Brian Guo

HOLOPROSENCEPHALY (NONSYNDROMIC)

Physiology

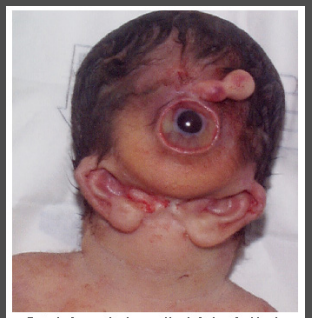
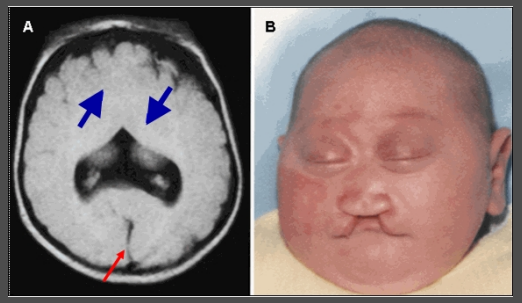
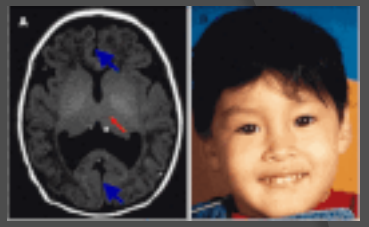


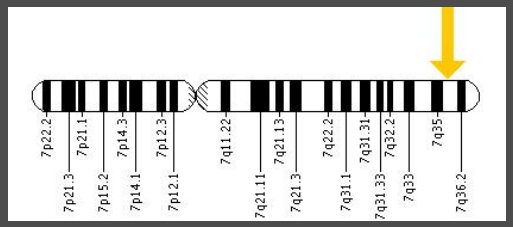
Foto 1. Ausencia de maxilar inferior, fusión de pabellones auriculares (sinotia)

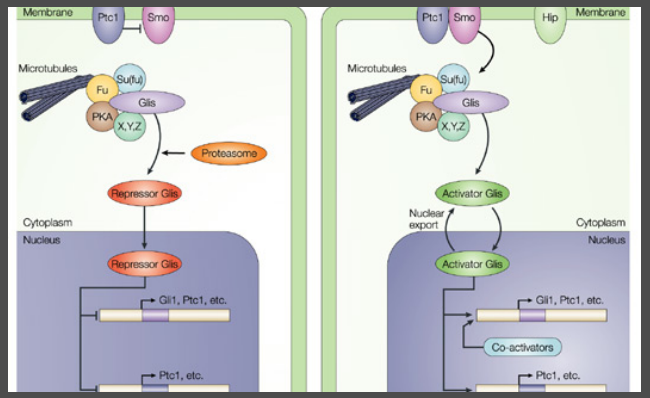




- Holoprosencephaly (HPE) is caused by a mutation in SHH, ZIC2, SIX3, or TGIF3/other various genes (HPE has been mapped to over 100 mutations across many different genes)
- HPE targets the brain tissues and brain cells. Essentially, it is a genetic disease in which the brain fails to fully divide into hemispheres.
- This disease happens before you're born, implying fetal onset
- Symptoms: Ultrasound showing signs of underdeveloped head or cleft lip are signs of Holoprosencephaly.
- Disease effects: Alobar (most severe): cyclopia, no division of eye, ears on the neck, proboscis sometimes above eyes, high mental deficiencies. Lobar: generally nothing severe, although cleft lips are still common as well as some mental deficiencies.

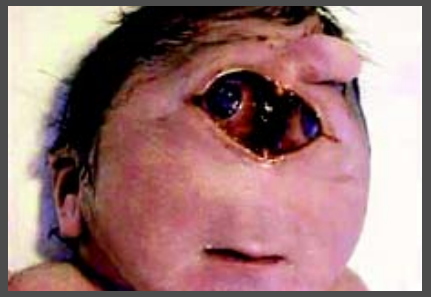
Molecular Cause

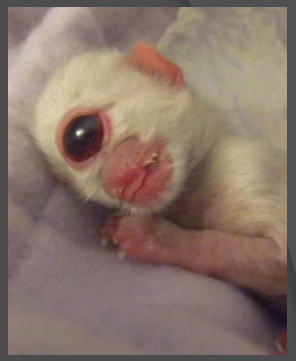




- SHH is the key molecule associated with HPE. It is located at 7q36, and HPE is inherited Autosomal dominantly, although it can form through spontaneous mutation
- ZIC2 stands for Zinc finger protein, it is a protein of the ZIC family located at 13q32, and controls the function of the eyes along the midline of the brain.
- SHH works by binding to PTC, which is normally a Smo inhibitor. Once SMO stops being inhibited, Smo activates the Gli complex, which is a collection of different enzymes including protein Kinase A, SuFu(suppressor of fused), Gli, and other proteins, which work to produce Gli activators. The Gli activators act to transactivate target genes, which allows the production of proteins that begin the separation of the brain

Treatment





- Currently there is no effective treatment of Holoprosencephaly
- This is because there is a 10-14 week timeframe for the baby to be diagnosed and cured before the brain has finished its division
- Right now, there is only treatment of the symptoms
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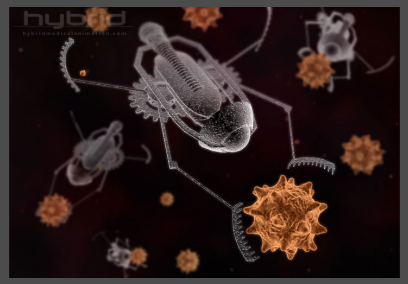
- This includes seizure medication (Phenobarbital), hormone treatment in case the pituitary gland is affected, heartburn medication in case of GERD (gastroesophageal reflux disease) and other treatments for symptoms that arise from the incomplete division of the brain
- There is no brain surgery that can fix holoprosencephaly, but there is surgery to fix cleft lips, as well as surgery in case of esophageal problems.

Cure



- My proposed cure is to use nanobots to deliver the protein to the baby
- Originally, I had thought an injection would be enough, but there is no way to get around the blood-brain barrier with a simple injection
- Nanobots, if used, should be small enough to carry the protein.
- There are some limitations to this, seeing as the nanobots haven't been used for such a practice before, on the other hand, unlike simple SHH proteins, nanobots would have to be able to disguise themselves as proteins or molecules that are able to diffuse into the brain. There is also the size of the nanobots to consider, seeing as the capillaries of a baby are extremely tiny.
- However, nanobots have potential because they may develop a way to bypass the BBB and they are the most flexible of any method available.

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