Holoproesencephaly

Holoprosencephaly

- First described in 1963
- Failure of proper formation of the midline structures of the forebrain is the common feature of the many variant forms.
- Occurs in about 1/10,000 liveborn infants but is much more frequent in prenatal studies.

Etiology of HPE

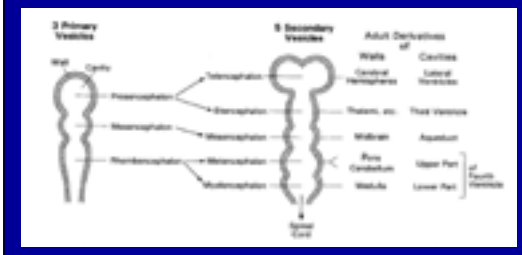
- Chromosomal
- Teratogens
- Syndromes
- Single gene disorders

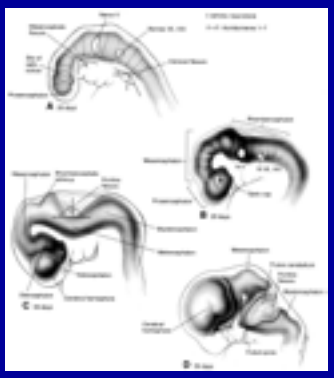
Famous Teratogens

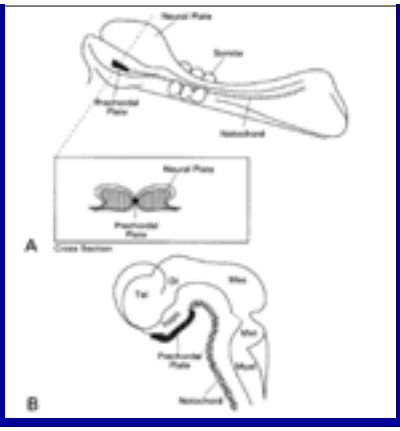
- Alcohol
- Cyclopamine

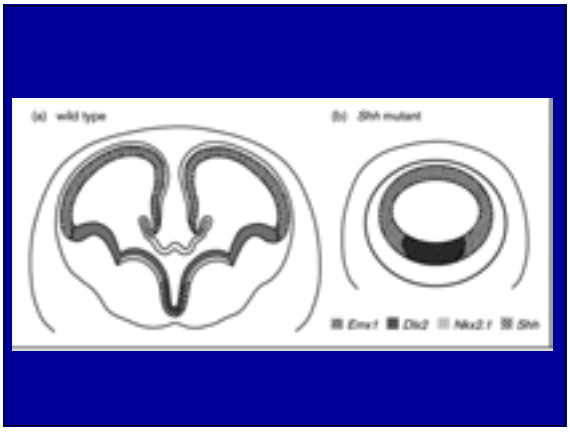
HPE Genes

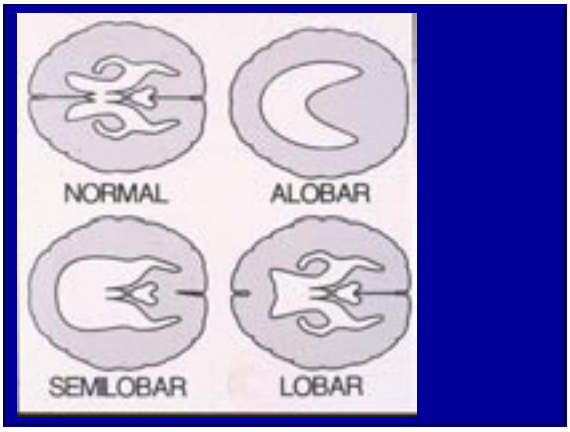
- Sonic Hedgehog (SHH); chromosome 7
- ZIC2 (chromosome 13q32)
- SIX3; chromosome 2
- TGIF, chromosome 18
- Others

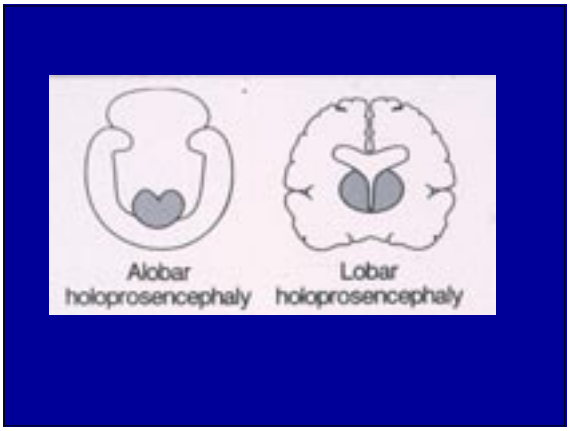


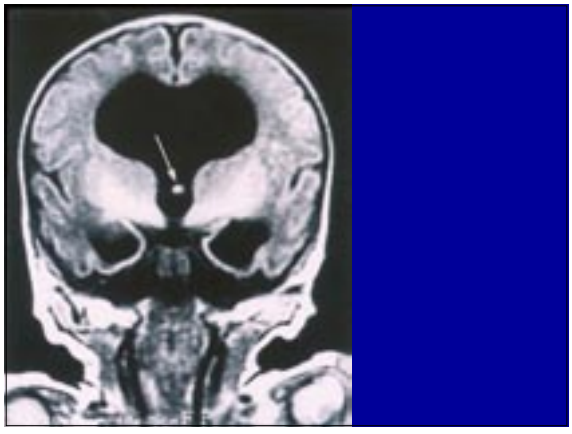



Neural Plate
Somite
Prechordal Plate
Notochord
Neural Plate
Prechordal Plate
A
Cross Section
Tel
Shh
Mes
Pros
Prechordal Plate
Notochord
B

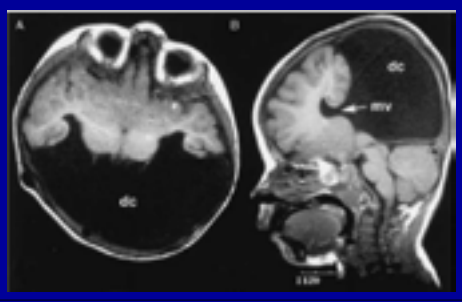

(a) wild type
(b) Shh mutant
Emx1
Dlx2
Nkx2.1
Shh


NORMAL
ALOBAR
SEMILOBAR
LOBAR

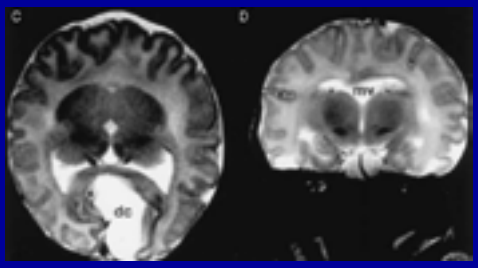

Alobar
holoprosencephaly
Lobar
holoprosencephaly



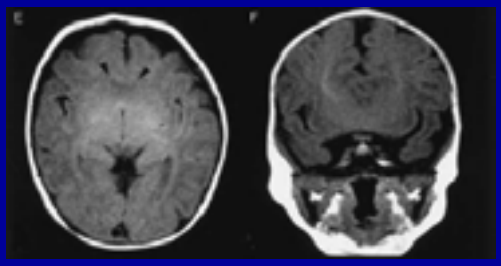
Alobar HPE. (A) lack of separation of the two hemispheres. Large dorsal cyst (dc) posteriorly. (B) reveals a midline ventricle, a monoventricle (mv), that communicates posteriorly with the dorsal cyst (dc).

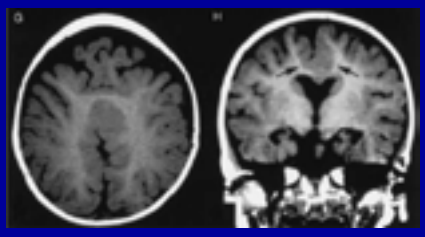


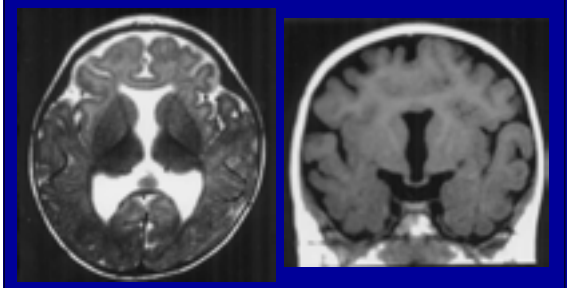
Semilobar HPE. (C) separation of the hemispheres posteriorly but not anteriorly. There is incomplete separation of the basal ganglia. (D) reveals a lack of interhemispheric fissure and a monoventricle (mv)



Lobar HPE. (E) reveals that two hemispheres are separated by an interhemispheric fissure both anteriorly and posteriorly. (F) documents incomplete separation of the inferior frontal lobes near the midline.

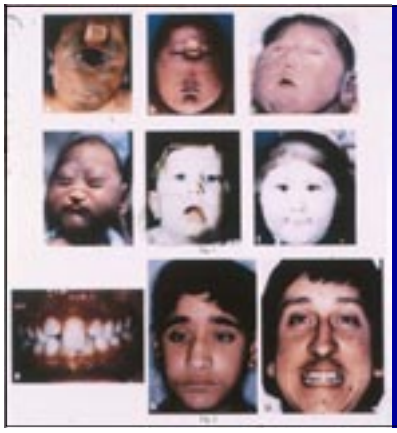


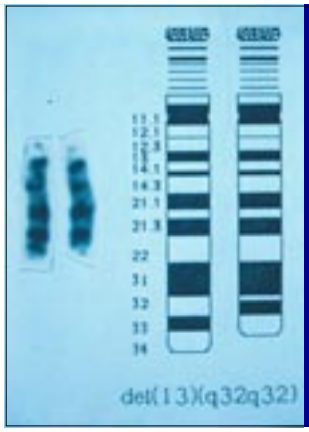




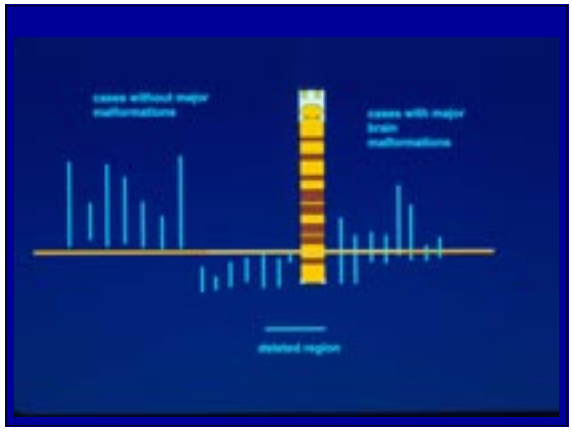
Face Predicts the Brain

- ~85% of HPE cases are associated with facial malformation of various types.
- Thus, brain imaging in the context of facial malformation is a good idea.
- Nonetheless, brain malformation can be severe even with a relatively normal face.

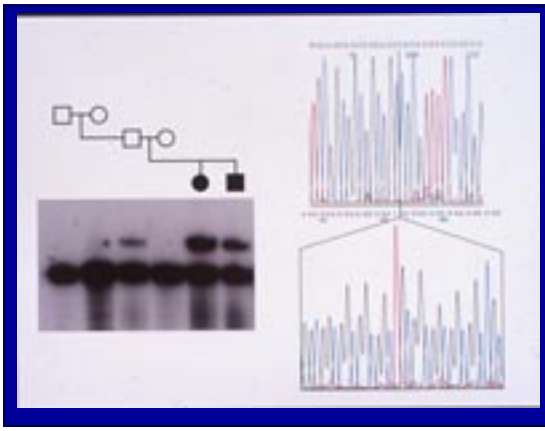


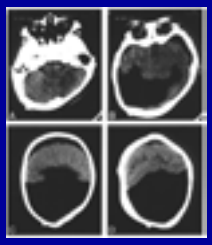


13q32 deletion in a fetus in which HPE was the only malformation.

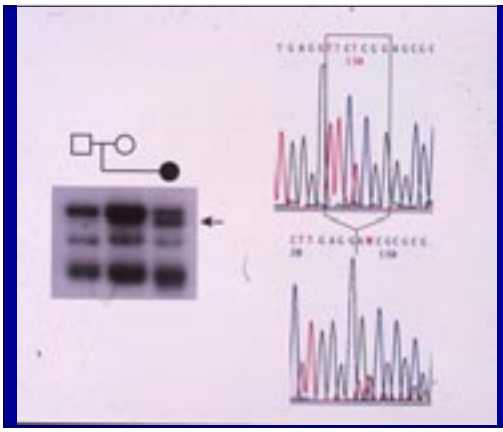


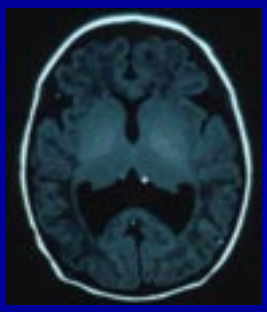
Alobar HPE and alanine tract expansion in 2 sibs. Father is a mosaic carrier of the mutation.





De-novo 7 BP deletion in zinc finger region. Alobar HPE.





12 AA in frame deletion near carboxy terminus.
Interhemispheric fusion defect.

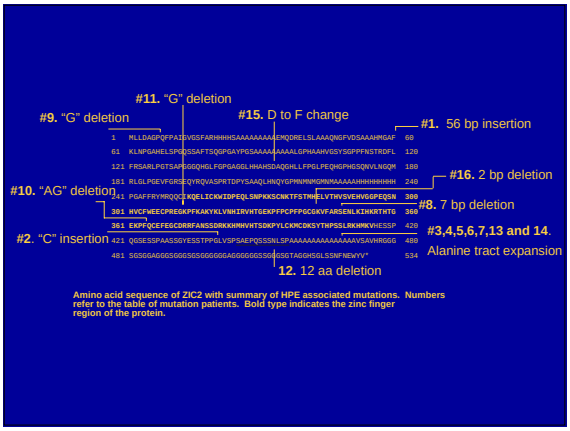
De-novo alanine tract expansion.
Semi-lobar HPE

Birth 21 Months

De-novo 2 base deletion at AA 365. Stop at 366. Semi-lobar HPE.

Aspartic acid to Phenylalanine change caused by 2 base change. Lobar HPE. Inherited from mother who is normal except for hypotelorism.

De-novo single base deletion at AA 312. Stop at 413. Semi-lobar HPE.



Day 15 coronal sections showing HPE like malformation in Zic2 mutant mice.

From Nagai et al., PNAS, March 2000