Cosegregation Online (COOL) v3

About

This server performs cosegregation analysis by the Full-Likelihood method [1] and outputs a Bayes factor that can be integrated into the variant classification guidelines developed by the American College of Medical Genetics and Genomics (ACMG) and the Association of Molecular Pathology (AMP) [2].

The website is designed for classifying variants in a known disease gene as pathogenic or benign within the context of clinical genetic testing. If you want to conduct cosegregation analysis for gene discovery research, i.e., to find out which gene associates with the disease of interest, then please see my other package VICTOR.

Quick start

Click here, provide a gene symbol and upload a pedigree file, then click the “Submit” button.

Pedigree File

Filename cannot contain spaces. The Pedigree File must be a tab- or space-delimited text file. If you edit data in Excel, please save as “Tab delimited Text (.txt)”. Missing values are represented by a period (“.”). Empty fields, space within fields, or quoted fields are not allowed. IDs are case-sensitive with alphanumeric characters or the _ character.

Required columns:

1. **PedID**: Pedigree_ID. Alphanumeric. It cannot be 0. Multiple pedigrees are allowed.
2. **IndID**: Individual_ID. Alphanumeric. It cannot be 0. IndID does not need to be unique across pedigrees.
3. **Father**: Individual_ID of father. Put 0 for founders. If one parent is 0, both parents must be 0.
4. **Mother**: Individual_ID of mother. Put 0 for founders. If one parent is 0, both parents must be 0.
5. **Sex**: Biological sex, not the personal identification of one's own gender. 0=UnknSex, 1=M=Male, 2=F=Female.
6. **Aff ***: Affection status. Value is UnknAff (unknown), Unaff (unaffected), or a disease name.
7. **Age**: Age-of-onset for affected and age-of-the-last-exam for unaffected individuals. 0 for unknown age.
8. **FPTP**: The first person tested positive for the variant in each pedigree. 1 for FPTP; 0 for others.

9. **Geno**: Genotype. 0=unknown, neg=negative, het=heterozygous-carrier, hom=homozygous-carrier. You don't need to input genotype for obligatory carriers as the program will infer automatically. You don't need to input negative genotype (non-carrier) for spouses even if you assume that the variant enters the pedigree only once. The program will fill in the genotype based on allele frequency.

Optional columns:

- Twin: Twin status. 0: not twin; positive integer: siblings with the same number are twins.
- Pop: Population. This column overrides the advanced option "Population" on the webpage.
- Cohort: Year range. This column overrides the advanced option "Year range" on the webpage.
- Comment: Information to be shown in pedigree drawings.

* For cancer-associated genes, Aff is the first diagnosis of any cancer. Below is a list of strings for the "Aff":

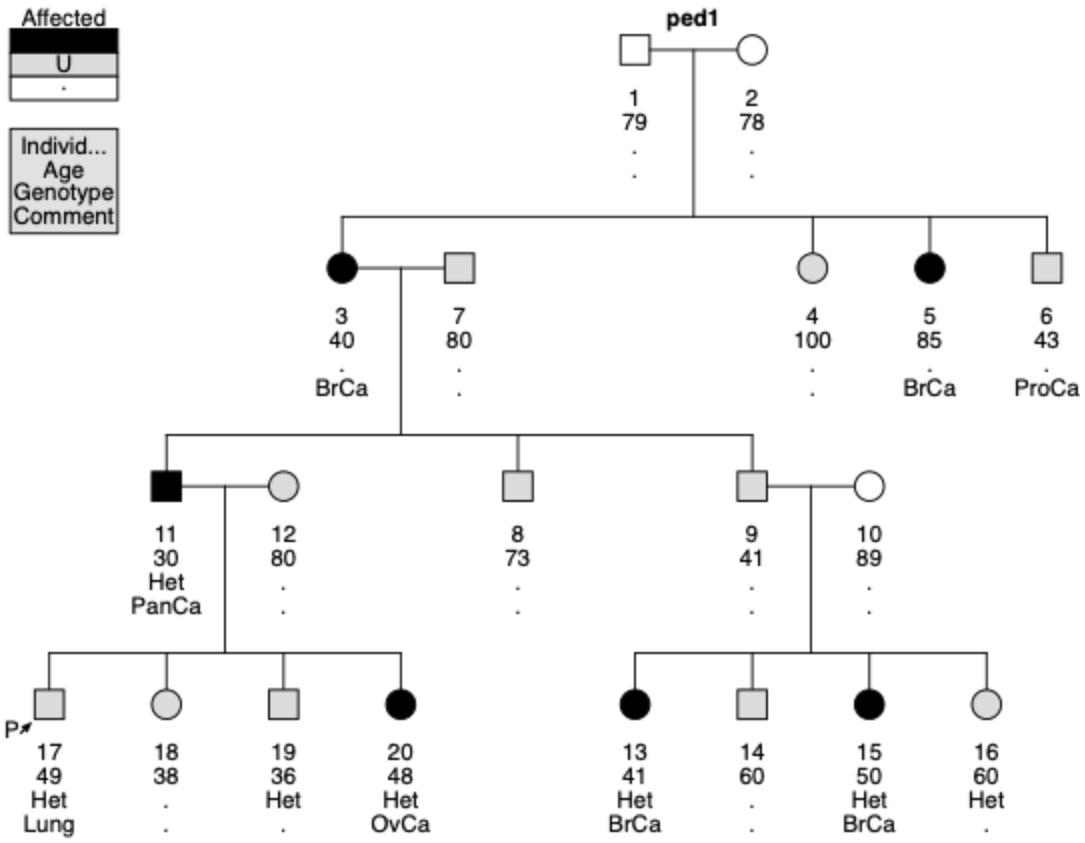
Name	Descriptions
unaff	unaffected
Lip	Lip
Tongue	Tongue
Mouth	Mouth
Oral	Oral cavity (lip, tongue, mouth)
Saliv	Salivary gland
Parotid	Parotid gland
Tonsil	Tonsil
Oroph	Oropharynx
Nasoph	Nasopharynx
Pyrifm	Pyriform sinus
Hypoph	Hypopharynx
Pharynx	Pharynx (include Oropharynx, Nasopharynx, Hypopharynx, Pharynx unspecified)
BCP	Buccal cavity and pharynx (include Lip, Tongue, Mouth, Saliv, Parotid, Tonsil, Pharynx)
Throat	Oropharynx, Tonsil, Base of tongue
Nasal	Nasal cavity and middle ear
A.sinus	Accessory sinuses
Larynx	Larynx
Trachea	Trachea
Oesoph	Oesophagus

Stomach	Stomach (synonym: Gastric)
SmBowel	Small intestine
Colon	Colon
RS.junc	Rectosigmoid junction
Rectum	Rectum
CRC	Colorectal cancer (include Colon, RS.junc, Rectum)
Anus	Anus
Liver	Liver
Gall	Gallbladder
Biliary	biliary tract
PanCa	Pancreas
SSBP	Stomach SmBowel Biliary PanCa
BilPan	biliary tract and Pancreas
Lung	Lung
Thymus	Thymus
Heart	Heart
Bone	Bone
Bone.l	Bone of limbs
Bone.o	Bone other than limbs
Osteo	Osteosacoma
Sarcoma	Soft tissue sarcoma and bone sarcoma
CM	Cutaneous Melanoma
NM.skin	Non-melanoma of skin
Meso	Mesothelioma
STS	Soft-tissue sarcoma (Mesothelioma, Kaposi, Peripheral nerves, Peritoneum & retroperitoneum, Connective & soft tissue)
BrCa	Breast
Vagina	Vagina
Cervix	Cervix uteri
Corpus	Corpus uteri
Uterus	Cervix or corpus uteri
OvCa	Ovary

Penis	Penis
ProCa	Prostate
Testis	Testis
UpUrin	Upper Urinary tract malignancy (kidney, renal pelvis, ureter)
Kidney	Kidney
RenalCC	Renal Cell Carcinoma (only for CI5-XI, a subset of UpUrin)
RCC	Renal Cell Carcinoma (only for CI5-XI, a subset of UpUrin)
Ureter	Ureter
Bladder	Bladder
Urinary	Urinary tract (include Kidney, Renal pelvis, Ureter, Bladder, Other urinary organs)
Eye	Eye
UM	Uveal melanoma
Mening	Meninges
CNS	Central nervous system
Brain	Brain
Thyroid	Thyroid
MTC	Medullary Thyroid Cancer
Adrenal	Adrenal gland
Hodgkin	Hodgkin lymphoma
NH.lym	Non-Hodgkin lymphoma
IPD	Immunoproliferative diseases
Myeloma	Multiple myeloma
L.leuk	Lymphoid leukemia
M.leuk	Myeloid leukemia
U.leuk	Cell-unspecified leukemia
Leuk	Leukemia
Lymph	Lymphoid Neoplasms (Hodgkin lymphoma, Non-Hodgkin lymphoma, MALT-lyphoma, Lymphoid leukaemia)

Below is an example Pedigree File and a drawing for *BRCA1*. Do not copy and paste; you can download the file here. Please note that affection status depends on the gene. Because the model for *BRCA1* involves only breast, ovarian, and pancreatic cancer, individual 6 (prostate cancer) and 17 (lung cancer) are “unaffected” in the figure. Also note that the proband, individual 17, is unaffected. This is correct as the definition of proband is the first person who tested positive for the variant.

PedID	IndID	Father	Mother	Sex	Aff	Age	Geno	FPTP
ped1	1	0	0	M	.	79	.	0
ped1	2	0	0	F	.	78	.	0
ped1	3	1	2	F	BrCa	40	.	0
ped1	4	1	2	F	unaff	100	.	0
ped1	5	1	2	F	BrCa	85	.	0
ped1	6	1	2	M	ProCa	43	.	0
ped1	7	0	0	M	unaff	80	.	0
ped1	8	7	3	M	unaff	73	.	0
ped1	9	7	3	M	unaff	41	.	0
ped1	10	0	0	F	.	89	.	0
ped1	11	7	3	M	PanCa	30	Het	0
ped1	12	0	0	F	unaff	80	.	0
ped1	13	9	10	F	BrCa	41	Het	0
ped1	14	9	10	M	unaff	60	.	0
ped1	15	9	10	F	BrCa	50	Het	0
ped1	16	9	10	F	unaff	60	Het	0
ped1	17	11	12	M	Lung	49	Het	1
ped1	18	11	12	F	unaff	38	.	0
ped1	19	11	12	M	unaff	36	Het	0
ped1	20	11	12	F	OvCa	48	Het	0



Penetrance

BRCA1, BRCA2

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BRCA1_Japan, BRCA2_Japan

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Nakagawa, Keitaro Matsuo, Yoshinori Murakami, Amanda B Spurdle, Michiaki Kubo. Expansion of Cancer Risk Profile for BRCA1 and BRCA2 Pathogenic Variants. *JAMA Oncol*. 2022 Jun 1;8(6):871-878. PMID: 35420638, PMCID: PMC9011177.

BRCA1:p.R1699Q

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TP53

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MLH1, MSH2, MSH6, PMS2

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POLE, POLD1

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RAD51C, RAD51D

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PTEN

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NF1

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CHEK2:c.1100delC

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- Charlotte Näslund-Koch, Børge G Nordestgaard, Stig E Bojesen. Increased Risk for Other Cancers in Addition to Breast Cancer for CHEK2*1100delC Heterozygotes Estimated From the Copenhagen General Population Study. *J Clin Oncol*. 2016 Apr 10;34(11):1208-16. PMID: 26884562.

CDKN2A

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CDH1

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APC

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Populations

Algeria
Zimbabwe
Uganda
Argentina
Brazil
Colombia
CostaRica
Ecuador
Canada
US_Natives
US_Hispanic
US_Asian
US_White
US_Black
China
India
Israel_Jews
Israel
Japan
Korea
Kuwait
Philippines
Thailand
Austria
Belgium

Belarus
Croatia
Czech
Denmark
Estonia
France
Germany
Iceland
Ireland
Italy
Latvia
Lithuania
Malta
Netherlands
Norway
Poland
Portugal
Slovenia
Spain
Switzerland
Turkey
UK
Australia
NewZealand

Relative Risk File

You can upload a Relative Risk File instead of using the relative risk tables provided by the server. This is useful for analyzing a gene not supported by the server or using an updated relative risk table. Penetrance will be calculated by combining the uploaded relative risk table with the incidence rate obtained from the Cancer Incidence in Five Continents (CI5). Therefore, this function is only useful for cancer-related genes.

Here is an example of a relative risk file. Lines starting with # are comments and will be ignored. Lines beginning with two hyphens are arguments. The --gene argument is mandatory; it specifies a gene name, which does not have to be an official symbol. Following the argument lines is a relative risk table. This table has three header rows, with the first column as “Geno”, “Sex”, and “Disease”, respectively. “Geno” can be “het” (heterozygous) or “hom” (homozygous). If you specify a --dominant argument, “hom” columns are unnecessary. Although a --recessive argument is not implemented, you can still analyze a recessive or additive model by providing both the “het” and “hom” columns. After the headers are data rows, the first column shows age ranges. The line “TableEnd” marks the end of the table. No blank lines are allowed within this block of data. You can specify multiple genes in one Relative Risk File by adding a blank line followed by another data block, as shown in the example file.

Grid search

The grid search option can be used to model reduced penetrance. It is set to “no” by default, i.e., no grid search. To use the grid search, set the option to 5 or 10 or 20. This number is the starting percentage of the elevated relative risk. The program will start from this number, do cosegregation analysis, and continue with an increment of 20%. For example, if you set grid search with 5, the program will conduct cosegregation analysis using 5%, 25%, 45%, 65%, 85%, and 100% of the original elevated relative risk. If you set it to 10, the analysis will be on 10%, 30%, 50%, 70%, 90%, and 100%. Note that the 100% is always conducted. I do a 20% increment just to reduce run time so that the results will be returned to your browser.

FAQ

You can add your own questions below. I may move some answers to History.

1. I got a warning “no year of birth” and “no population info”
   The warning you've received is due to the absence of birth years in your pedigree file. Our cosegregation analysis relies on the background incidence rate, which will be retrieved from the Cancer Incidence in Five Continents (CI5). CI5 has several versions, each five years apart. To determine the most suitable version, COOL needs the birth years. However, at least for some populations, the influence of the birth year on the results is small. Therefore, you may disregard the warning. The "Year range" option on the website provides another simple method to determine which CI5 version to use without needing to specify birth year for each individual in a pedigree file.
2. So, how do you specify a birth year?
   You can add a column to the pedigree file with the header “YOB”.
3. I cannot specify a penetrance file. Uploads are not accepted.
   This function has not been tested yet. I will do that later.

References

1. Thompson D, Easton DF, Goldgar DE. A Full-Likelihood Method for the Evaluation of Causality of Sequence Variants from Family Data. *The American Journal of Human Genetics* 2003;73(3):652-655.
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History

2024-10-25 fixed this problem when the Pedigree File name contained a space. Previously it will give an error: “/bin/sh: line 1: xxx: command not found”. Now the server will show a message “Pedigree File name cannot contain spaces.”