# 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

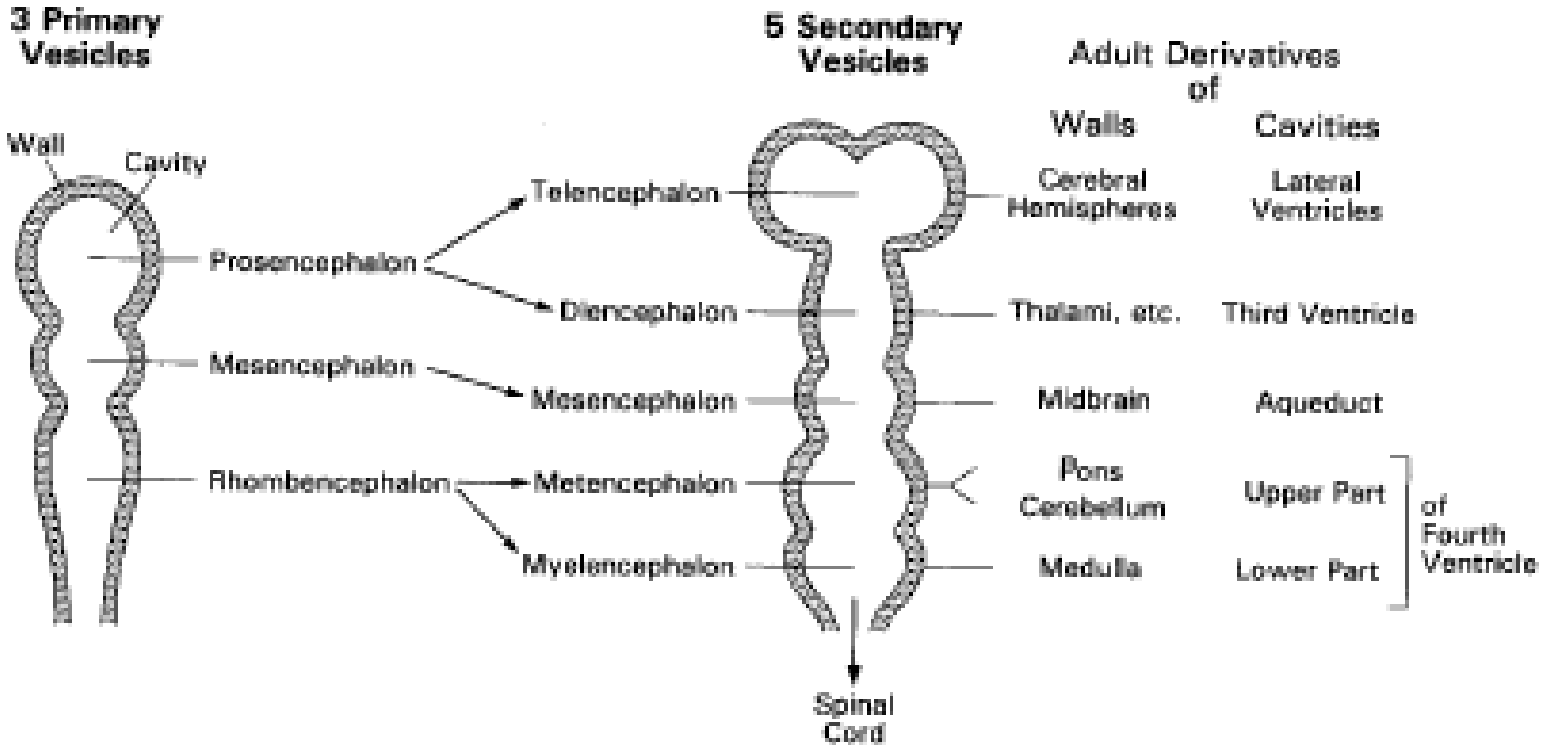
- Chromosomal
- Teratogens
- Syndromes
- Single gene disorders

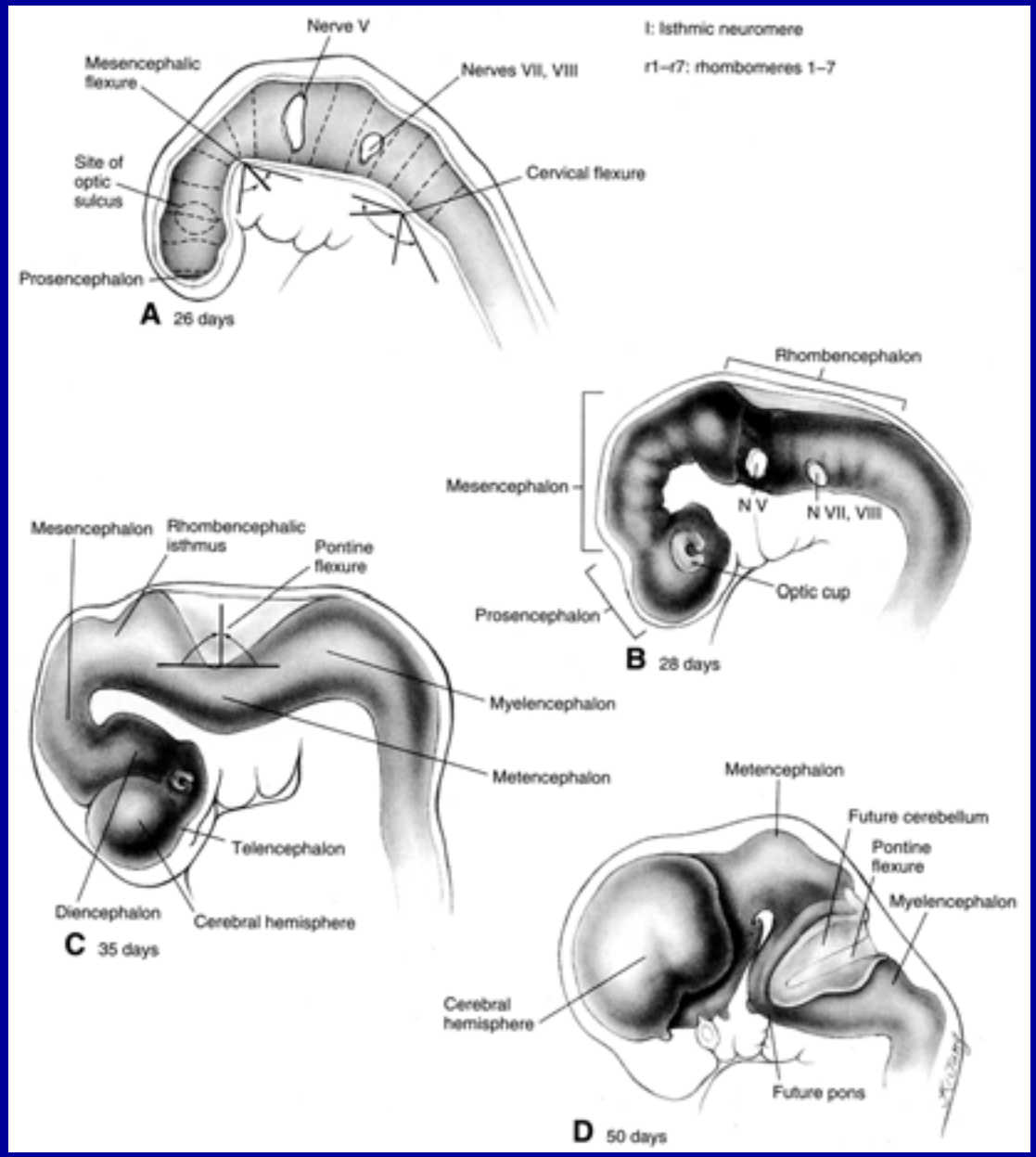
# Famous Teratogens

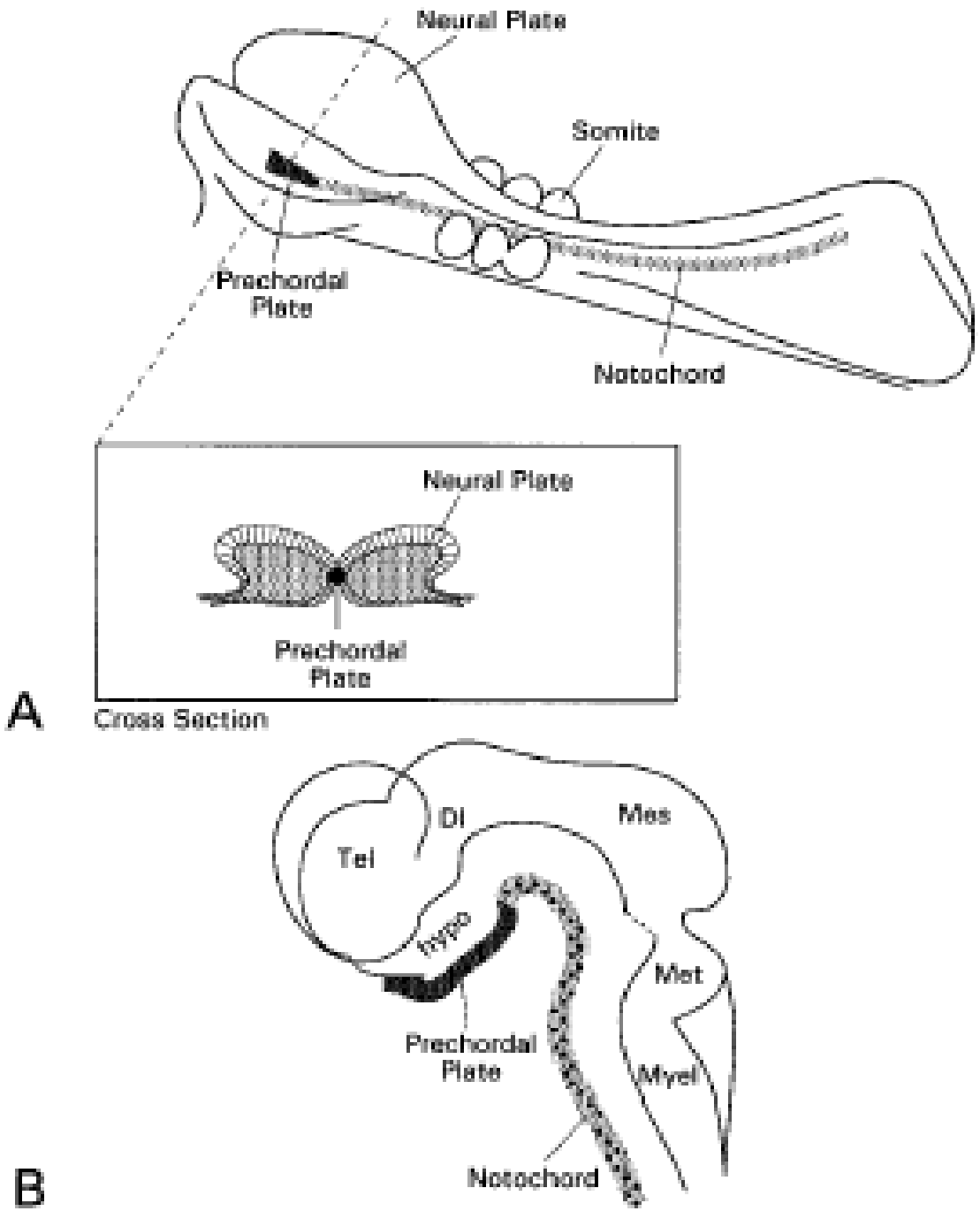
- Alcohol
- Cyclopamine

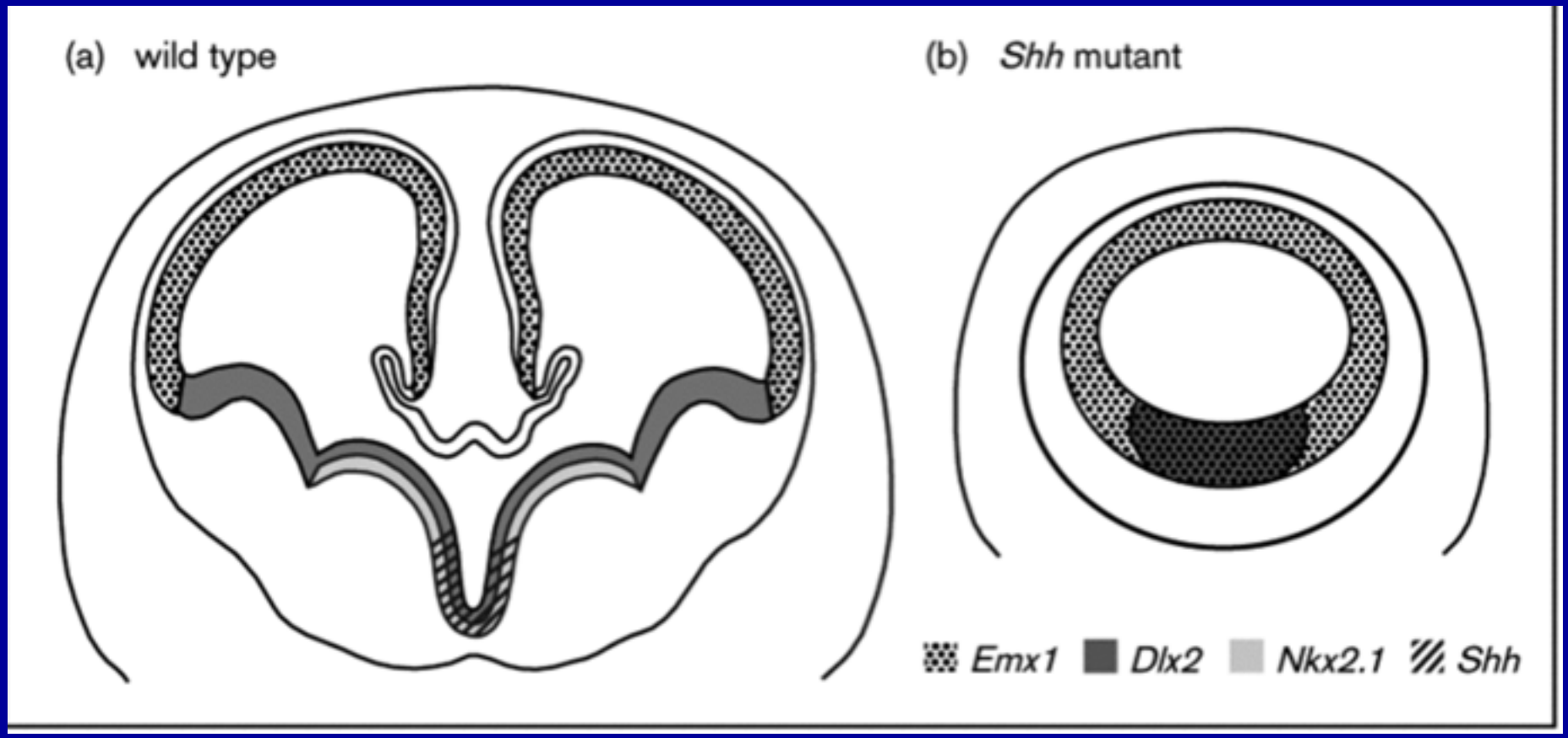
# HPE Genes

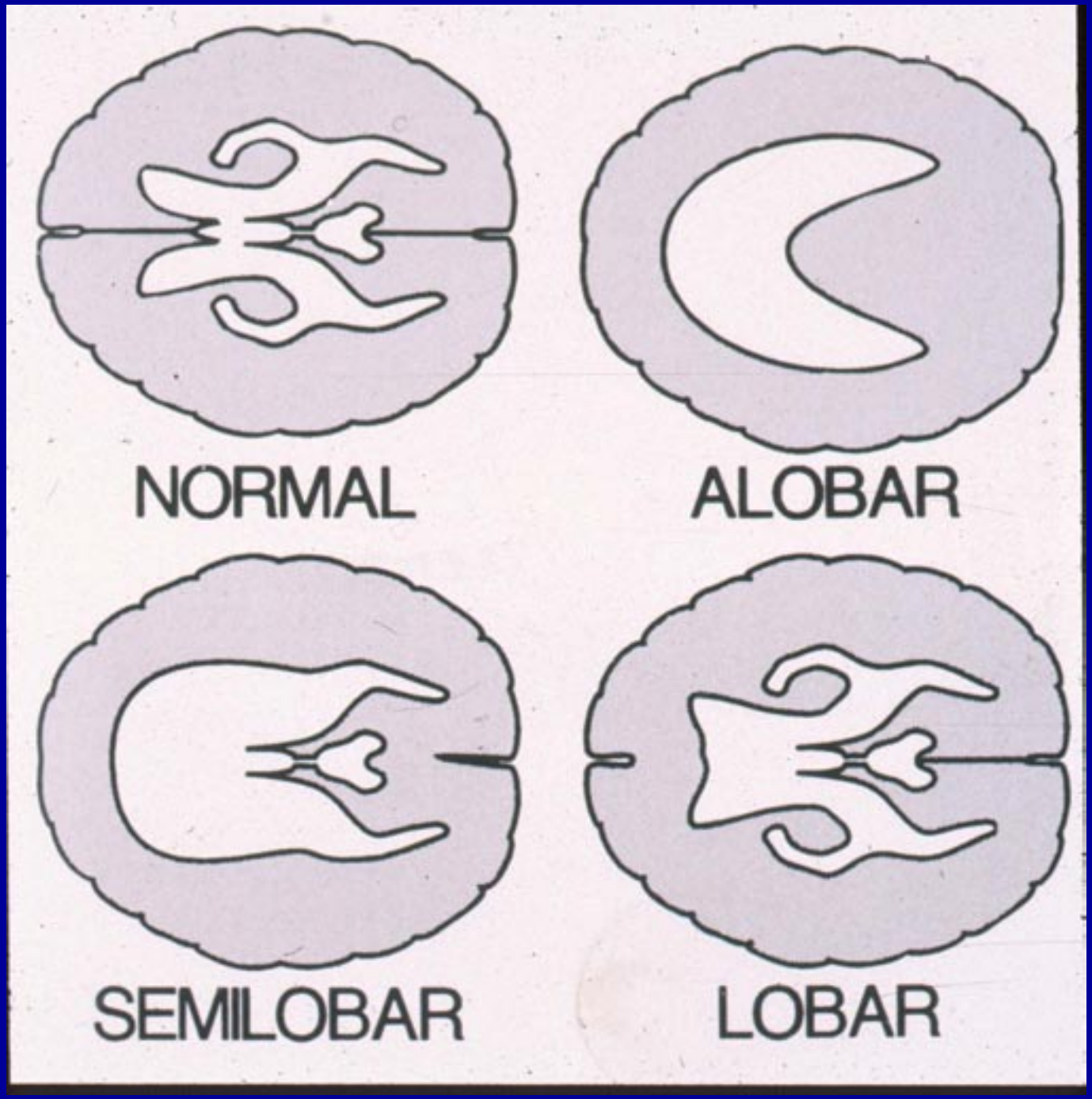
- Sonic Hedgehog (SHH); chromosome 7
- ZIC2  (chromosome 13q32)
- SIX3; chromosome 2
- TGIF, chromosome 18
- Others

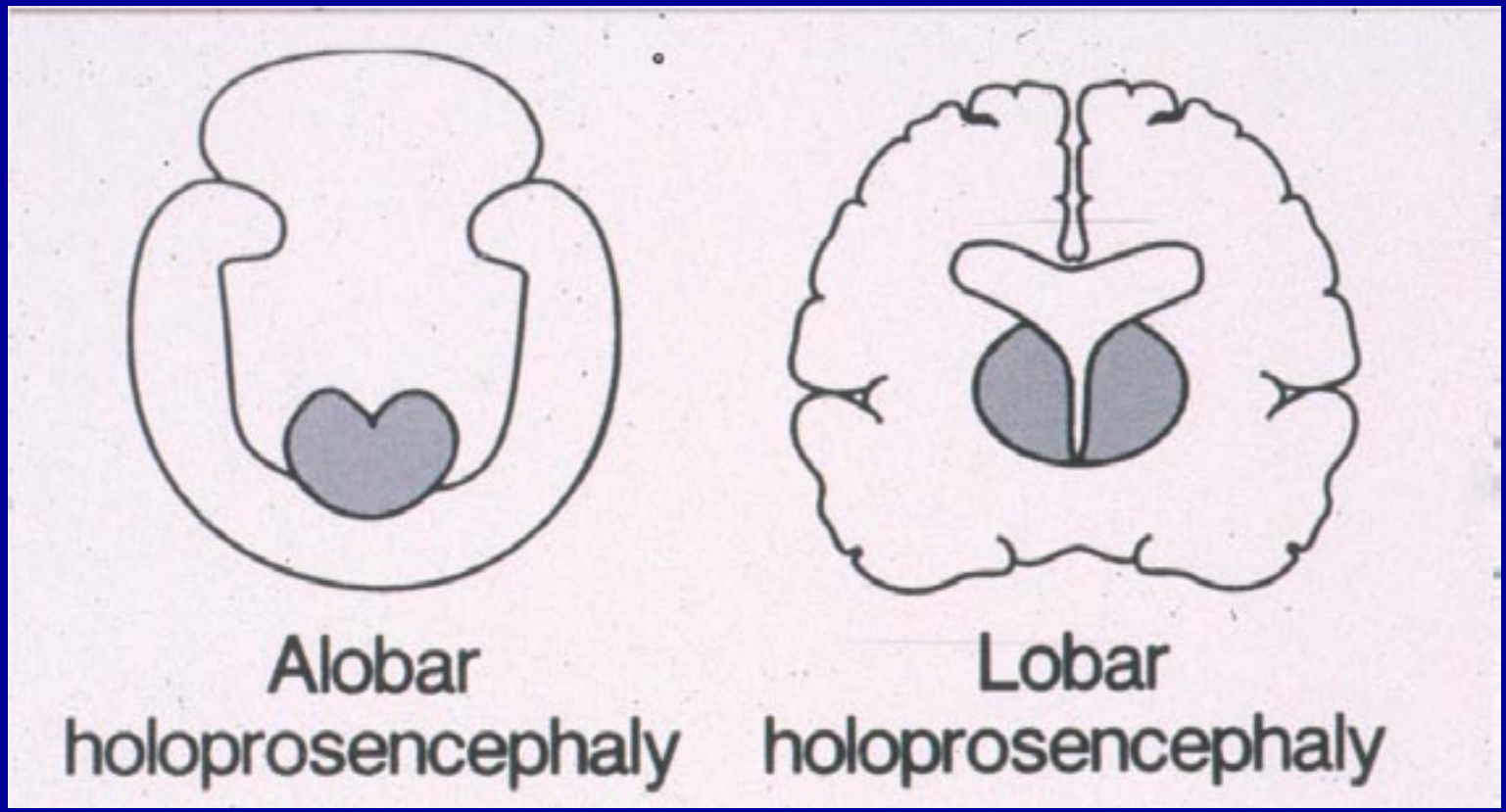

3 Primary Vesicles
5 Secondary Vesicles
Adult Derivatives of
Walls
Cavities
Wall
Cavity
Prosencephalon
Mesencephalon
Rhombencephalon
Telencephalon
Diencephalon
Mesencephalon
Metencephalon
Myelencephalon
Cerebral Hemispheres
Lateral Ventricles
Thalami, etc.
Third Ventricle
Midbrain
Aqueduct
Pons
Cerebellum
Upper Part
Medulla
Lower Part
of Fourth Ventricle
Spinal Cord

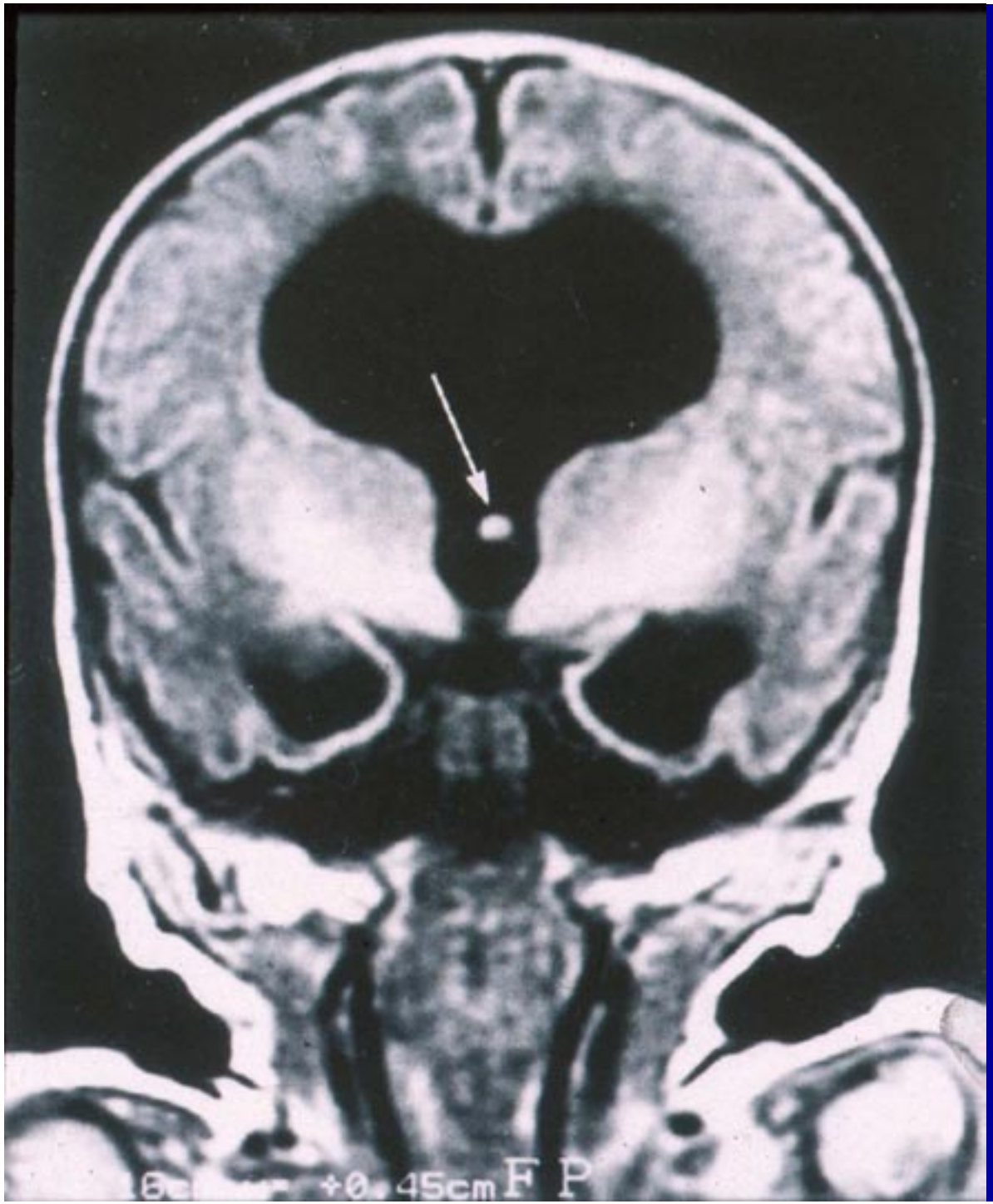

Nerve V
I: Isthmic neuromere
Mesencephalic flexure
Nerves VII, VIII
r1–r7: rhombomeres 1–7
Site of optic sulcus
Cervical flexure
Prosencephalon
A 26 days
Rhombencephalon
Mesencephalon
N V
N VII, VIII
Optic cup
Prosencephalon
B 28 days
Mesencephalon
Rhombencephalic isthmus
Pontine flexure
Myelencephalon
Metencephalon
Telencephalon
Diencephalon
Cerebral hemisphere
C 35 days
Metencephalon
Future cerebellum
Pontine flexure
Myelencephalon
Cerebral hemisphere
Future pons
D 50 days


Neural Plate
Somite
Prechordal Plate
Notochord
Neural Plate
Prechordal Plate
A
Cross Section
Tel
Di
Mes
Hypo
Met
Myel
Prechordal Plate
Notochord
B

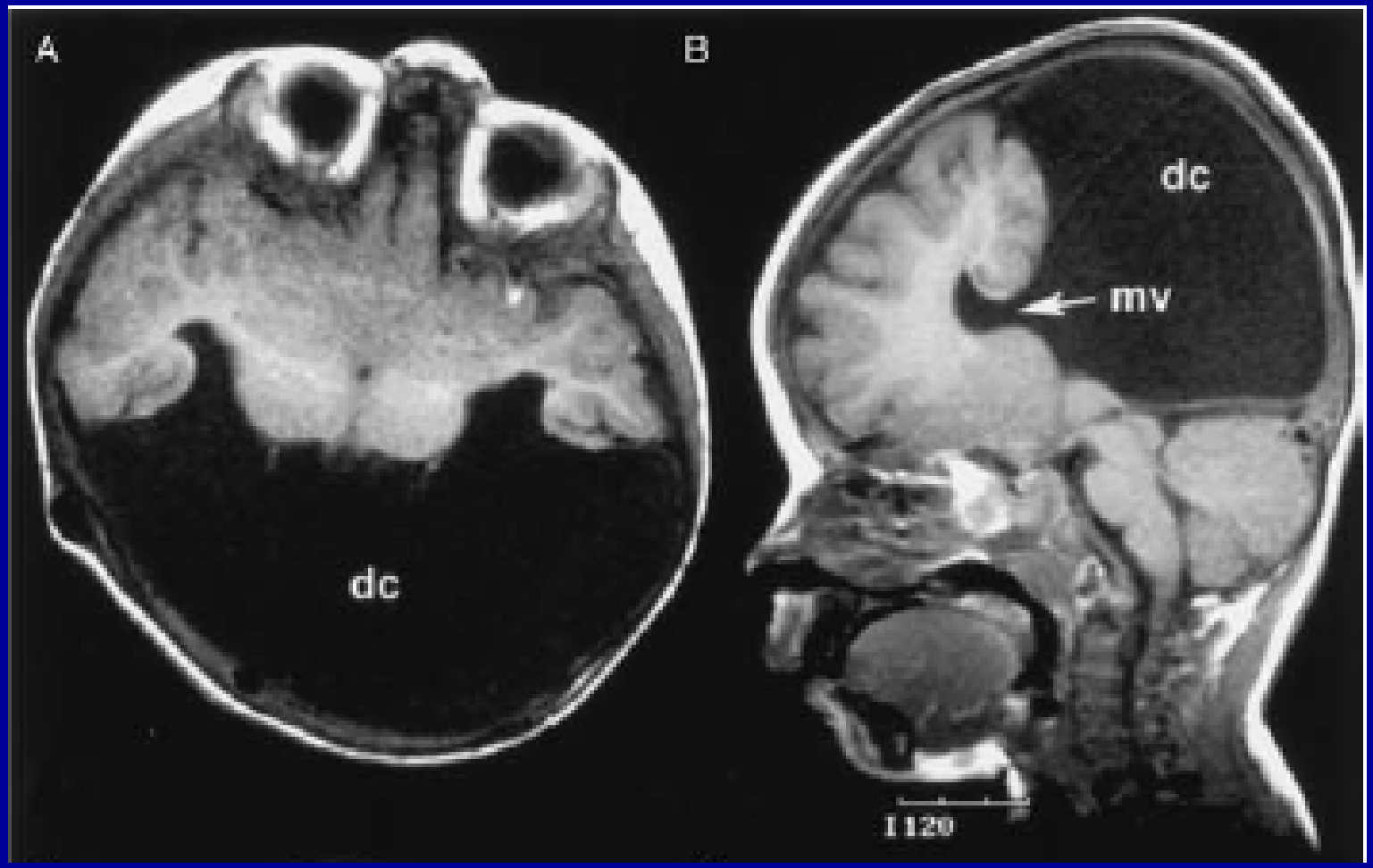

(a) wild type
(b) Shh mutant
Emx1
Dlx2
Nkx2.1
Shh


NORMAL
ALOBAR
SEMILOBAR
LOBAR

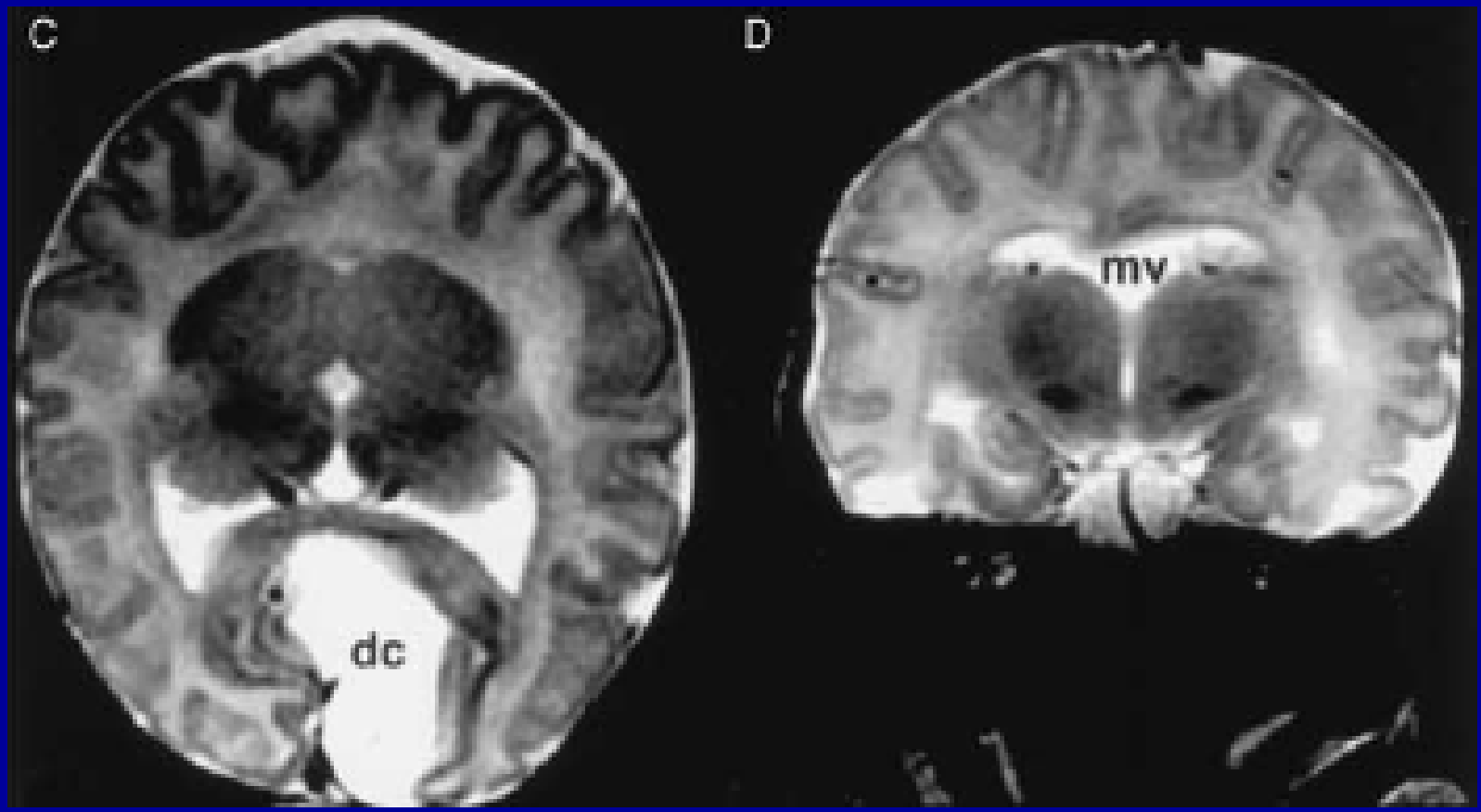

Alobar
holoprosencephaly
Lobar
holoprosencephaly


+0.45cm F P

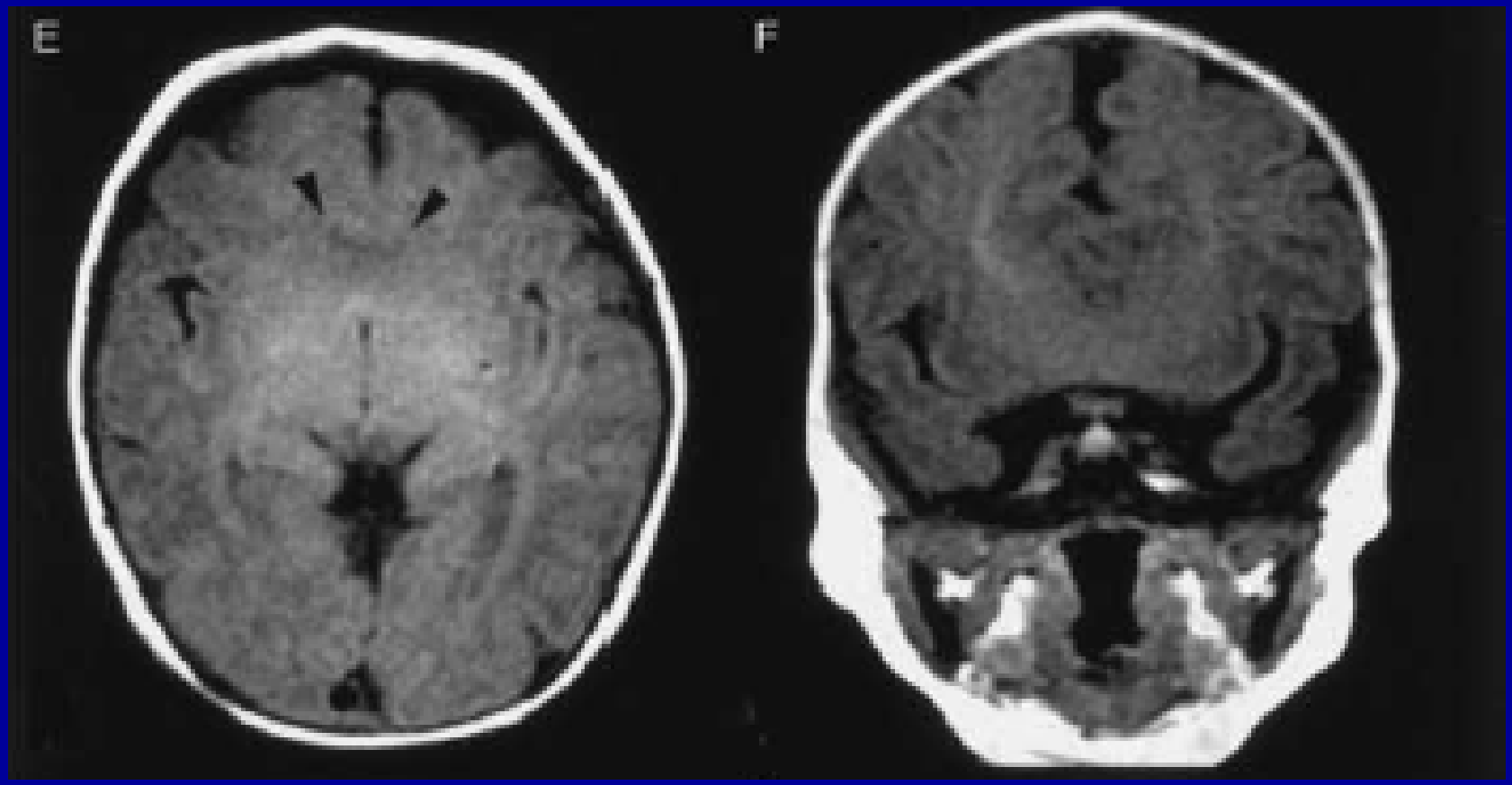
Alobar HPE. (A) lack of separation of the two hemispheres. Large dorsal cyst (dc) posteriorly. (B) reveals a midline ventricle, a monoventricle (mv), that communicates posteriorly with the dorsal cyst (dc).

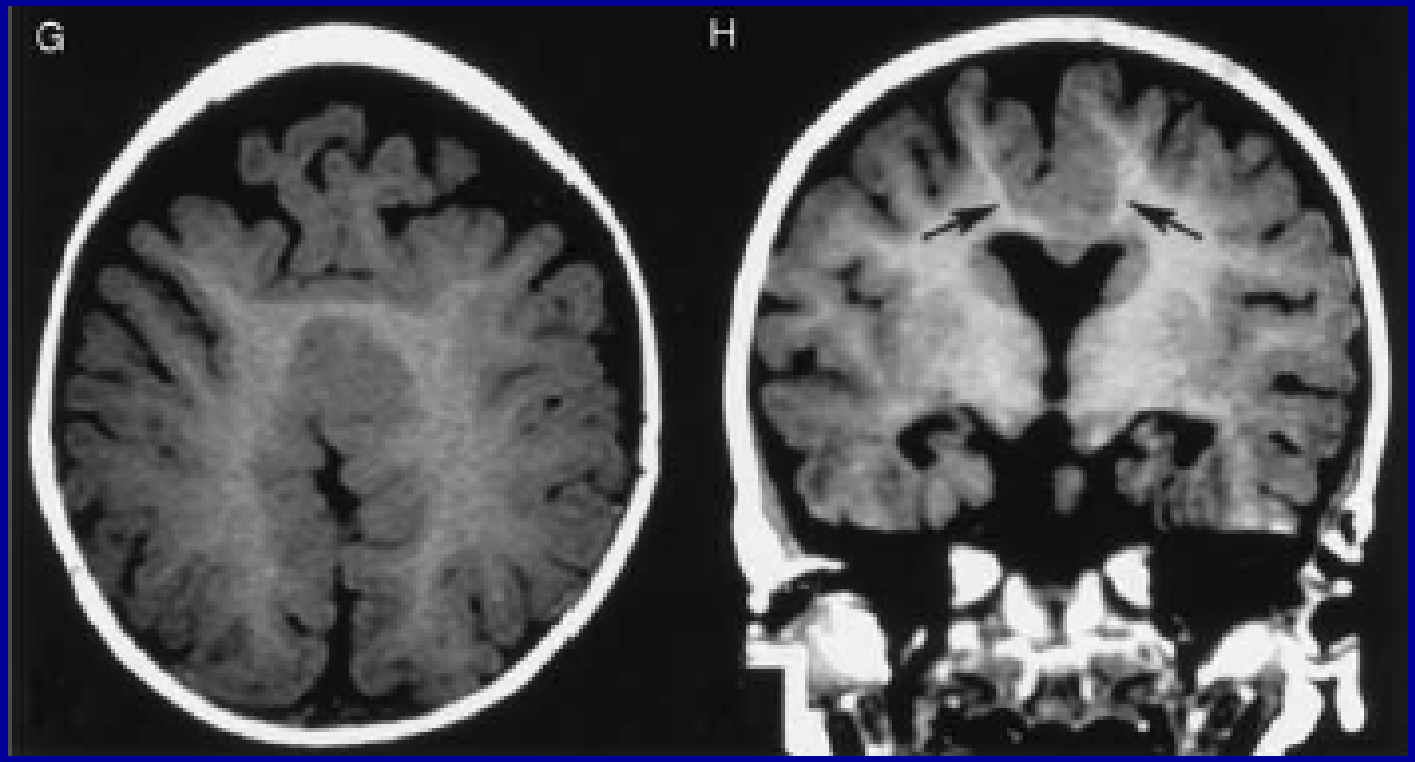


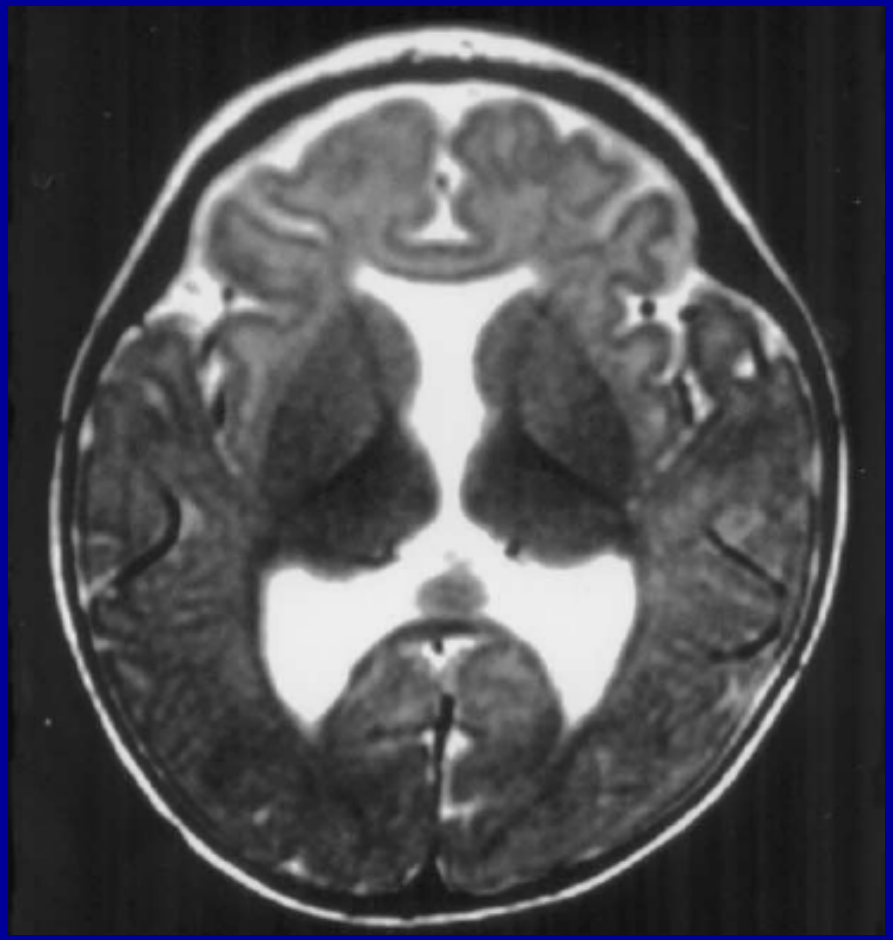
Semilobar HPE. (C) separation of the hemispheres posteriorly but not anteriorly. There is incomplete separation of the basal ganglia. (D) reveals a lack of interhemispheric fissure and a monoventricle (mv)

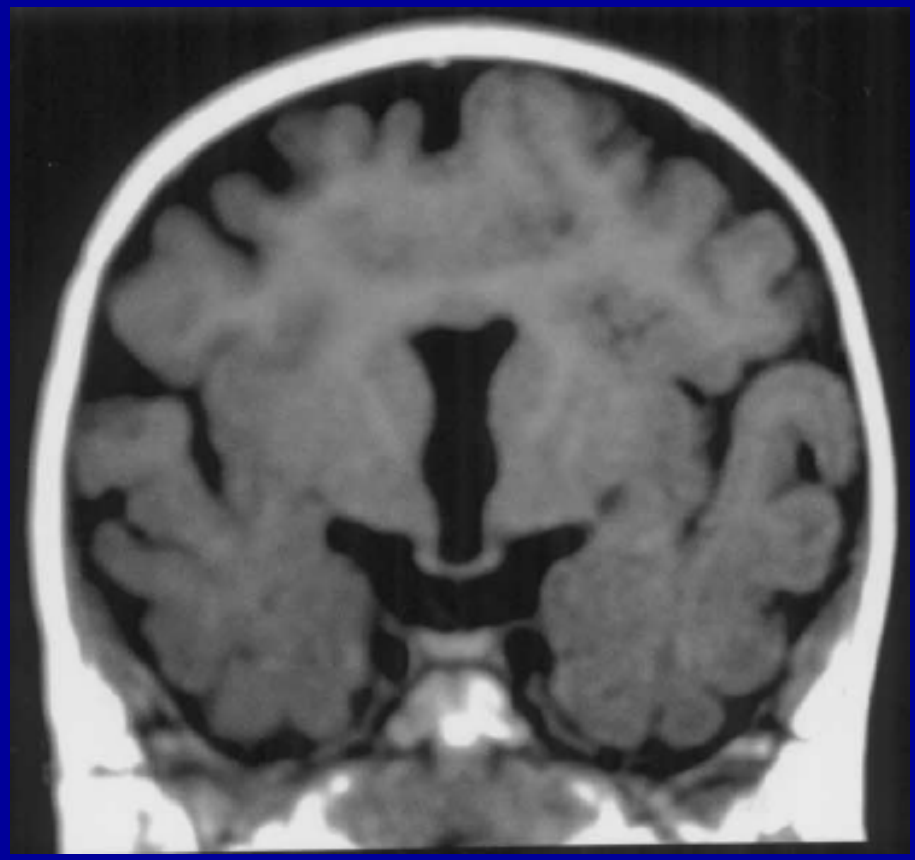


Lobar HPE. (E) reveals that two hemispheres are separated by an interhemispheric fissure both anteriorly and posteriorly. (F) documents incomplete separation of the inferior frontal lobes near the midline.




G
H





# 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.

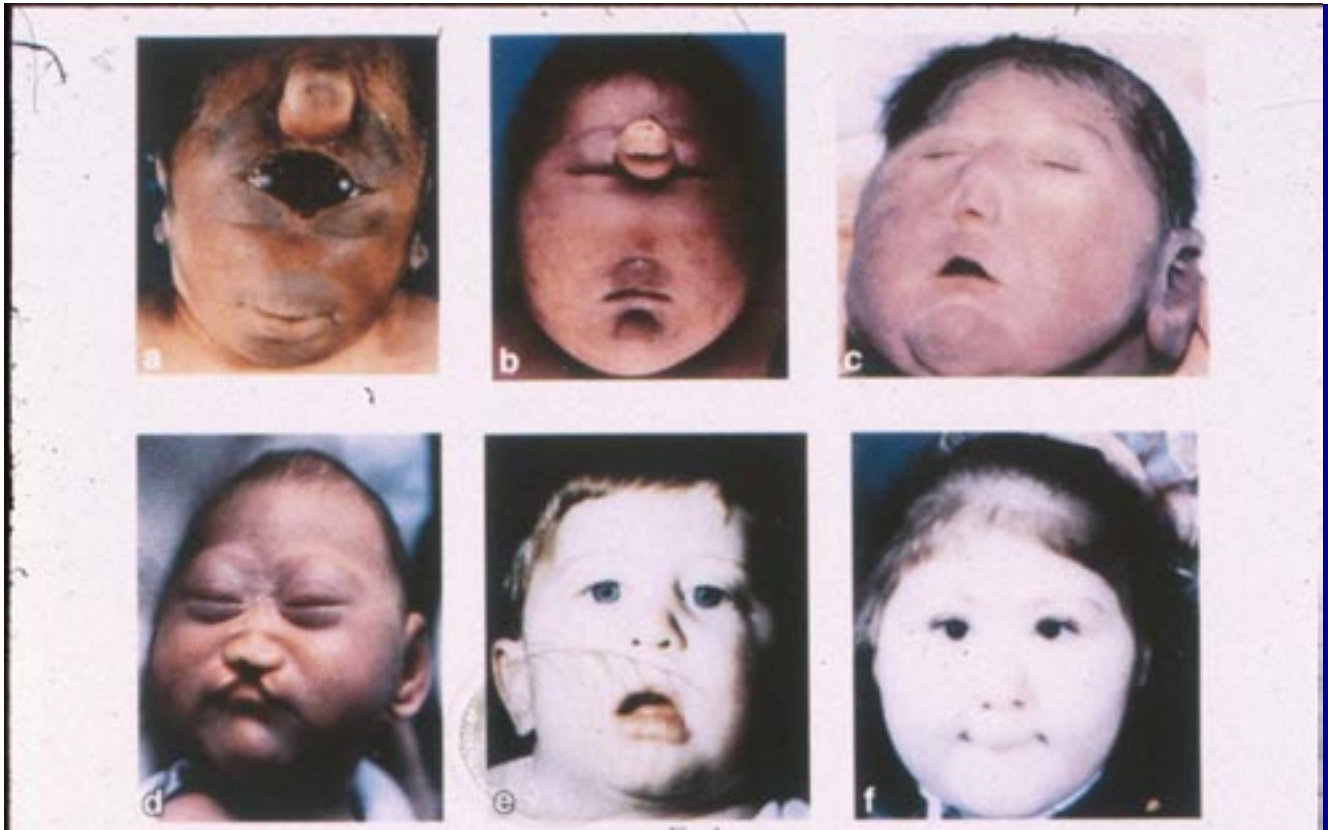



Fig. 1

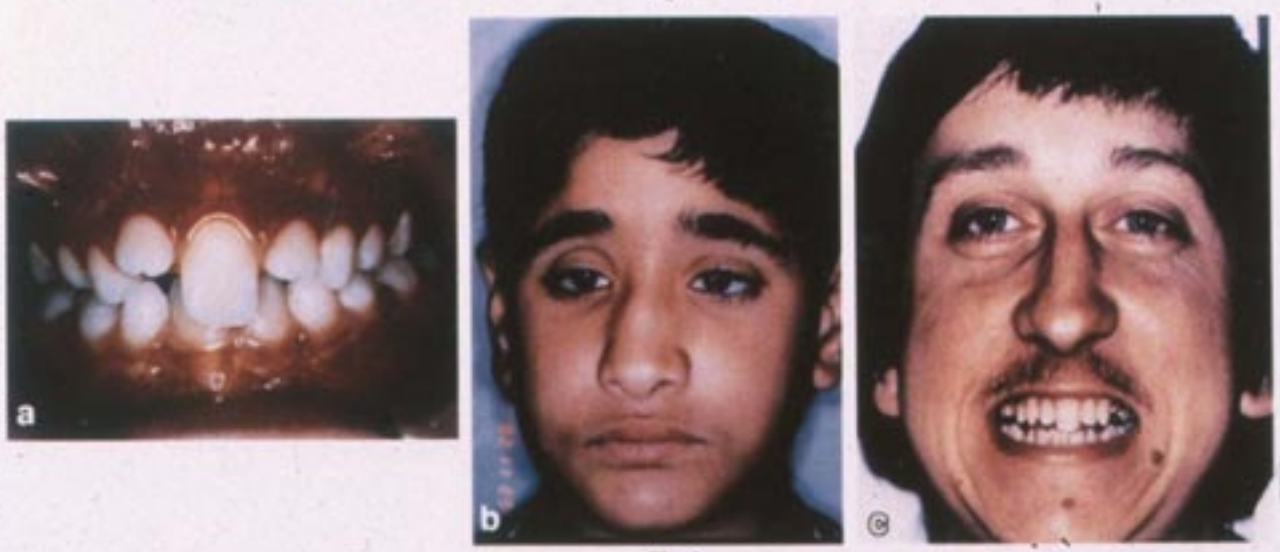
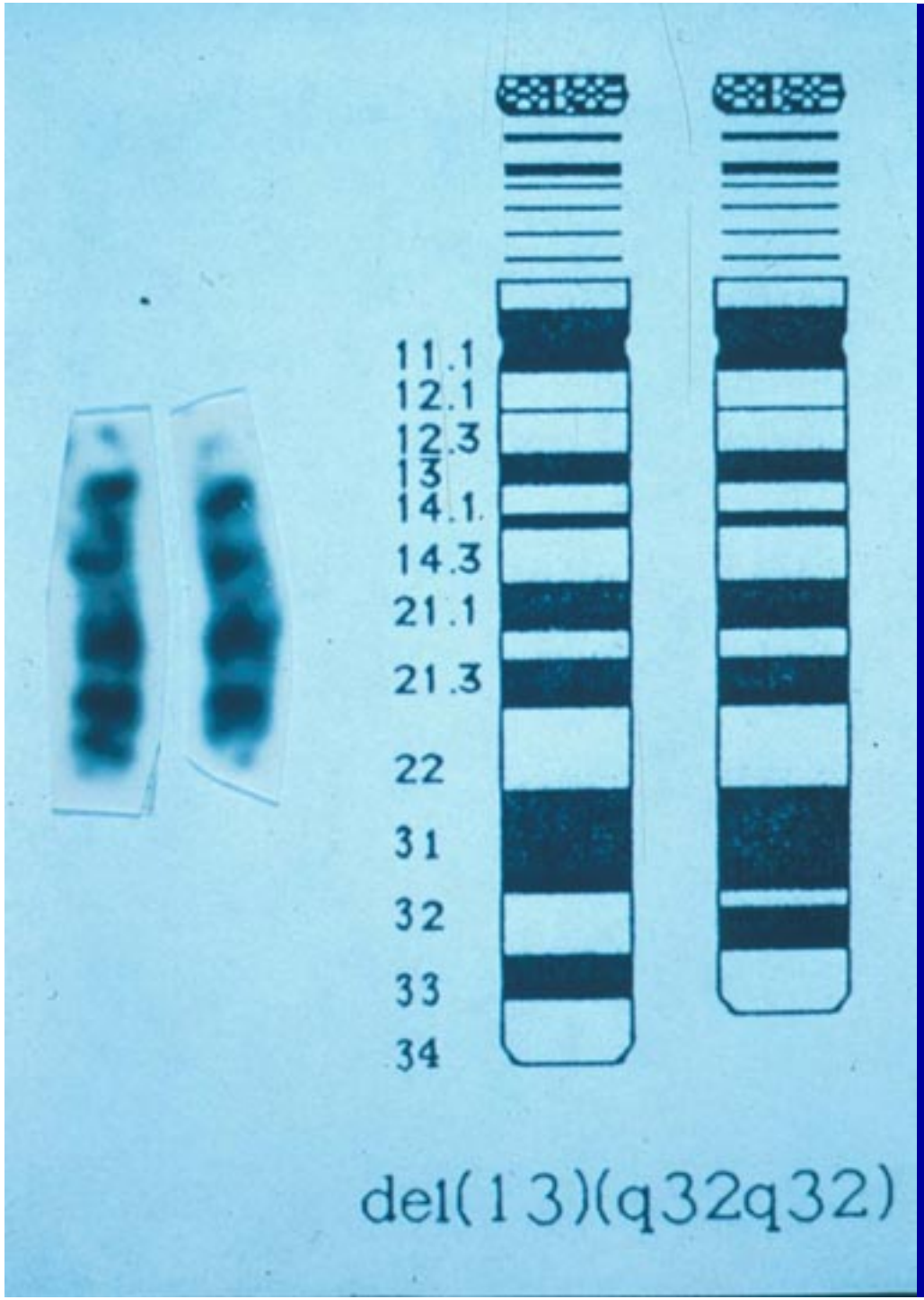
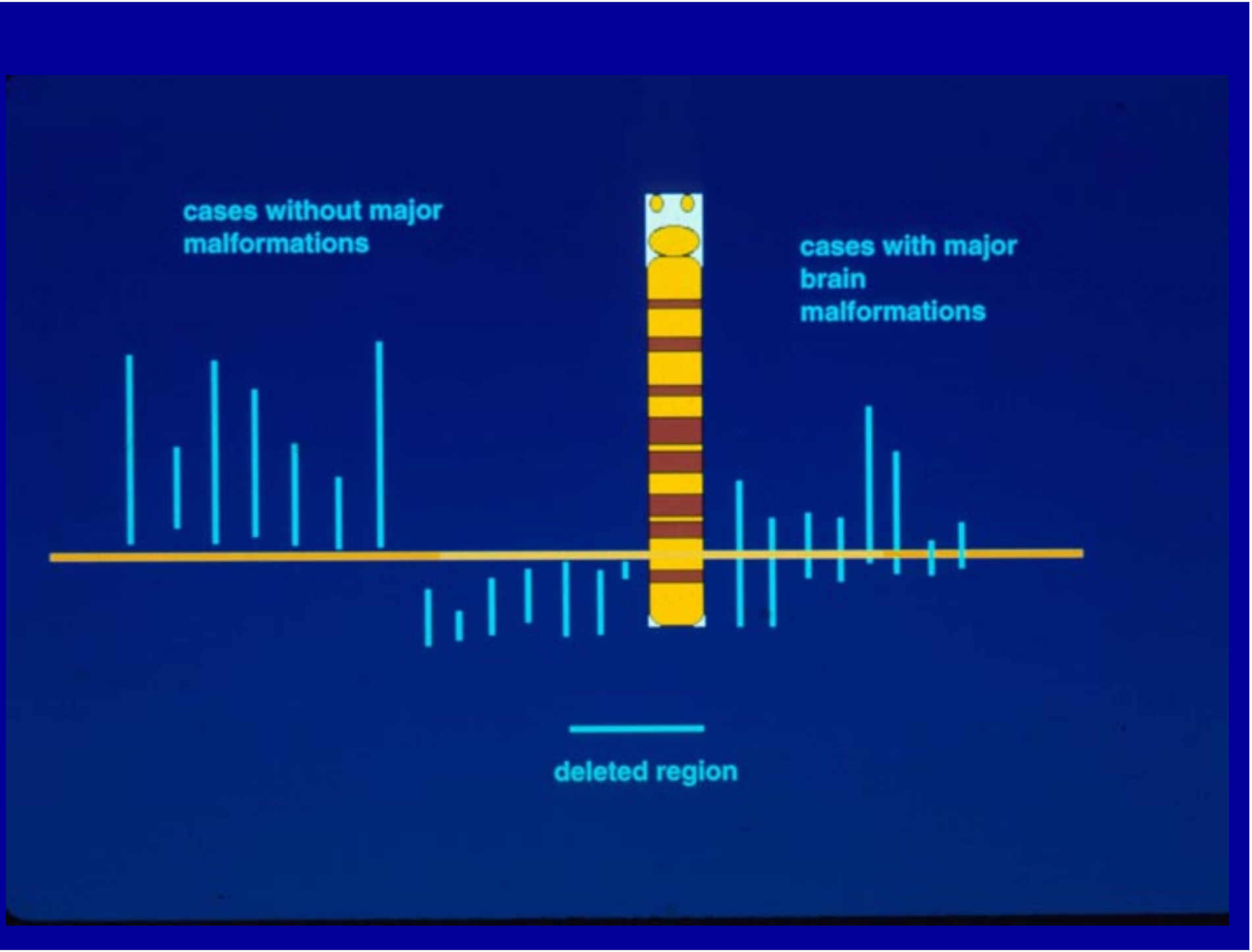
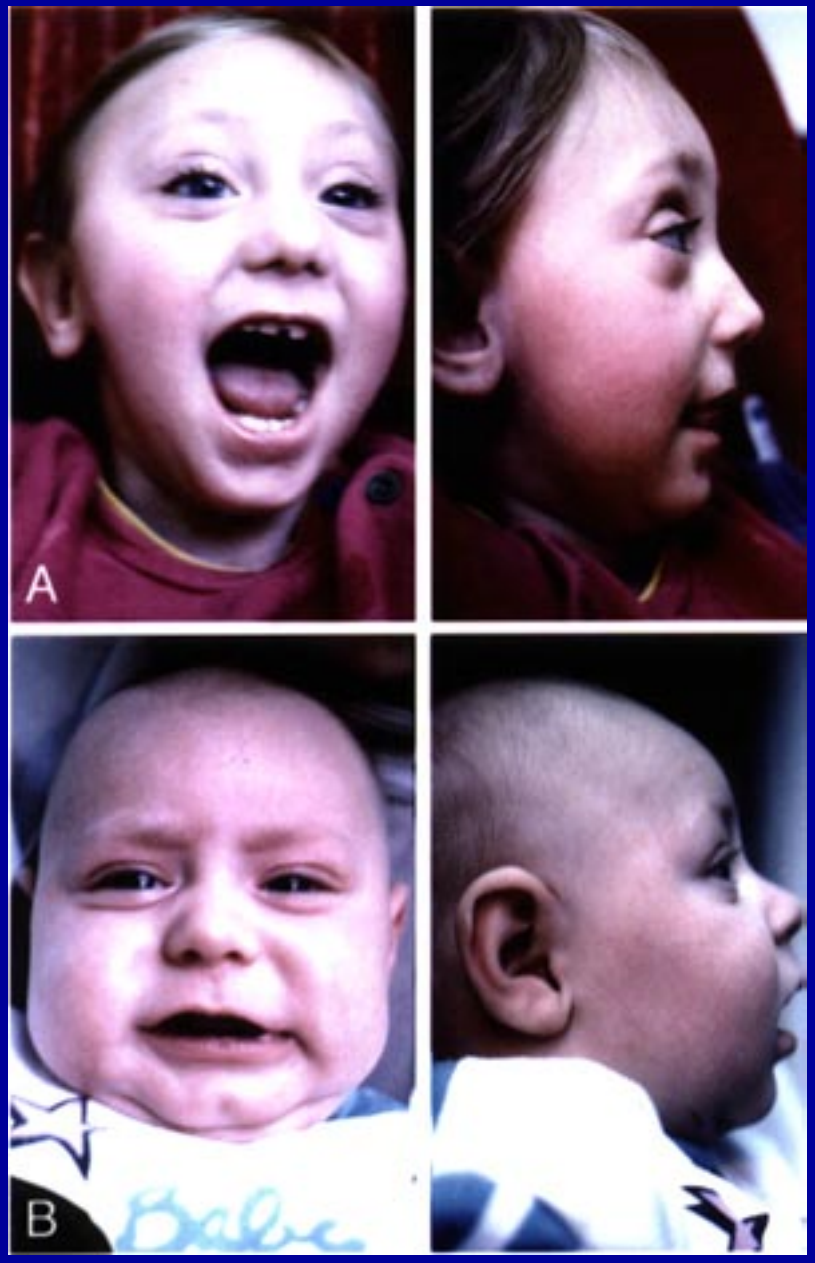



Fig. 2

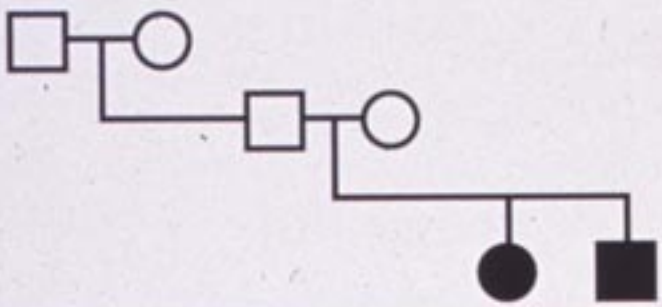


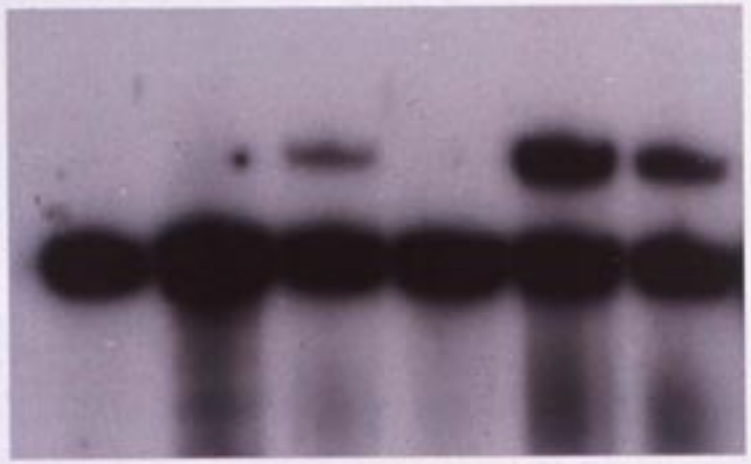

**13q32 deletion in a fetus in which HPE was the only malformation.**

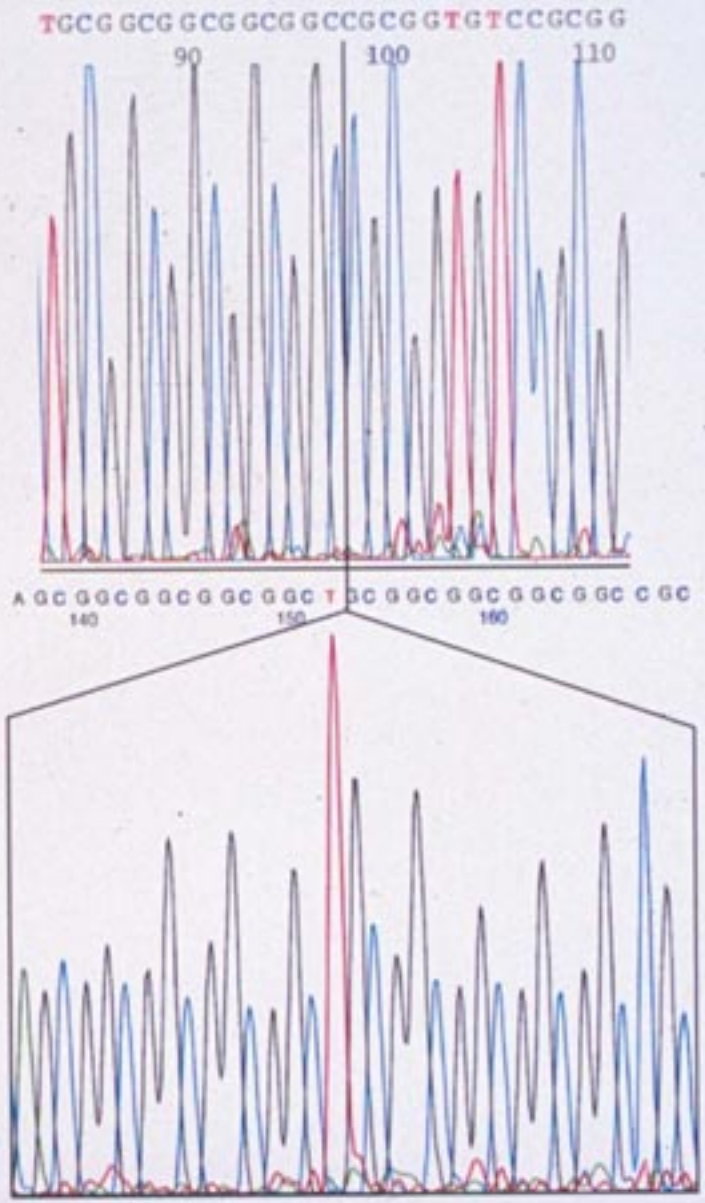

cases without major malformations
cases with major brain malformations
deleted region

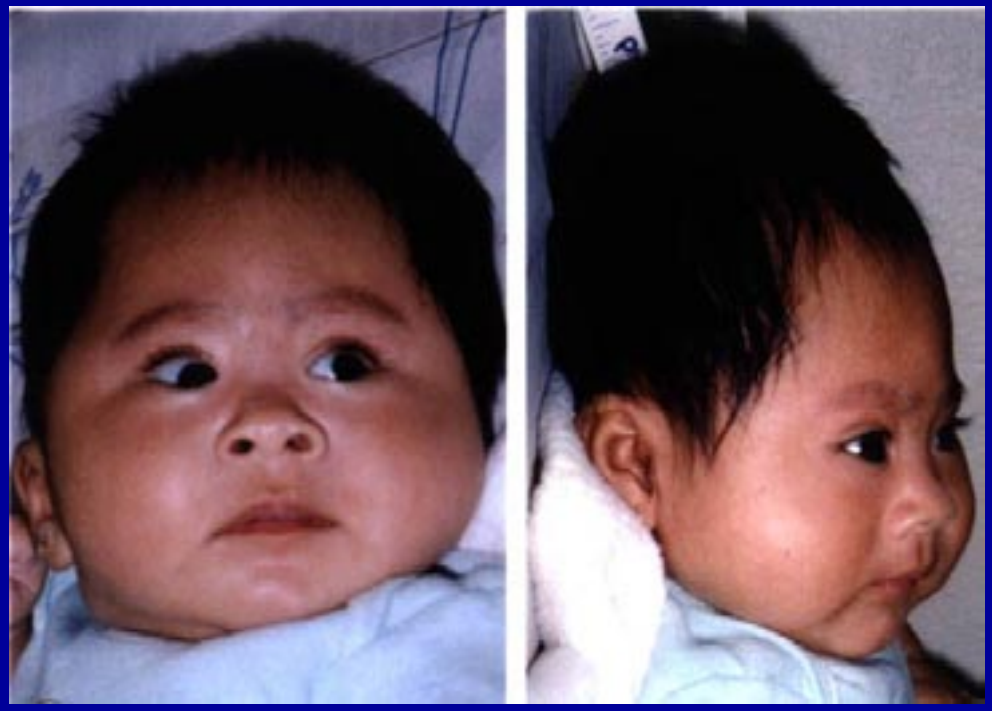


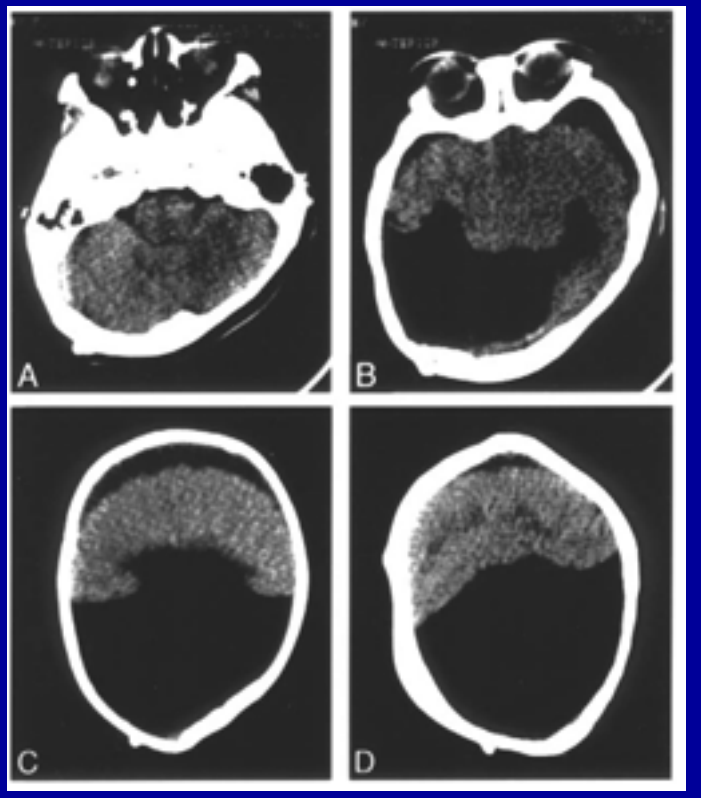

Alobar HPE and alanine tract expansion in 2 sibs. Father is a mosaic carrier of the mutation.



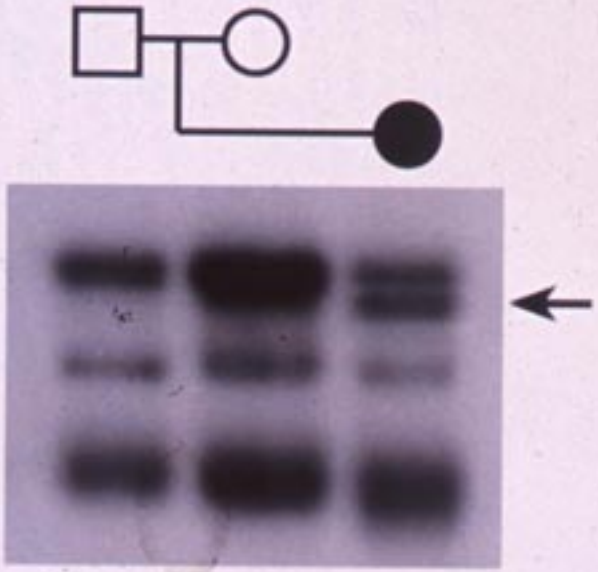


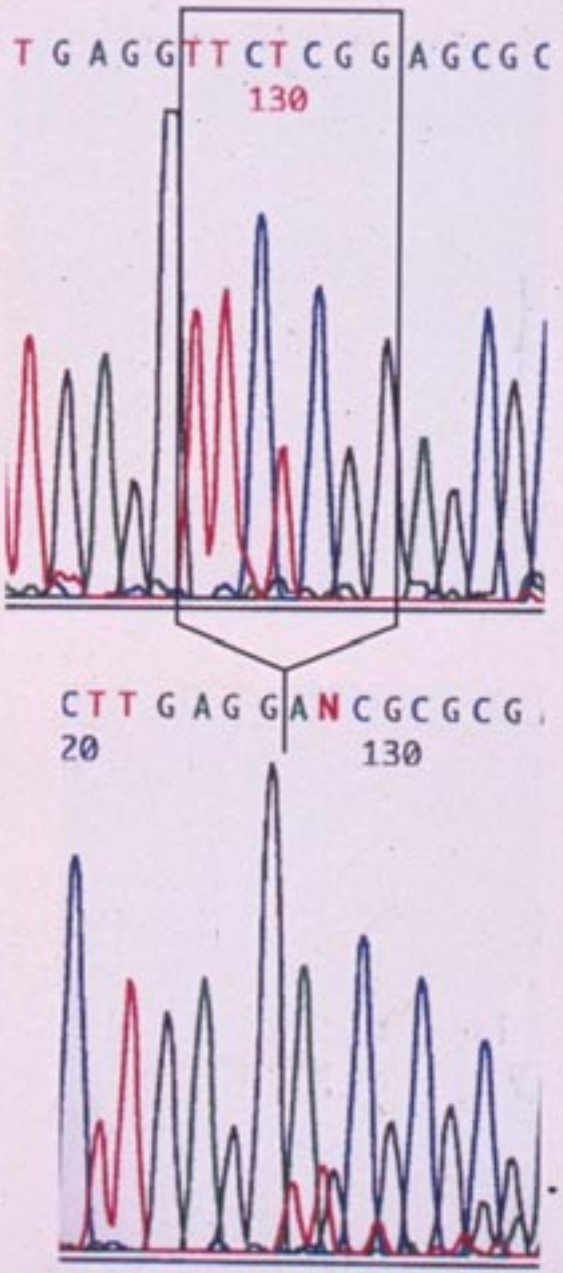

TGCG GCG GCG GCG GCCGCG GTGTCCGCGG
90
100
110
A GC GGC G GC G GC G GC T GC G GC G GC G GC G GC C GC
140
150
160

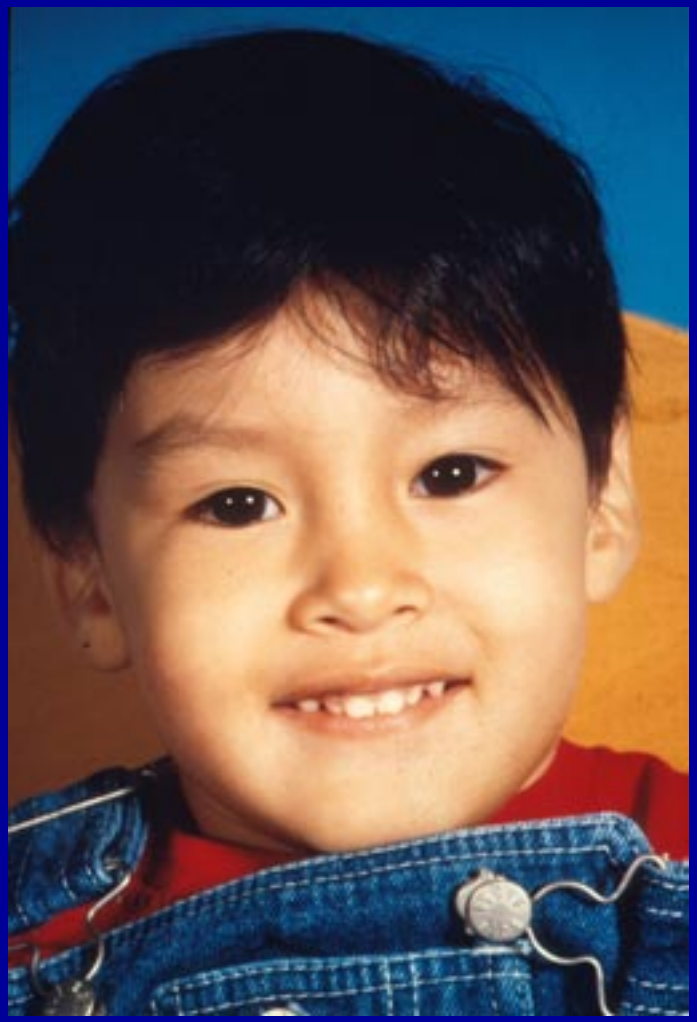


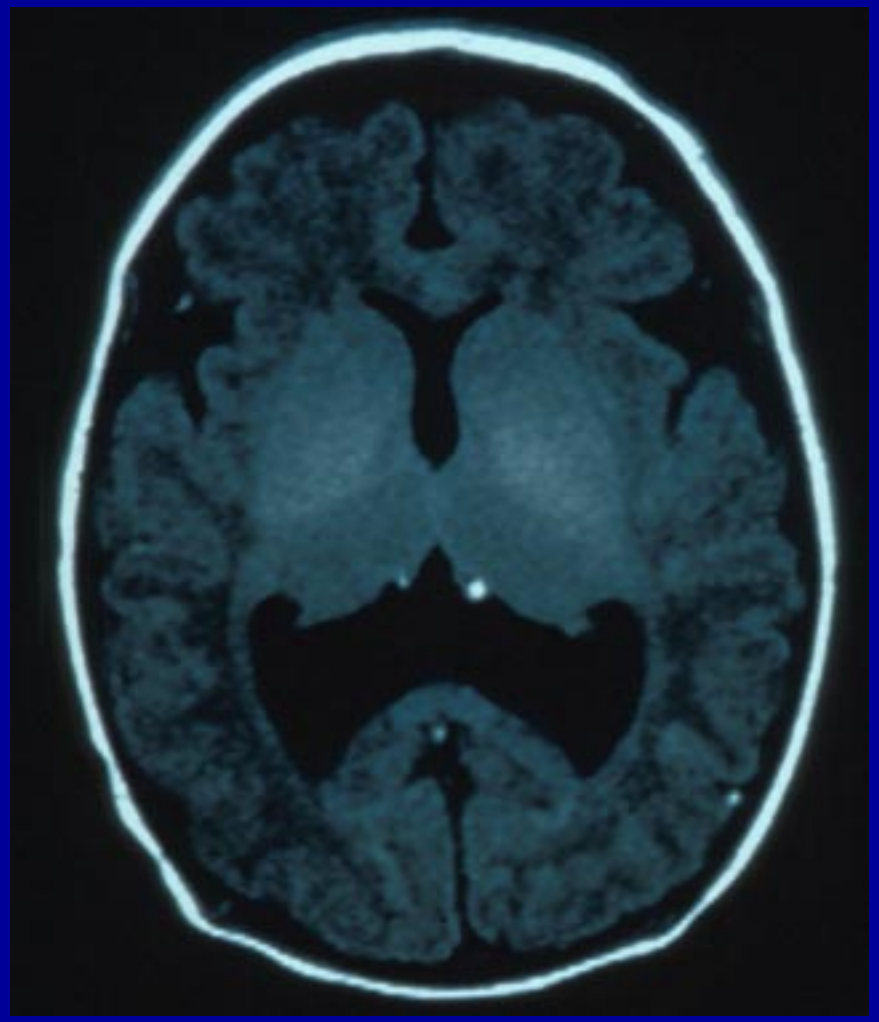



De-novo 7 BP deletion in zinc finger region. Alobar HPE.

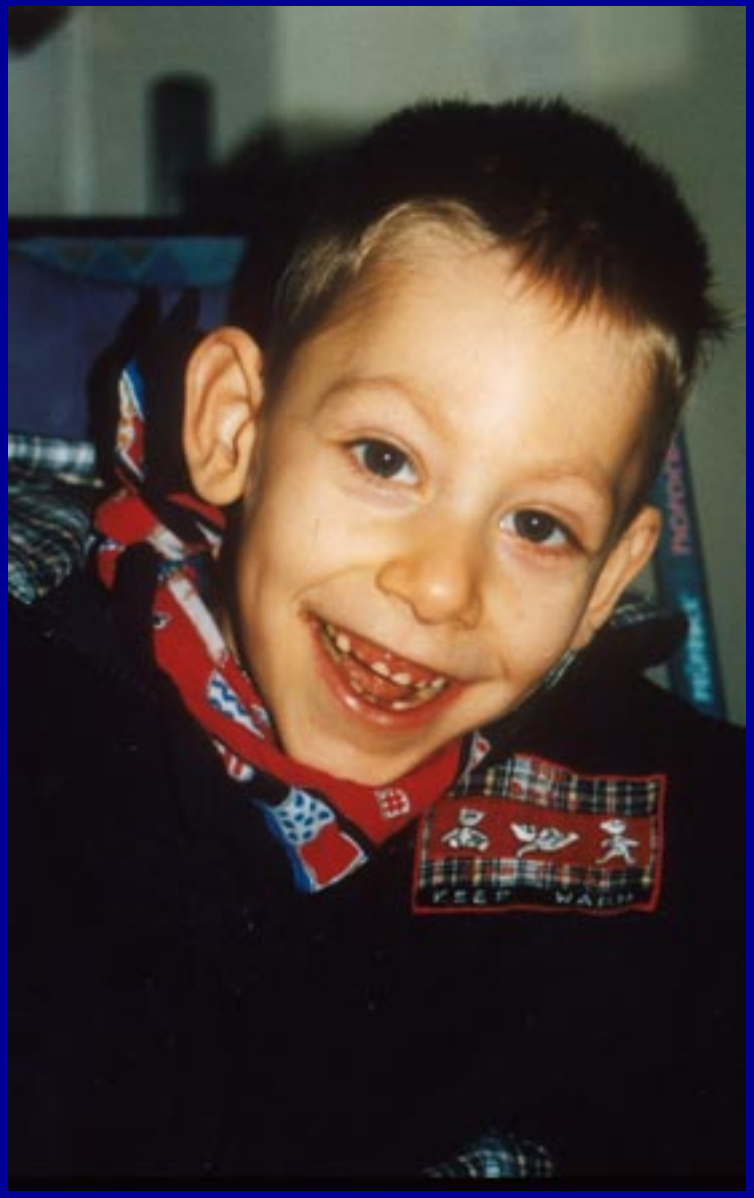



T G A G G T T C T C G G A G C G C
130
C T T G A G G A N C G C G C G
20
130

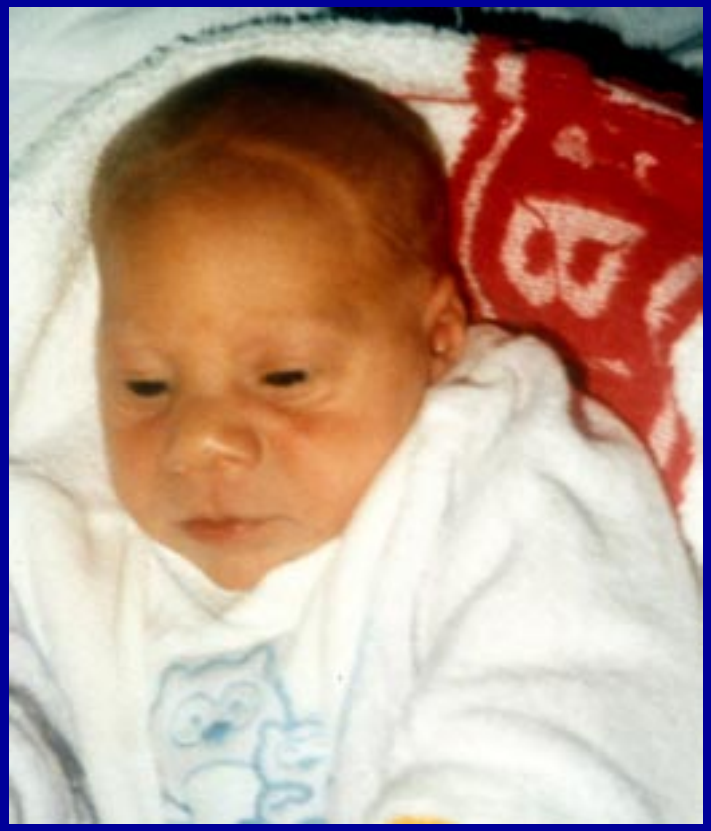




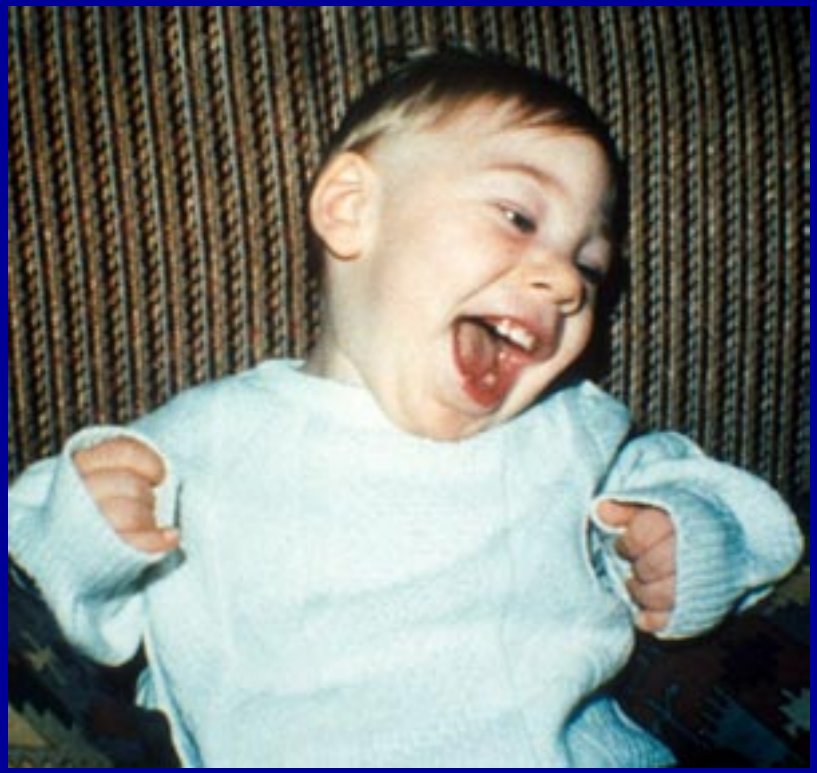
12 AA in frame deletion near carboxy terminus.
Interhemispheric fusion defect.



De-novo alanine tract expansion.
Semi-lobar HPE

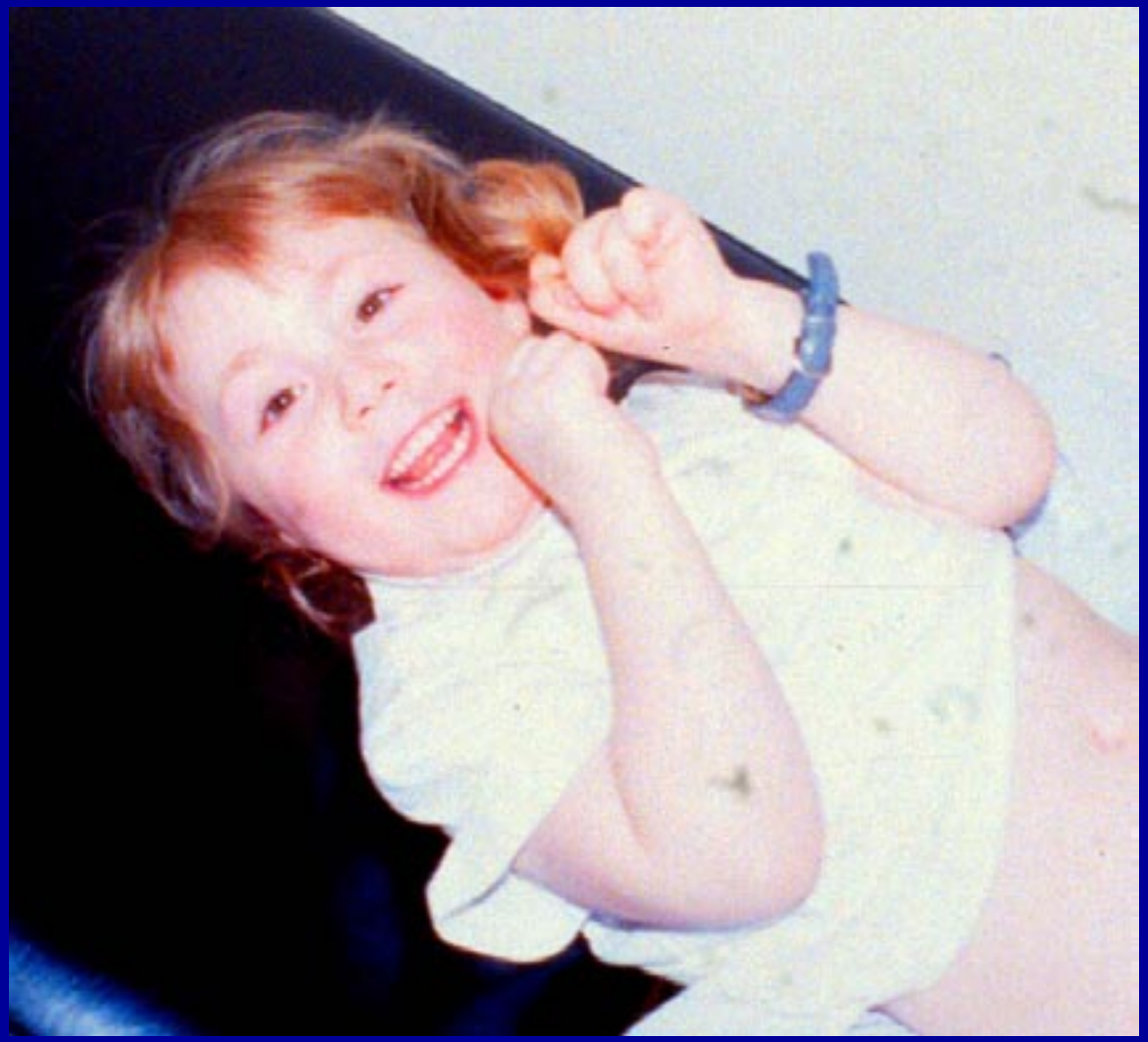


Birth

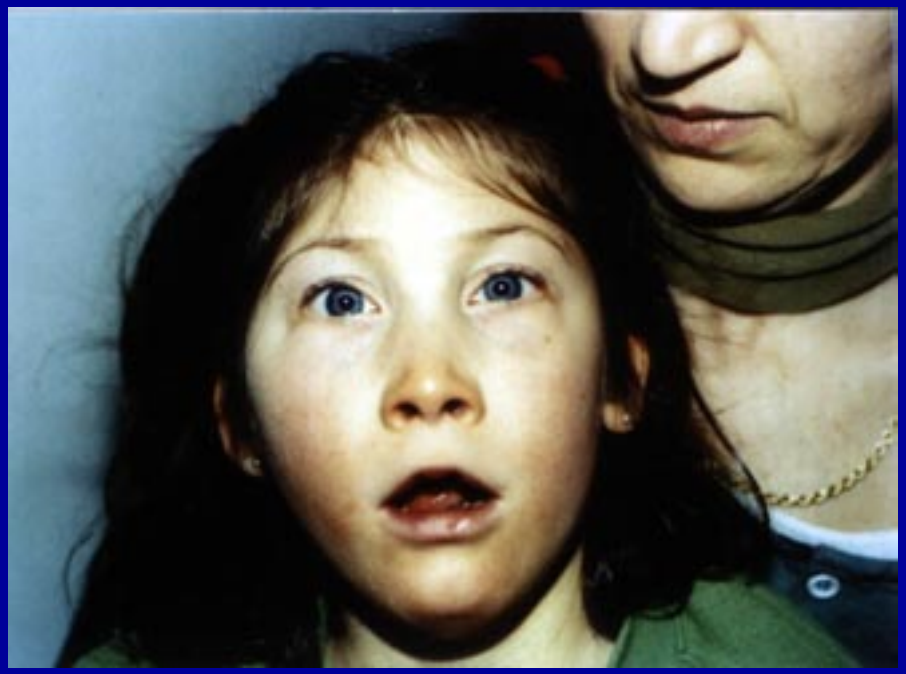


21 Months

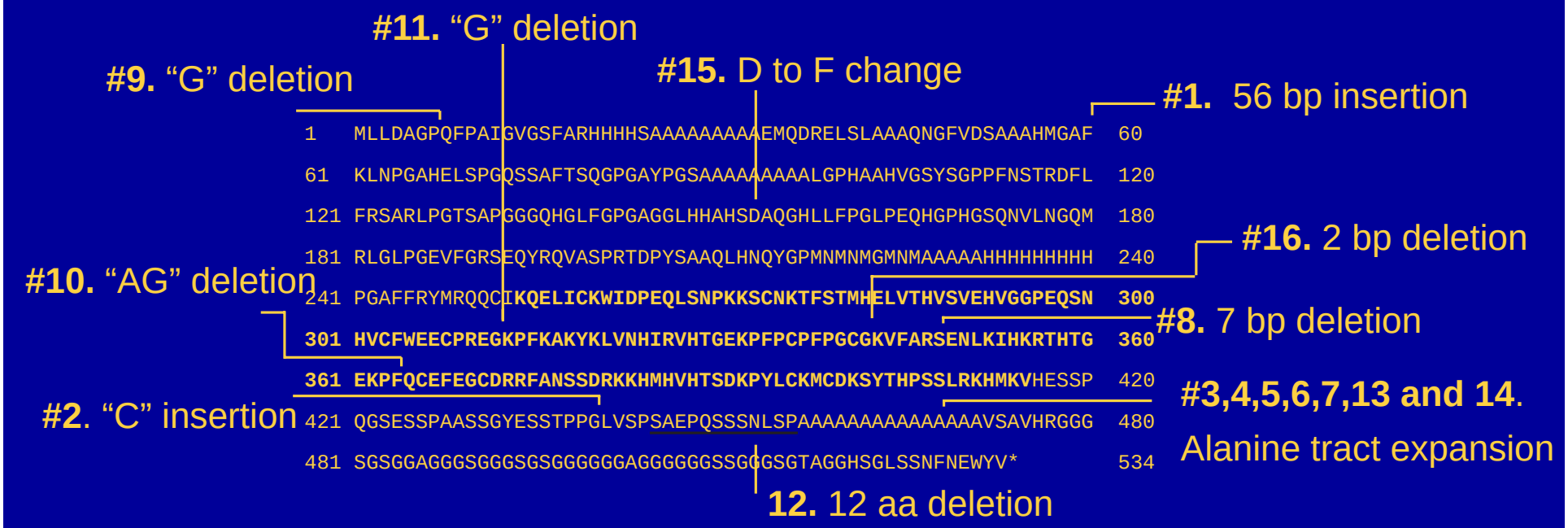
De-novo 2 base deletion at AA 365. Stop at 366. Semi-lobar HPE.



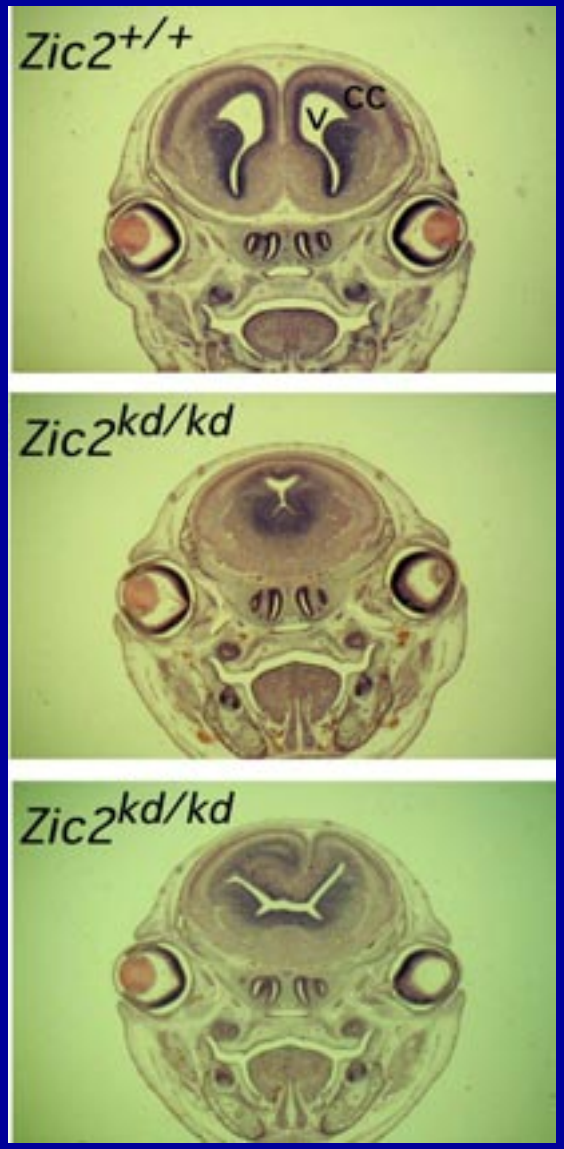
Aspartic acid to Phenylalanine change caused by 2 base change. Lobar HPE. Inherited from mother who is normal except for hypotelorism.



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




**Amino acid sequence of ZIC2 with summary of HPE associated mutations. Numbers refer to the table of mutation patients. Bold type indicates the zinc finger region of the protein.**




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

From Nagai et al., PNAS, March 2000