Holoprosencephaly
Syntelencephaly
DISP1

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« Genetics of Development Related Pathologies »
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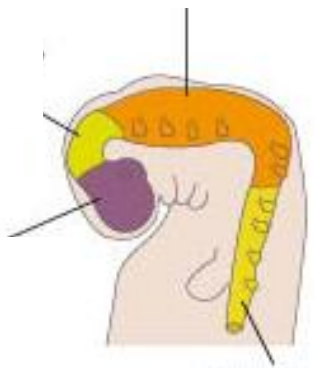
Holoprosencephaly and midline defects

Holoprosencephaly (HPE):

- Incomplete cleavage of the forebrain
  - Between the 18th and 28th day of gestation
- Craniofacial and eye defects



Genetic Factors: *SHH signaling deficiency*

French cohort = unique

French National Reference Center
> 2000 Patients
Lab diagnosis (University Hospital)

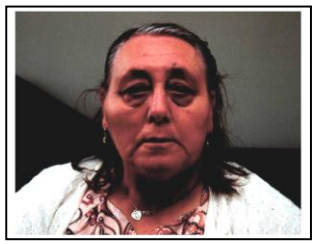
Experts:
Clinical diagnosis (Pr Sylvie Odent)
Molecular diagnosis (Dr Christele Dubourg)
Bioinformatics (Dr Marie De Tayrac)
Functional studies (Dr Valérie Dupé)

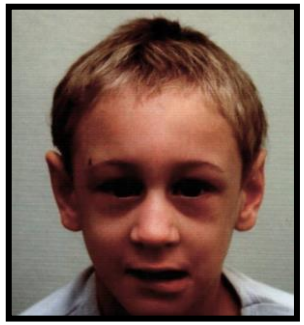
CENTRE DE REFERENCE
Anomalies du développement
et syndromes malformatifs

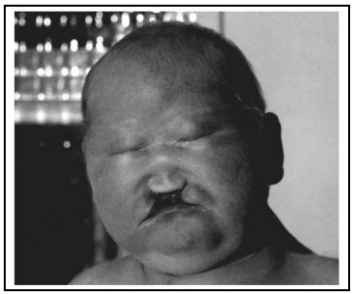
CHU Rennes

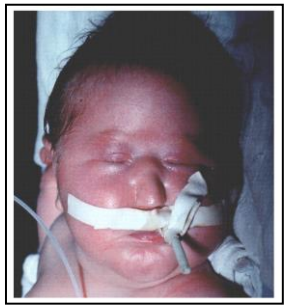
SHH: familial midline defects

p.(Tyr158*)









Odent et al. 1999

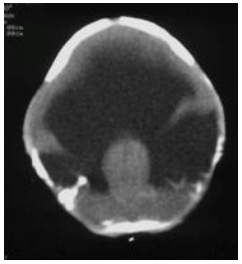
Arhinia

Alobar **HPE**

Growth failure, microcephaly, **hypotelorism**, mild ID, single median incisor, corpus callosum dysgenesis

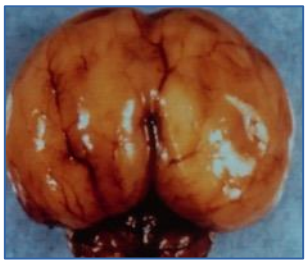
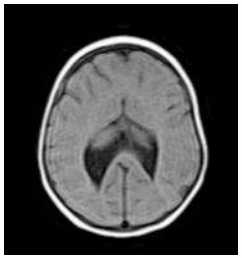
Growth failure, microcephaly (-7DS), choanal stenosis, pituitary hypoplasia

Brain, Facial and Eye anomalies

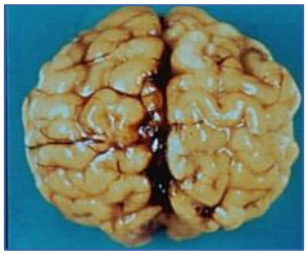
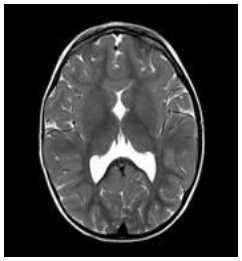
Alobar HPE

unique ventricule

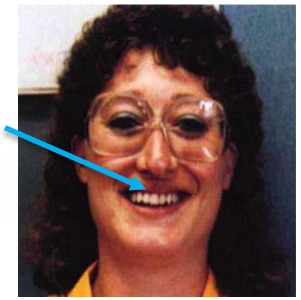
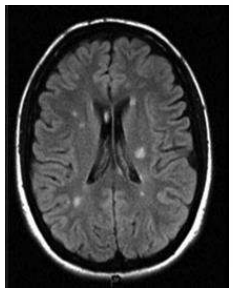
Semilobar HPE

incomplete interhemispheric scissure

Lobar HPE

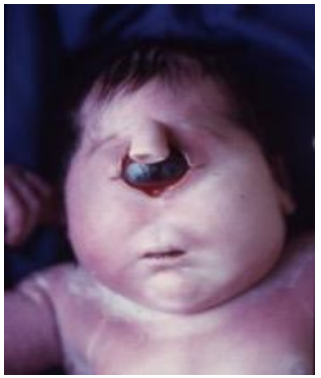
complete scissure non-separation of frontal cortex on the midline

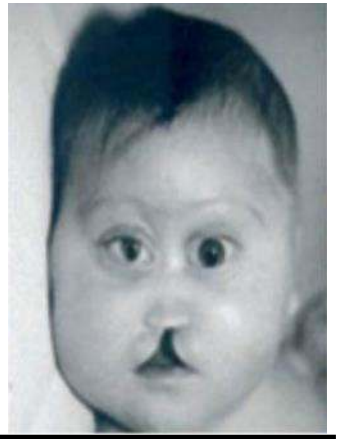
Microform

Complete separation of cortex

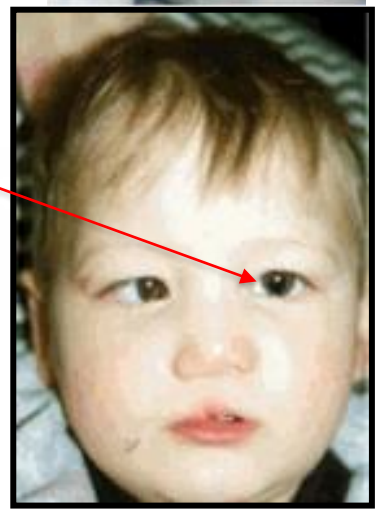
Facial anomalies : **cyclopia**, proboscis



Facial anomalies : **hypotelorism, microphtalmia,** cleft lip and palate

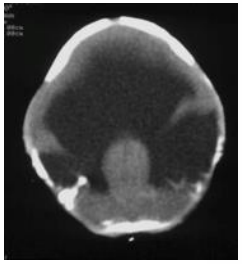


Facial anomalies : **coloboma** epicanthus single solitary median central incisor



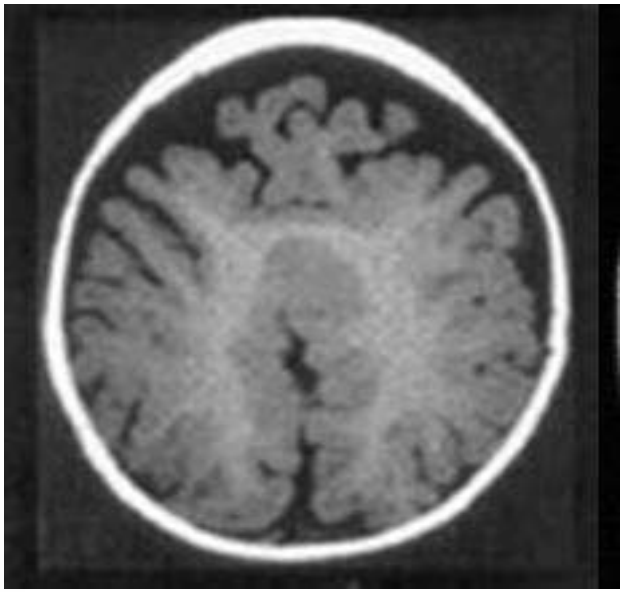
phenotypic heterogeneity

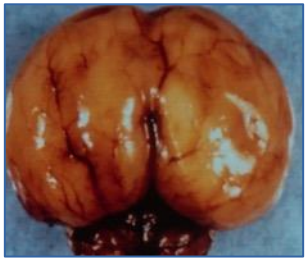
Syntelencephaly = Midline interhemispheric fusion (MIH)

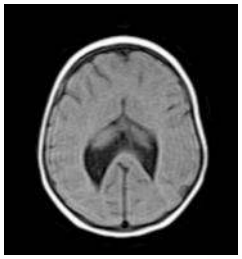


Alobar HPE

unique ventricule



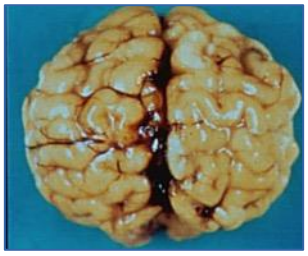


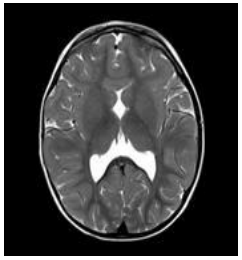


Semilobar HPE

incomplete

interhemispheric scissure

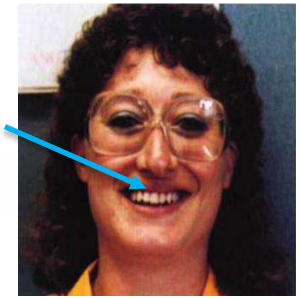


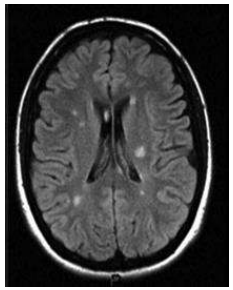


Lobar HPE

complete scissure

non-separation of frontal cortex on the midline





Microform

Complete separation of cortex

Syntelencephaly

hemispheric fusion does not occur at rostral forebrain but rather across posterior frontal region

Syntelencephaly = Midline interhemispheric fusion (MIH)

Syntelencephaly: MRI appearance

Axial T1-weighted inversion recovery (IR) sequence shows **absence of septum pellucidum with fusion of the cingulate gyrus** (white arrow) (A) and continuous white matter across middle part of interhemispheric region (B). Sagittal T1-weighted IR sequence (C) with **absence of midbody of corpus callosum** (black arrows) and presence of genu and splenium (white arrows).

Arundeep Arora et al. Neurology 2012;79:e86

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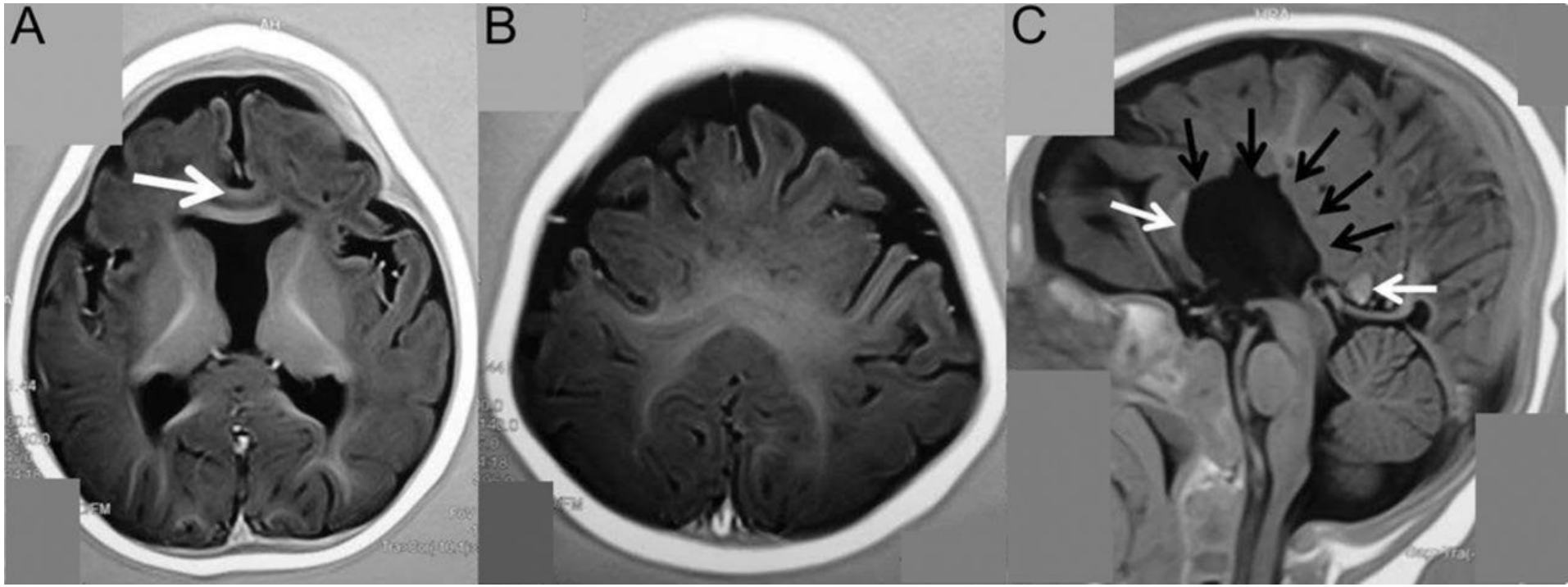
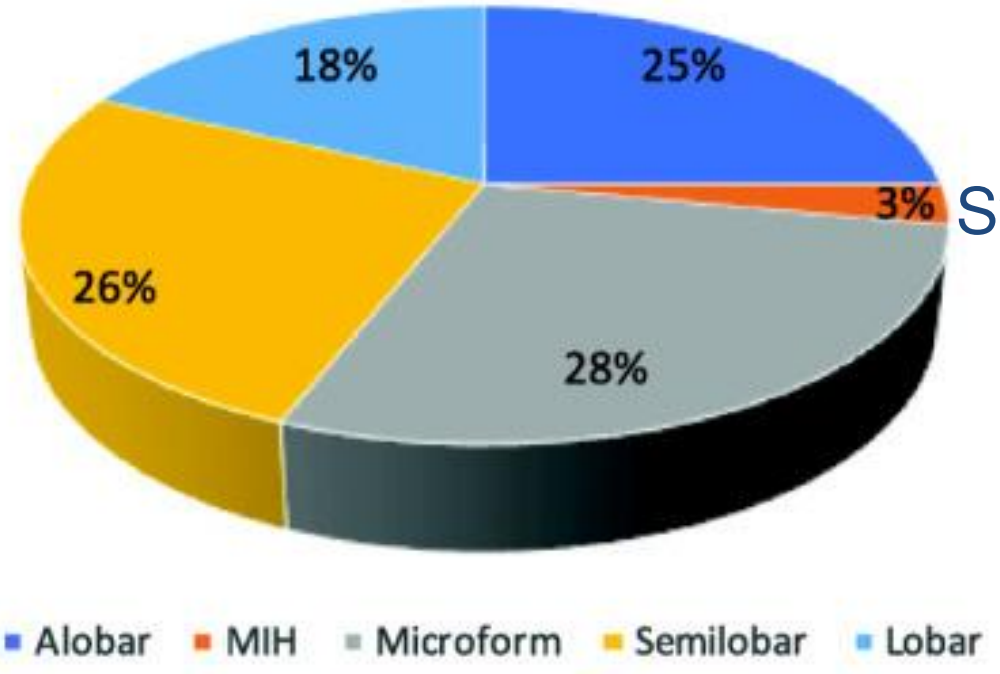
AMERICAN ACADEMY OF NEUROLOGY.



Syntelencephaly = Midline interhemispheric fusion (MIH)

(a) **Distribution of brain anomalies in European HPE cohort**



Syntelencephaly

Dubourg, 2018

Syntelencephaly = Midline interhemispheric fusion (MIH)

Genetics:

- *ZIC2*+

- Gene panel only for the majority of patients:

-> new genes with WES / WGS?

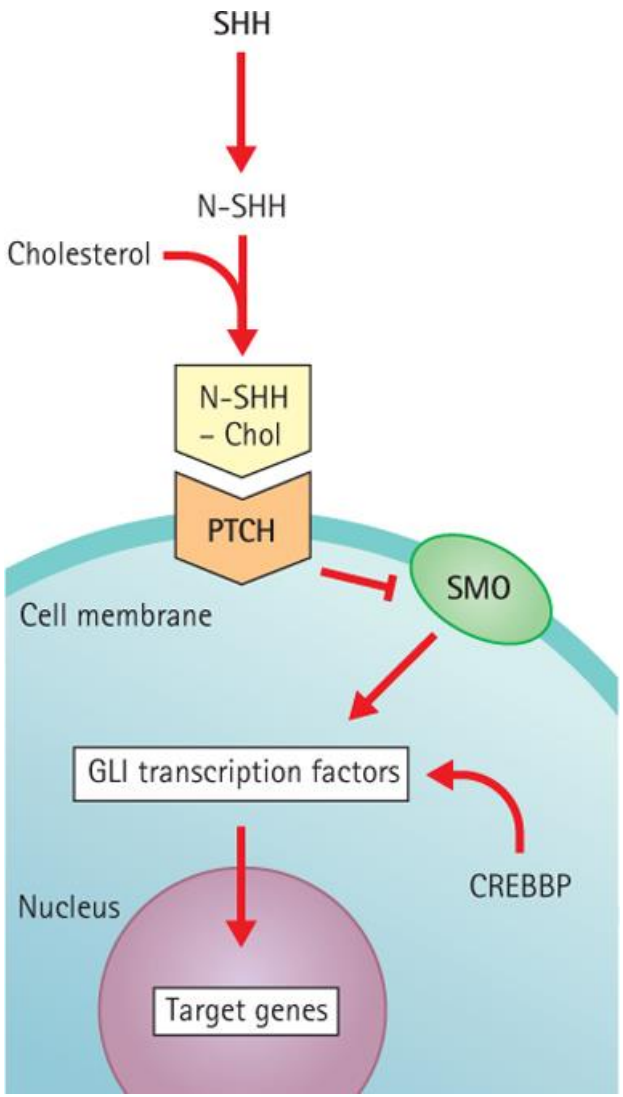
Neurodevelopment:

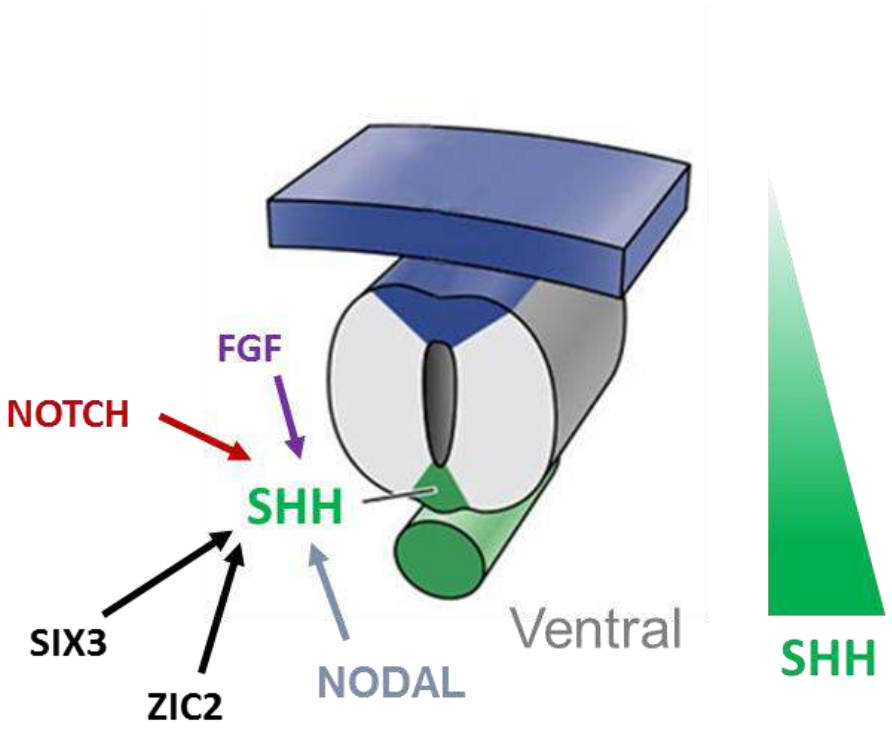
- Highly variable depending on the patients
- Syntelencephaly antenatally : future prognosis ?

-> Recruitment of patients to allow correlation between neuroimaging and neurodevelopment / neurologic symptoms

(collaboration with Pr Laurent Guibaud, Lyon, France)

SHH Pathway and genetic heterogeneity in HPE





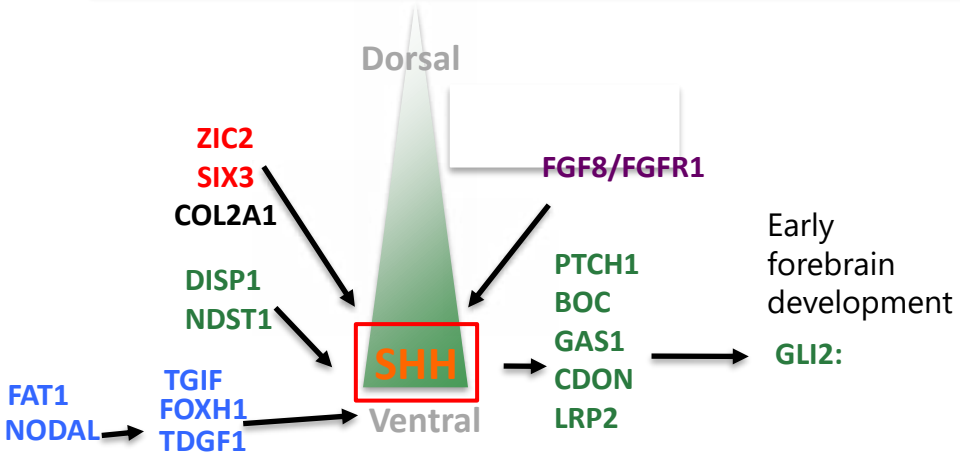
Adapté de Gilbert, 2010

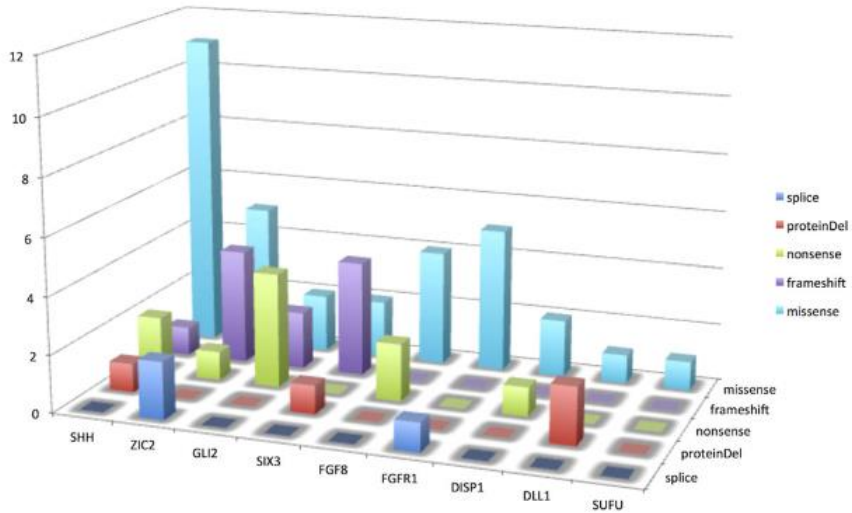
These genes belong to the major pathways of brain and eye development (SHH, NODAL, FGF)

All HPE genes are involved in the regulation of SHH activity

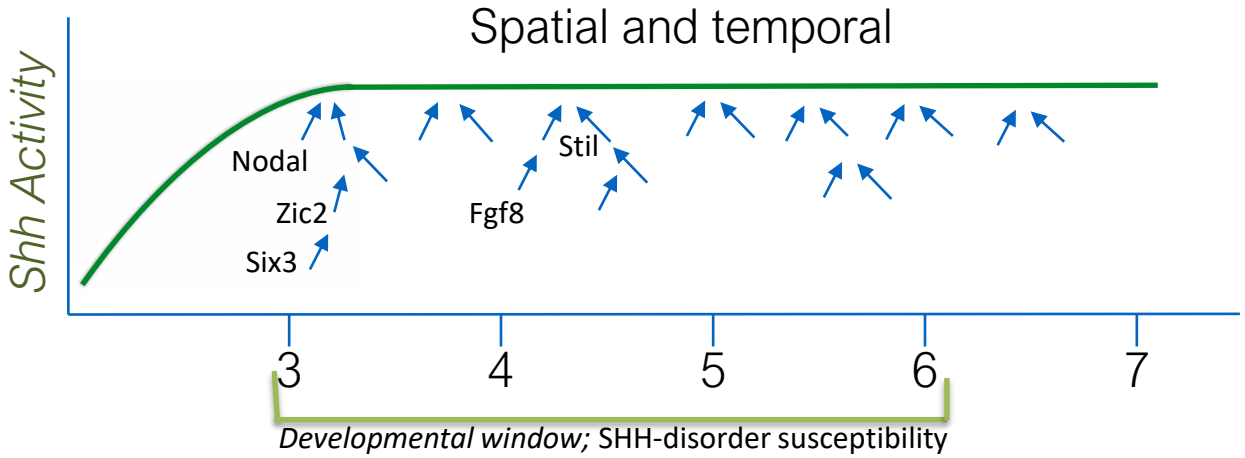
Dubourg et al., 2016; Dubourg et al., 2018; Kim et al., 2019

Autosomal dominant *(de novo)*	Autosomal recessive	Digenism	Oligogenism
~35 %	*<1 %*	*? %*	*? %*
SHH (30%) *ZIC2 (70%)* *FGFR1 (50%)* *SIX3 (30%)*	*STIL/STIL* *DISP1/DISP1* *TGIF1/TGIF1* *FGF8/FGF8* *...*	*SHH/DISP1* *SIX3/PTCH1* *SHH/DLL1* *FGF8/FGFR1* *...*	*SHH/FAT1/NDST1* *HIC1/BOC/SCUBE2* *LRP2/COL2A1/FAT1* *...*

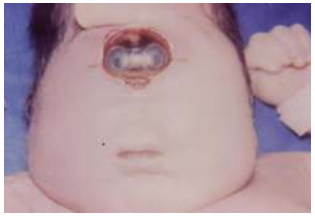


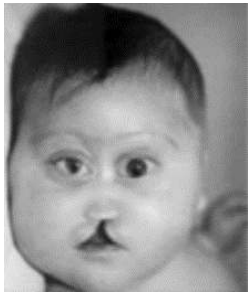


A tight control of SHH activity is crucial during craniofacial development



The genetic contribution to HPE is shaped by the interplay between multiple genes

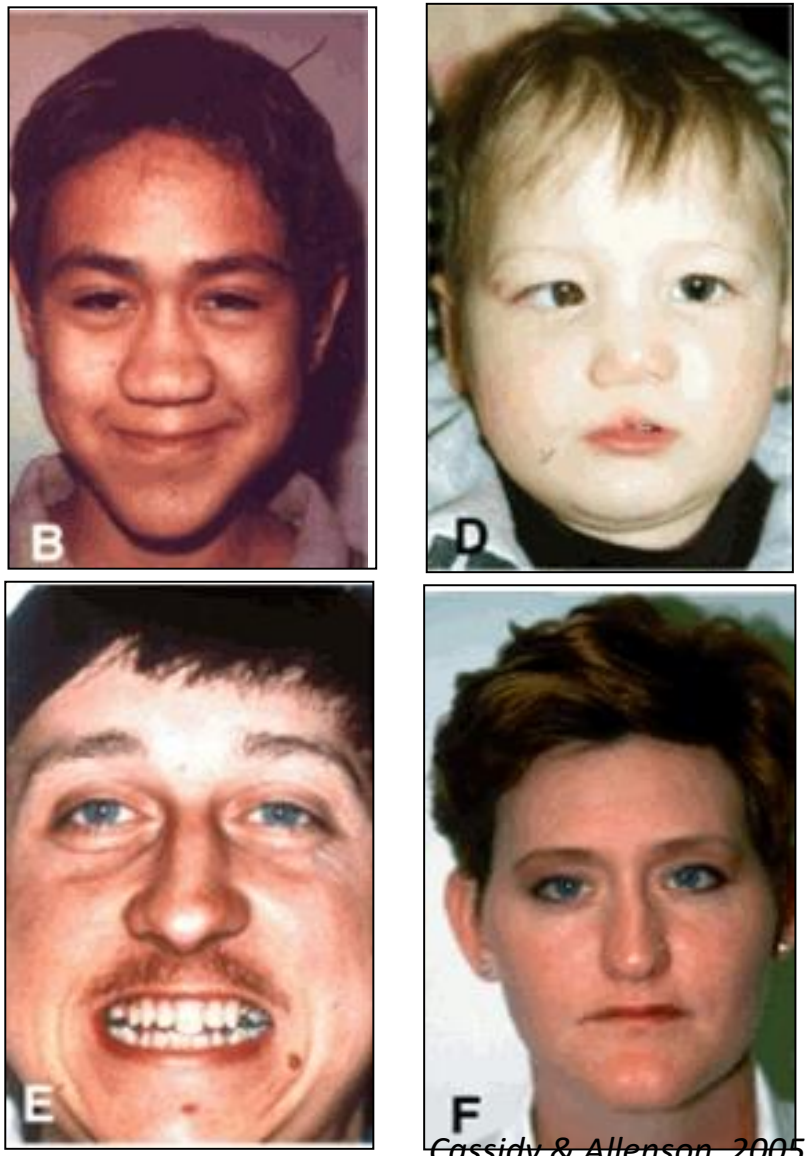




Our hypothesis : accumulation of rare variants of genes implicated in SHH activity would lead to craniofacial malformations

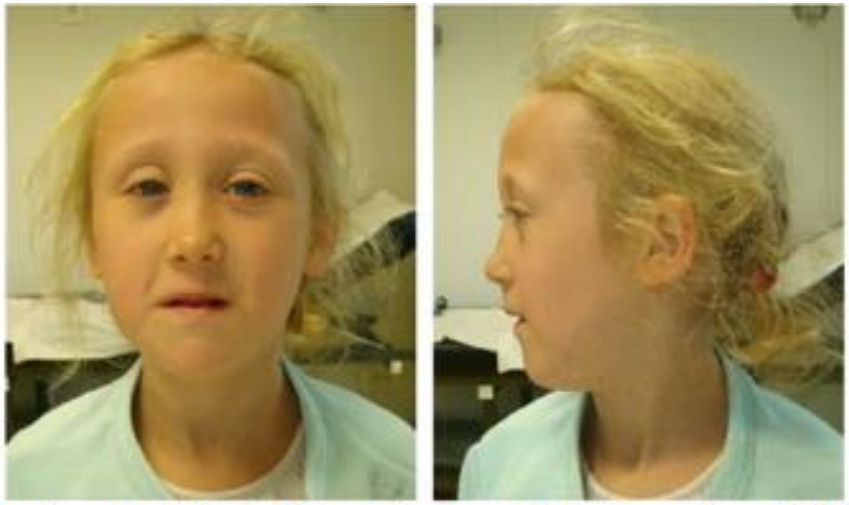
Craniofacial midline anomalies: microform HPE

- ***Craniofacial anomalies:***
  - Hypotelorism
  - Coloboma
  - Microphtalmia
  - **Solitary median maxillary central incisor (SMMCI)**
  - **Median cleft** (palate and/or lip)
  - **Pyriform aperture stenosis**
  - Choanal atresia / stenosis
  - Microcephaly
  - **Arhinencephaly**
  - Hypothalamic pituitary dysfunction
  - Corpus callosum anomalies

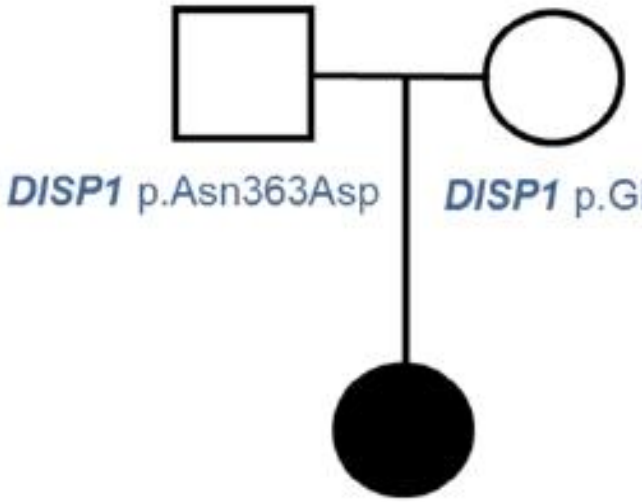


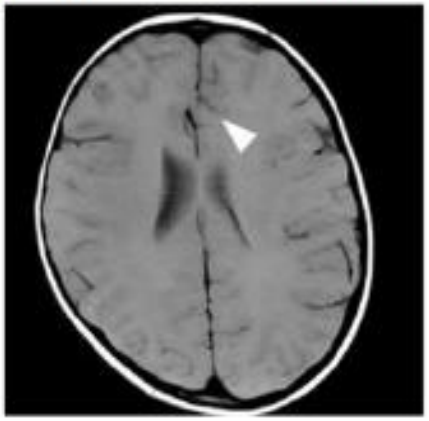
Cassidy & Allenson, 2005

Disp1: recessive inheritance



Patient with cleft palate, mild learning difficulties



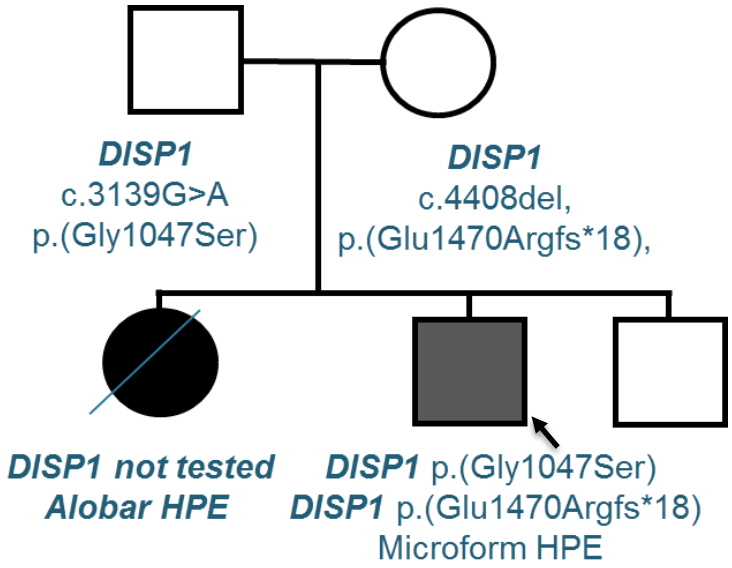


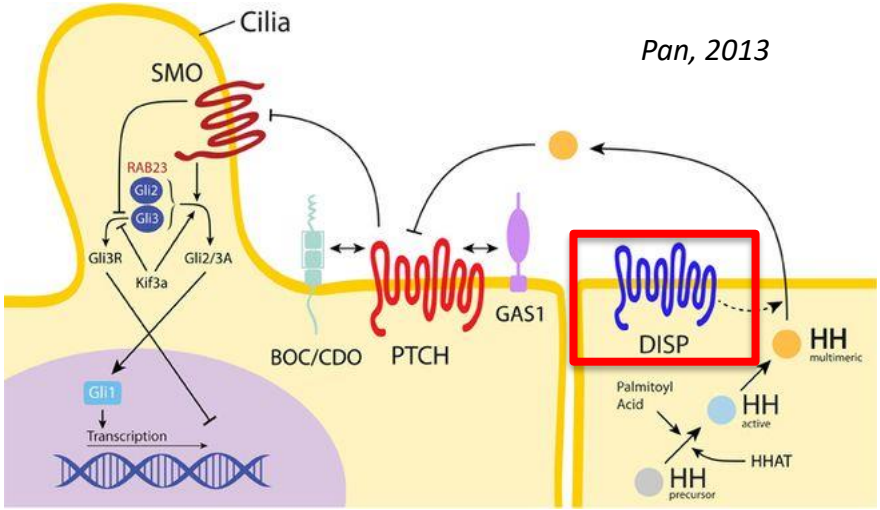
mild form of **lobar HPE** with a very localized fusion of hemispheres in the forebrain

DISP1 (NM_032890)

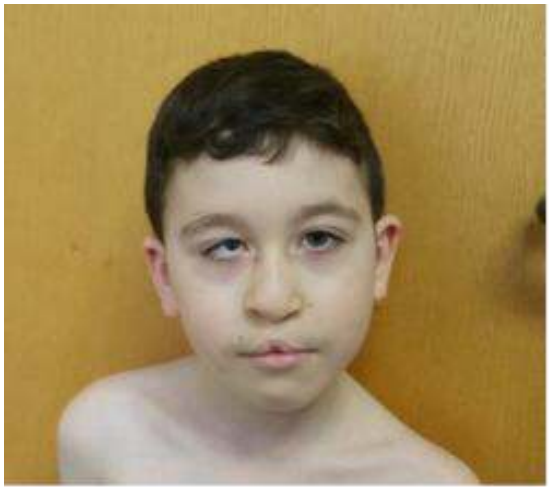
Mouden et al, *Clinical Genetics* 2016

Disp1: recessive inheritance





Pan, 2013



<u>Microform HPE:</u>

Eye coloboma with impaired vision

Cleft lip and palate

Regular schooling with visual adaptations

Normal brain MRI

Unpublished data

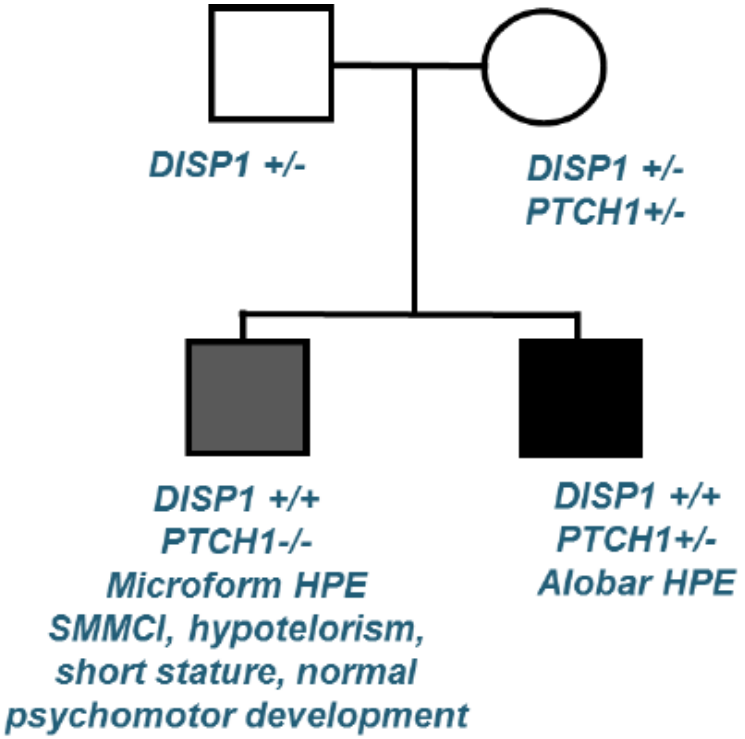
In collaboration with Dr S. Whalen, Dr B. Keren (Paris)

Disp1: recessive inheritance

- ***DISP1 variants:***
  - **c.2558T>C, p.(Ile853Thr)**
  - **c.3128C>T, p.(Ser1043Leu)**

We identified an additional variant in the affected boy with alobar HPE:
-heterozygous variant in *PTCH1* :
NM_000264.4:c.1318A>T or p.(Ile440Phe) inherited from the mother
This variant is absent in public databases, is predicted as damaging (score CADD = 24.2, score DANN = 0.98) and involves a very conserved residue (score GERP = 4.51 >> threshold = 2).

This additionnal variant combined with the *DISP1* variants (oligogenism) might explain the phenotypic variability in this family



Unpublished data in collaboration with Dr J Bos , Dr Y Hendriks Amsterdam

Conclusion / Call for collaborative clinical research

Shh deficiency syndrome

Syntelencephaly: very rare

Recruitment of patients

Correlation neuroimaging / neurodevelopment

Genetic causes

DISP1:

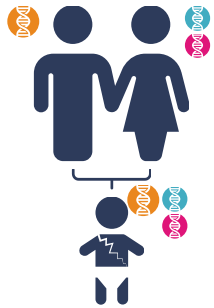
Recessive inheritance

Functional studies soon: we recruit patients!

New funding:

Exome/genome sequencing for microform HPE patients

Oligogenism? New genes?



GPLD Team

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Thanks!

Patients and families
Clinicians, Fetopathologists
And all colleagues

Holoprosencephaly and midline defects

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  - Between the 18th and 28th day of gestation
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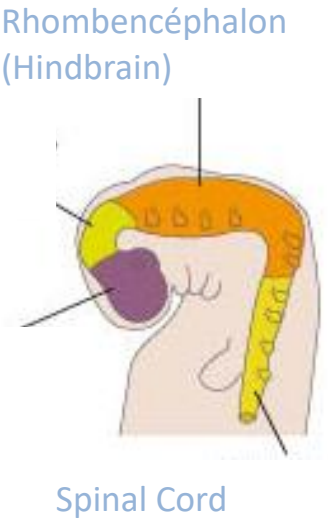

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