Hirschsprung's Disease

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Hirschsprung's disease is a congenital birth defect where nerve cells (ganglion cells) fail to form in the enteric nervous system of the large intestine during embryonic development. This absence of ganglion cells (aganglionosis) prevents normal intestinal peristalsis, leading to functional bowel obstruction, severe constipation, abdominal distension, or failure to pass meconium in newborns.

Primary Genetic Causes & Pathways

The genetic architecture of Hirschsprung's disease is complex, characterized by non-Mendelian, polygenic inheritance with incomplete penetrance. However, several high-penetrance single-gene mutations disrupt the migration, proliferation, and survival of neural crest cells during fetal gut development:

- **The RET Proto-Oncogene (*RET*):** The primary gene driver, responsible for approximately 50% of familial cases and 15–20% of sporadic cases. *RET* encodes a receptor tyrosine kinase that is critical for the survival and migration of enteric nerve precursors.
- **Endothelin Signaling Pathway (*EDNRB* & *EDN3*):** Mutations in the Endothelin Receptor Type B (*EDNRB*) or its ligand Endothelin-3 (*EDN3*) disrupt late-stage colonization of the colon by enteric neural crest cells.
- **Transcription Factors (*SOX10* & *PHOX2B*):**
    - *SOX10* directly regulates *RET* and *EDNRB* gene expression.
    - *PHOX2B* regulates autonomic neuron differentiation.
- **RET Ligand/Co-Receptors (*GDNF*, *NRTN*, *GFRA1*):** Glial cell line-derived neurotrophic factor (*GDNF*) and Neurturin (*NRTN*) bind to the RET complex; mutations in these helper proteins impair upstream activation of the *RET* pathway.

Syndromic & Chromosomal Associations

Roughly 20%–30% of Hirschsprung cases occur as part of broader genetic syndromes or chromosomal abnormalities:

- **Trisomy 21 (Down Syndrome):** The most common chromosomal association, present in 2% to 10% of individuals diagnosed with Hirschsprung’s disease.

- **Waardenburg Syndrome Type IV (Shah-Waardenburg):** Caused by *SOX10*, *EDNRB*, or *EDN3* mutations, combining Hirschsprung's with hearing loss and hair/eye pigmentation changes.

- **Haddad Syndrome:** Caused by *PHOX2B* mutations, combining Hirschsprung's with Congenital Central Hypoventilation Syndrome (breath-holding/apnea during sleep).

- **Mowat-Wilson Syndrome:** Linked to mutations in the *ZEB2* gene, causing distinct facial features, microcephaly, and enteric aganglionosis.