deleted BGCs; chemical supplementation with exogenous surfactants. |

This comparative matrix highlights how nature uses diverse chromosomal configurations to balance genetic stability, dosage compensation, and environmental adaptability. These mechanisms span from the rigid structural control of human monocentric chromosomes to the dynamic plasticity of bacterial chromids and parasitic B-chromosomes.

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