Nonsydromic Holoprosencephaly

An unfortunately devastating disease that is (mainly) caused by the humorously named Sonic hedgehog gene.

By: Phillip Huynh
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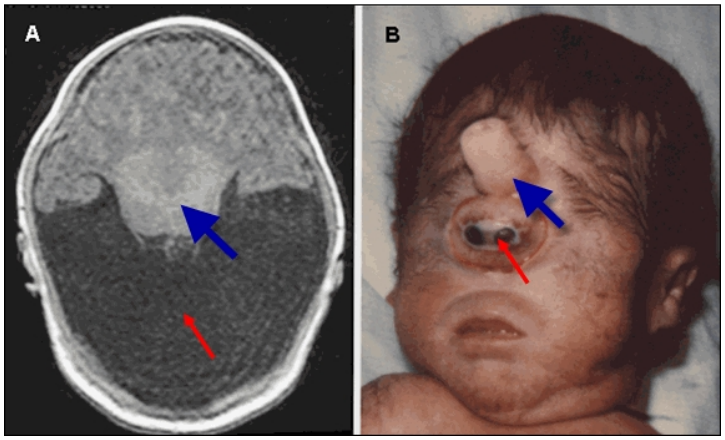
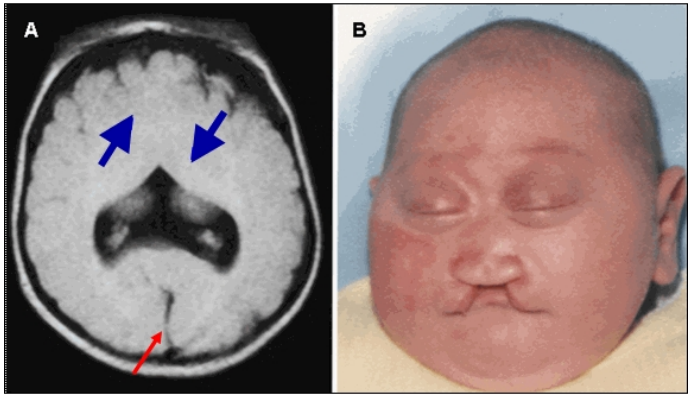
Physiology

- Autosomal dominant disease.
- Three main types of HPE (shown on the next slide):
  - Alobar: Most severe. No separation of brain's hemispheres.
  - Semilobar: Left and right frontal and parietal lobes are fused. Interhemispheric fissure in the brain only present in posterior.
  - Lobar: Brain is mostly separated. Lateral ventricles separated, but fused frontal lobes.
- There are many different phenotypic manifestations.
  - Cyclopia (one central eye)
  - Proboscis (tubular nasal structure above eye)
  - Macrocephaly, microcephaly (enlarged and shrunken heads)
  - Cleft palate, cleft lip (an opening or gap)
  - Developmental delays, seizures, pituitary dysfunction, feeding difficulties…
- Severity of facial deformity is directly correlated to life span.
- The more severe the facial dysmorphism, the lower. This is especially prevalent in babies that suffer alobar HPE, as they can die before they are even born.

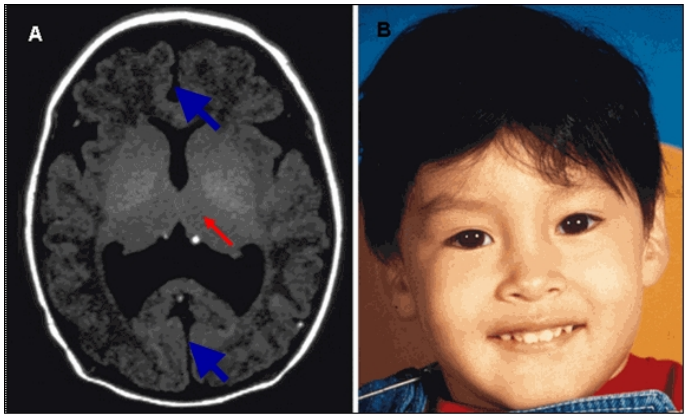
Alobar HPE



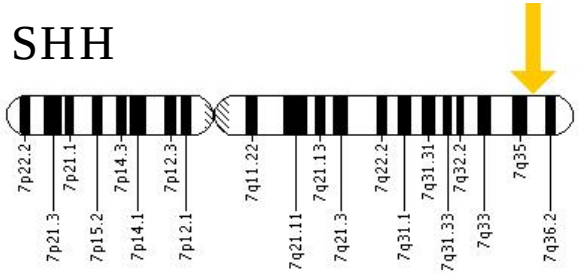
Semilobar HPE



Lobar HPE



SHH



Sonic hedgehog protein encoded by SHH. →

Molecular Causes

- There is a severe lack of information about all causes of the disorder, but the best known version is autosomal dominant.
- Many HPE-associated genes found to be involved in hedgehog signaling, but focus is on SHH, as it is most common in HPE patients.
  - For example, transcriptional factors that resolve hedgehog signals and their binding motifs (such as ZIC2, Zic family member 2, which encodes a classical Gli-type zinc finger DNA binding motif that recognizes the transcriptional factors) can have mutations that cause HPE, but precise functions are unclear.
- SHH is a gene that manufactures Shh, which is key in the hedgehog signaling pathway that is detailed on the next slide.
  - One possible mutation would be a base transition from G to A at codon 127, which swaps tryptophan for a stop codon.
  - Shh establishes the role of cells during development, aids in cell growth, and shaping of the body.
  - It is important for formation of hemispheres of the brain, and formation of the eyes.
- However, the more general answer for the cause would be a dysfunction in the hedgehog signaling pathway.

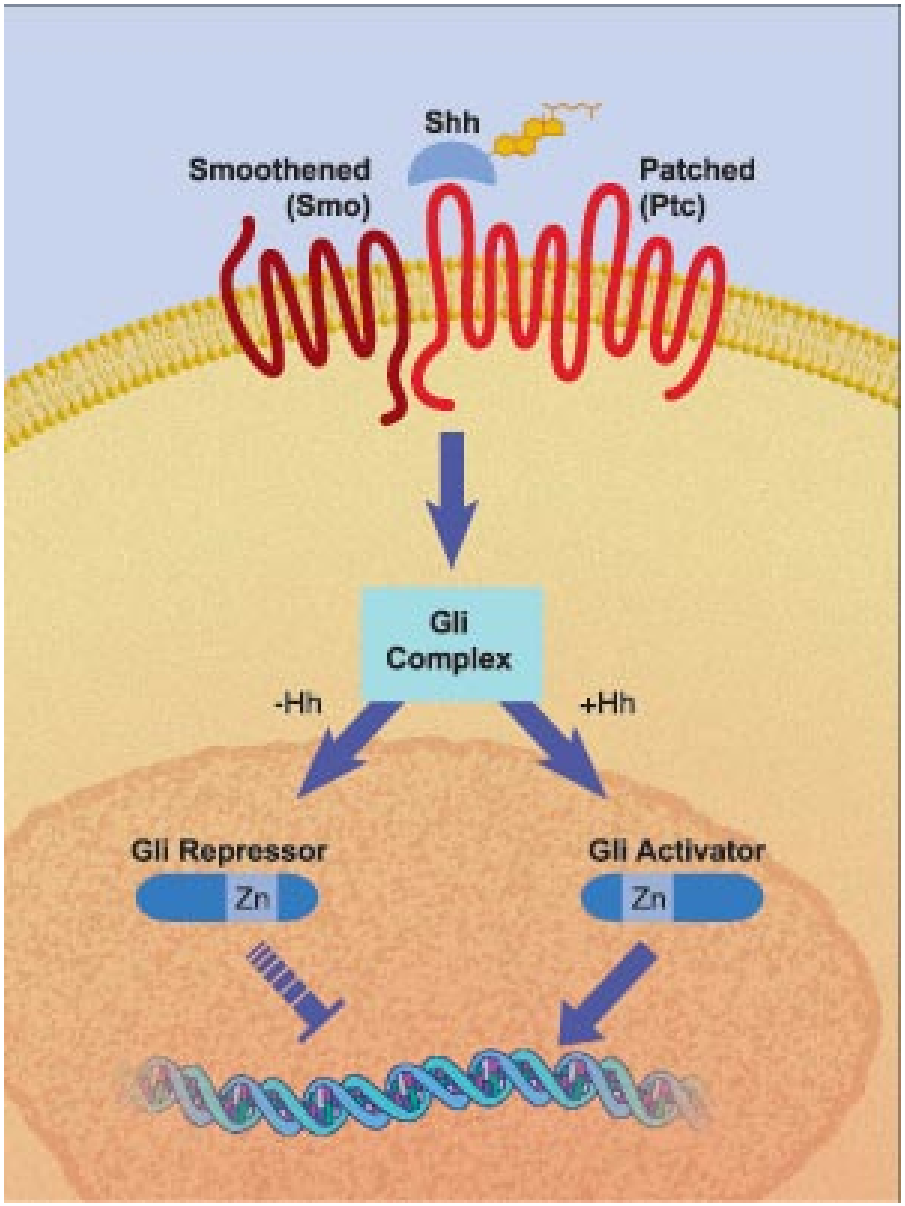
The Shh Pathway

In the normal pathway:

-The receptor PTCH1 will repress signaling unless Shh binds to it.

-This will allow Smo to get to work, and become active within the cell membrane.

-This allows Gli transcription factors to activate, eventually leading to the proper gene products.



Current Treatments

- We don't know too much about the hedgehog signaling pathway that is the main target of study at the moment.
  - So far, we've made great progress by analyzing a similar pathway in Drosophilia flies and in Mus musculus.
- Thus, we don't have any cures.
- We can only treat the symptoms of HPE.
- Palliative treatments include:
  - Hormone replacement therapy – helps with pituitary dysfunction
  - Surgery to fix cleft palate/lip – helps with feeding difficulties
  - 1/6 of children need a cebrospinal fluid shunt to treat hydrocephalus
  - Suctioning and chest physiotherapy can be helpful for HPE patients with pulmonary issues.
  - Gastronomy tubes can help with gastroesophageal reflux.
  - Esophageal surgery can be performed if muscles in the esophagus need to be surgically tightened.

Proposed Cures

(and why they are not viable right now)

- Intervention must be extremely early due to the nature of the disease, while the baby is developing.
- One way would be to increase the amount of Shh in the baby's body, perhaps through placental diffusion in the mother.
  - Shh is hydrophobic, meaning it would diffuse easily. However, there are too many variables to do so, and it may be dangerous for the mother as Shh and its pathway is implicated in certain cancers (brain, lung, mammary gland, prostate, skin).
- Futuristic cures are the only ones that are viable right now.
- Nanobots could make for a safe delivery because of their size and maneuverability (as well as being able to control them) make them ideal.
  - Nanobots can theoretically build the missing Gli proteins atom by atom, but the technology has yet to be developed.
  - Nanotechnology could also be used to force binding of Shh (if that is the issue) to PTCH1. It would resolve issues in SMO, and end with the proper gene products. "Surgically" removing PTCH1 from SMO, allowing SMO to function, is another possibility with "future-tech".
- The main problem: lack of information about causes of the disease, lack of technology for experimentation..

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