HIRSCHPRUNG'S DISEASE

(HSCR)

Peter Yang

SBS11QHG-02 Pd. 6

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PHYSIOLOGY

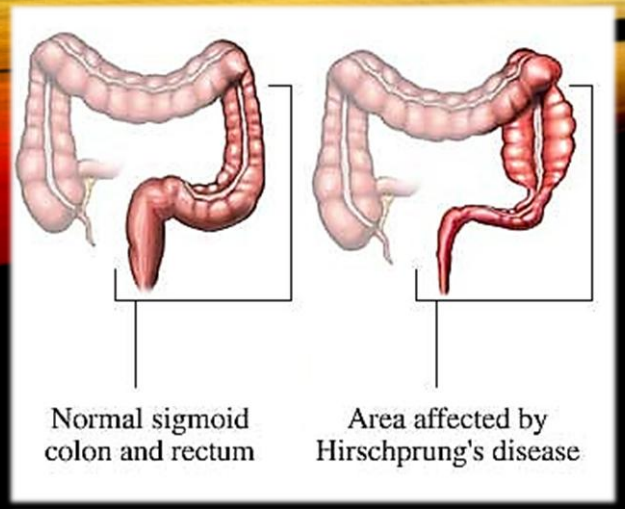

Fig 1

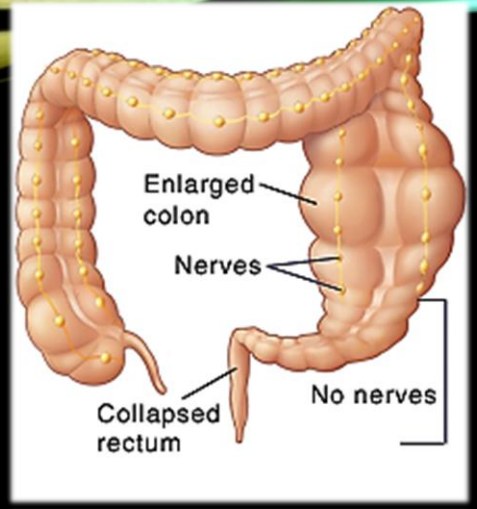

Fig 2

- Early onset:1 in 5,000 children affected; 4:1 male to female bias.
- Lack of nerve cells in the large intestine; leads to blockage and swelling of the abdomen as well as difficulty passing stool
- Common symptoms (in newborns):
  - Failure to pass stool within 48 hours of birth
  - Constipation and/or gas (which will make infant fussy)
- Common symptoms (in older children):
  - Lack of weight gain due to difficulties absorbing nutrients
  - Dehydration
  - Constipation
- Mortality rate low (6%), however some extreme cases or complications during treatment can lead to death

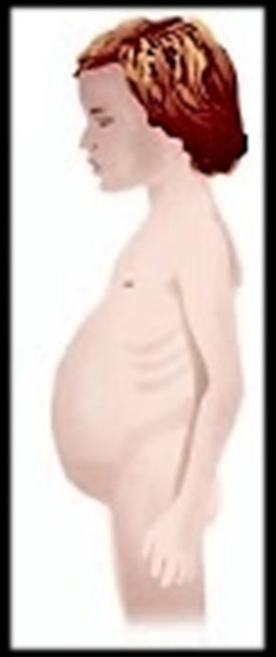

Fig 3

MOLECULAR CAUSE

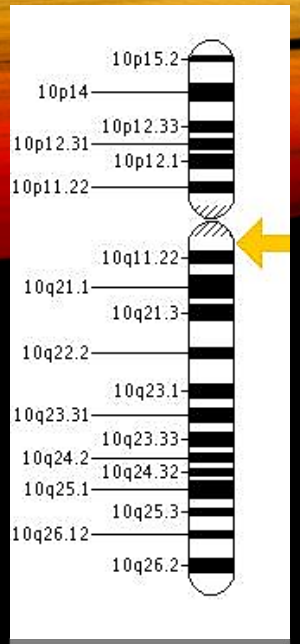

Fig 4

- Complicated and polygenic inheritance; 8 or more genes located on different chromosomes can cause disease state
  - Autosomal dominant and recessive cases show up occasionally
- Mutations in RET gene (chromosome 10) appear to cause a majority of cases
- RET codes for receptor tyrosine kinase protein which communicates with other proteins to affect gene transcription

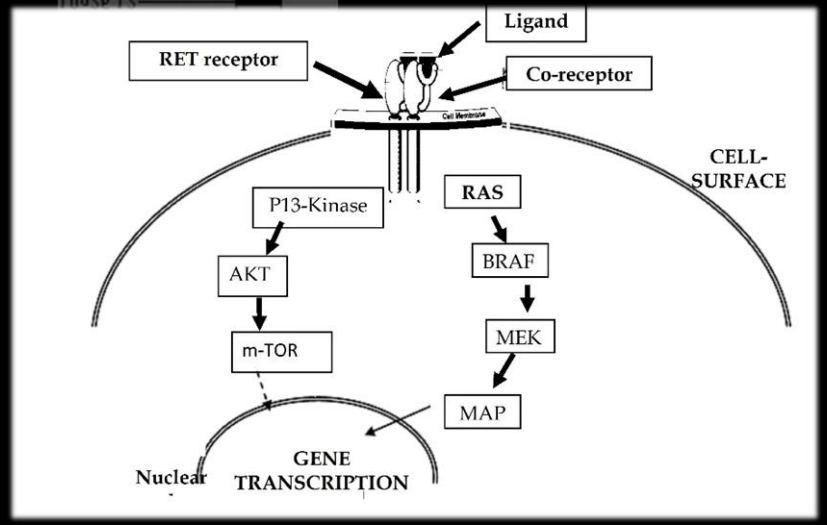

Fig 5

- There are 4 classes of RET mutations that can result in HSCR:
  - Class I mutations disrupt RET maturation and prevent translocation at the plasma membrane.
  - Class II mutations cause replacement of one of the four cytosine residues by a different amino acid.
  - Class III mutations affect the tyrosine kinase (TK) domain and catalytic activity.
  - Class IV mutations interfere with the binding of transduction effectors to RET

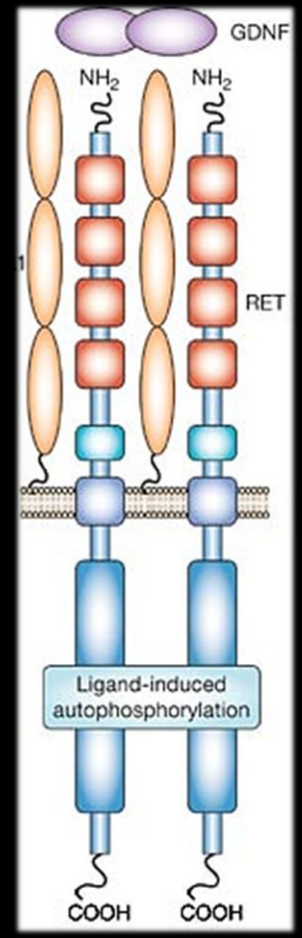

Fig 6

CURRENT TREATMENT: RISKS/LIMITATIONS

- Fairly dependable treatment already exists
  - Pull-through procedure connects functional part of bowel with anus, bypassing the aganglionic section.
- After surgery, the child will have a normal life span and be able to pass stool
  - Special training for the child and/or a special diet may be required to avoid constipation and dehydration.
- In rare cases where there is no viable portion of bowel at all, an ileostomy may be performed, but this will cause many more problems than a normal pull-through procedure would.
  - A colostomy bag would be required, and after the wound has had time to heal the doctor may decide to connect the small intestine to the anus to allow normal bowel movements.
- Enterocolitis may develop due to complications with surgery or even beforehand, if too much stool gathers in child's intestines.
- Attempts have been made to isolate the neuronal precursor cells from the developing enteric nervous system (intestinal nervous system)

PROPOSED CURE: RISKS/LIMITATIONS

- Because RET protein is large and multiple changes in function can occur, the best way to deal with a mutation leading to function change is to replace the faulty DNA with a functional copy inserted using a viral vector.
- Viruses are harmful to the human body by nature
  - Can lead to unwanted immune response that can ultimately be fatal
- Assuming a viral vector can be used without harm, the best choice would be a Lentivirus or Retrovirus vector, as they are both relatively stable and do not cause major immune responses. They also both possess the ability to integrate their DNA into the target cell genome.
- Another possible cure, although not fully on the molecular level, is to extract a sample of the child's intestinal stem cells, and grow a graft-able sample ex vivo, or approach it the same way as replacing the RET gene by simply modifying stem cell DNA, although that would also have the same disadvantages.

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Proposed Cure

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