Hirschsprung Disease
(HD/HSCR)

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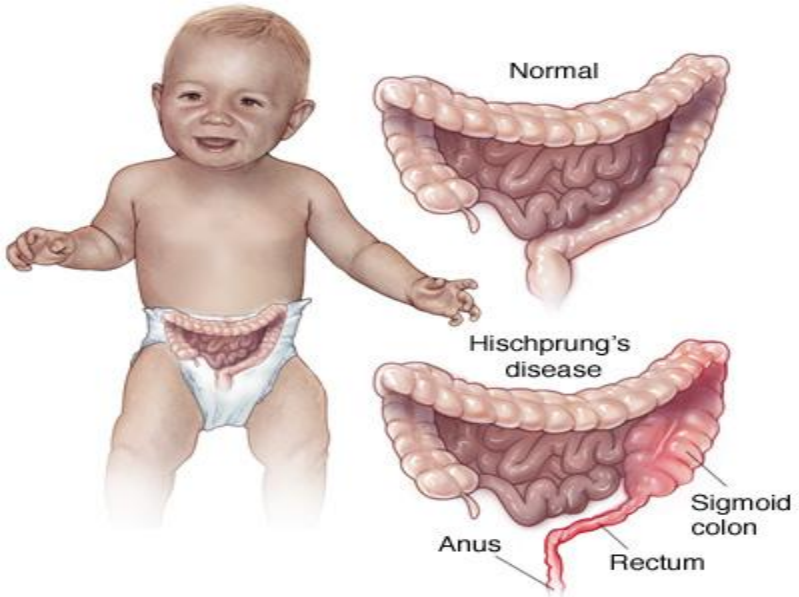
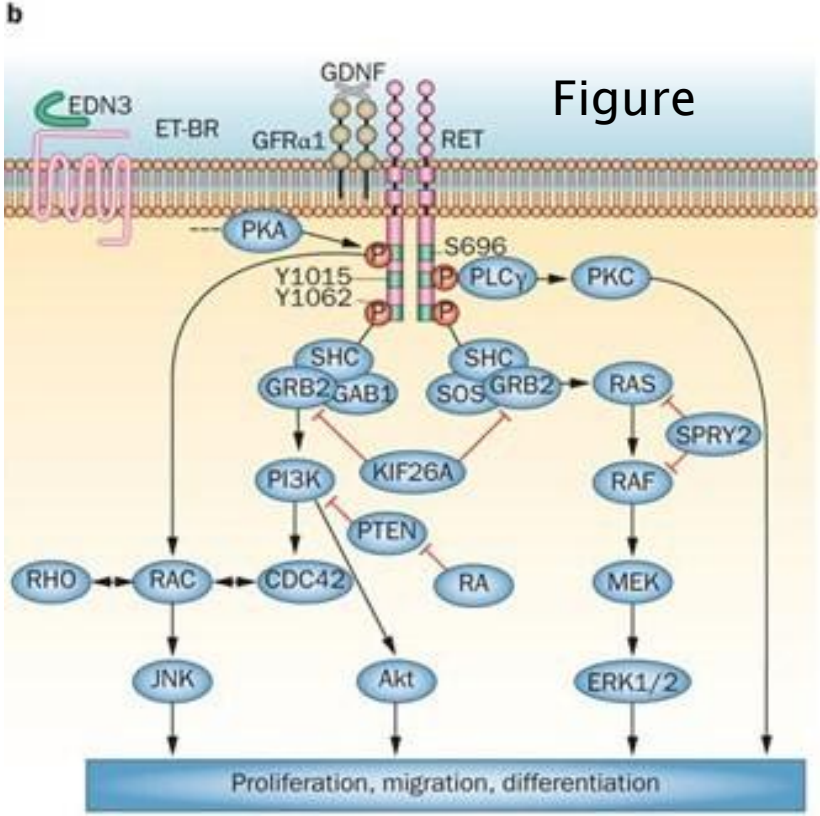
Physiology

- **Incidence Rate:** 1 in 5000 Births
  - 4:1 male to female ratio in short-segment (type 1) HD
  - No gender bias in long-segment (type 2) HD
- **Inheritance Pattern** is Complicated
  - 70% of cases are spontaneous
  - Can present as autosomal dominant inheritance
  - Also displays multigenic inheritance patterns
- **Target System:** Enteric Nervous System
  - Patients lack nerve cells in a portion of their intestinal tract
- **Early Onset**
- **Symptoms:** severe constipation, failure to pass meconium within the first two days of birth, intestinal blockage, abdominal swelling and pain, vomiting, jaundice (yellowish skin), and explosive bowel movements when a doctor inserts his or her finger into the patient's rectum.
- **Late onset symptoms** include fatigue, slow growth, anemia, diarrhea, malnutrition, appetite loss, lack of weight gain, and small, watery stools.



Molecular Cause

- There have been **eight associated genes** discovered: GDNF (Glial cell-derived neurotrophic factor), NRTN (neurturin), EDNRB (endothelin receptor type B), EDN3 (endothelin 3), ECE1 (endothelin converting enzyme 1), SOX10 (sex determining region Y box 10), and ZFHX1B/SMADIP (zinc finger E-box-binding homeobox 2).
- Most common: **RET** (proto-oncogene tyrosine-protein kinase receptor)
  - Found in 50% of familial HD cases and 10 – 20% of sporadic HD cases. It is found at chromosome 10q11.2.
  - Produces the **RET protein (tyrosine kinase receptor RTK)**
  - **over 200 RET mutations discovered** to result in HD.
- Many of these genes produce intercellular signaling proteins that are important in the proliferation, survival, migration, and differentiation of the enteric neural crest cells.
- Multigenic inheritance: a combination of these mutated genes, not a single mutated gene, is responsible for HD.
- **The RET pathway:**
  - Growth factors attach to RTK → RTK dimerize and autophorsphorylates different cytoplasmic tyrosines → the tyrosines become binding sites for intracellular molecules that'll initiate additional signaling pathways
- When RET is mutated, it produces a nonfunctioning form of the RTK, which doesn't respond to growth factor signals, and so the resulting pathways don't occur.



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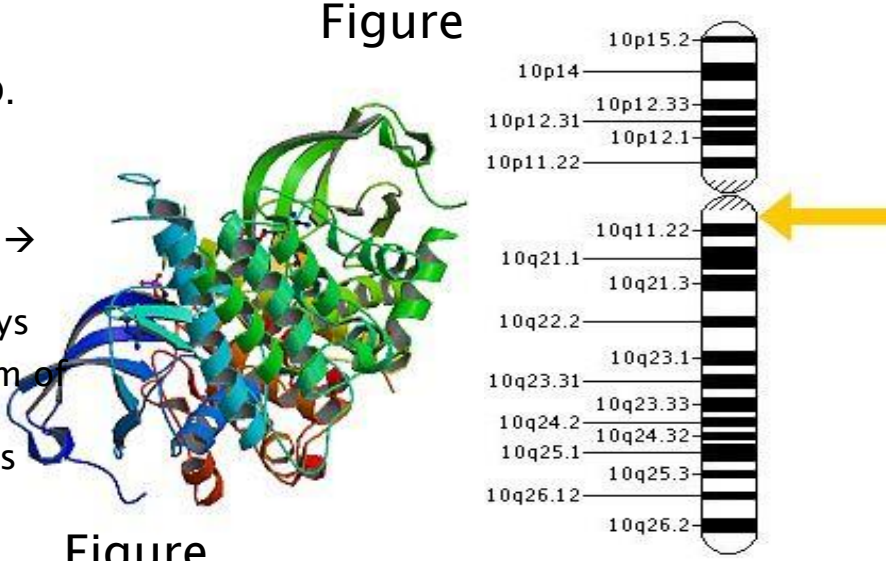

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Treatments/Risks and Limits

- There is **no cure** and no current succesful molecular intervention therapies for HD.
- The treatment for HD is a **pull through procedure**, which removes the affected portion of the intestine that lacks nerve cells, and connects the remaining, healthy intestine to the anus.
- In more severe cases, such as when an abnormally long portion of the intestine is affected, a colostomy is needed as an intermediary step before the pull through procedure.
- In a **colostomy**, the affected portion of the intestine is removed and the healthy portion is attached to an opening in the abdomen wall, where feces will pass through and into a bag.
- The patient uses the colostomy bag for a 4-6 month stabilization period, where the doctors will monitor the patient's condition to see if the ideal conditions have been reached for a pull through surgery.
- **Drawbacks of Current Treatment:**
  - While the procedure has low risks of mortality, like any surgery, there is still a risk of death.
  - HD patients have **a <5% risk of death**, often due to enterocolitis and rupturing of the colon.
  - **Post-operative enterocolitis** is the inflammation of the small intestine and colon.
    - It can occur within two, and up to ten, years after the surgery.
    - Symptoms: abdominal pain, diarrhea, nausea, vomiting, poor feeding, and abdominal pain.
    - It can be treated with antibiotics and rectal irrigation several times daily.
  - Constipation affects up to 10% of patients post-surgery
  - **Fecal incontinence** (the involuntary release of stool or mucus from the rectum)
  - **Short bowel syndrome**
    - Associated with dehydration, fatigue, weight loss, and malnutrition.
      - These complications can be managed with laxatives, high fiber diets, enemas, and suppositories.
        - **15% of HD patients still lack full bowel control following the treatment.**

Proposed Cure/Limits

- There is a recent study that involves the inhibition of the Notch signaling pathway in a dissociated enteric nervous system cells (ENSC). By increasing neuronal differentiation and decreasing proliferation, they believed they could control the behavior of ENSC after it is implanted into the patient.
- The ENSC were isolated, dissociated, and cultured, before being treated with a gamma-secretase inhibitor DAPT and silencing-RNA (siRNA) to inhibit Notch signaling transcription factors (RBP-jK). This stopped the Notch signaling pathway and so, proliferation decreased while early neuronal differentiation increased.
- As of October 2012, the team successfully isolated and transported human bowel ENSC into an aganglionic mouse. A normal pattern of contractility was obtained and this study poses great potential for the future of HD cures.
- In addition, inhibiting Notch signaling may prevent the uncontrolled proliferation of the ENSC cells after being transplanted, avoiding further complications.
- Proposal is to administer adult nerve stem cells with functioning RET proteins into the aganglionic region of the affected patient's intestinal tract.
- These stem cells should proliferate/ differentiate into enteric nervous system cells, restoring function to the bowel.
- Adult stem cells are undifferentiated cells collected from an adult that have the potential to differentiate into other types of cells when transplanted.
  - Neural stem cells can give rise to neurons.
- First, the stem cells will be harvested and processed from the donor's nervous system, before being cultured in vitro to form neurospheres.
- Before the stem cells are administered to the patient, immunosuppressive drugs will be given in order to reduce the risk of the patient rejecting the drugs.
- In addition, the nerve cells will be treated with FOXO (forkhead box) proteins to inhibit Wnt signaling pathways. Research has shown that FOXO repressed Wnt signaling nerve cells exhibit a stronger proliferative response.
- These stem cells will incorporate themselves into the intestinal lining within a matter of days or weeks, and begin responding to growth signals that will allow for differentiation and proliferation.
- Drawbacks: possibility of rejection, threat of lifethreatening complications resulting from immunosuppresive drugs, and difficulty of predicting whether the stem cells will undergo rapid proliferation and cause complications.

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