The genetic basis of human hydrocephalus

Hindbrain development, growth regulation and more

William B Dobyns, MD
Department of Pediatrics
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and

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

The genetic basis of hydrocephalus

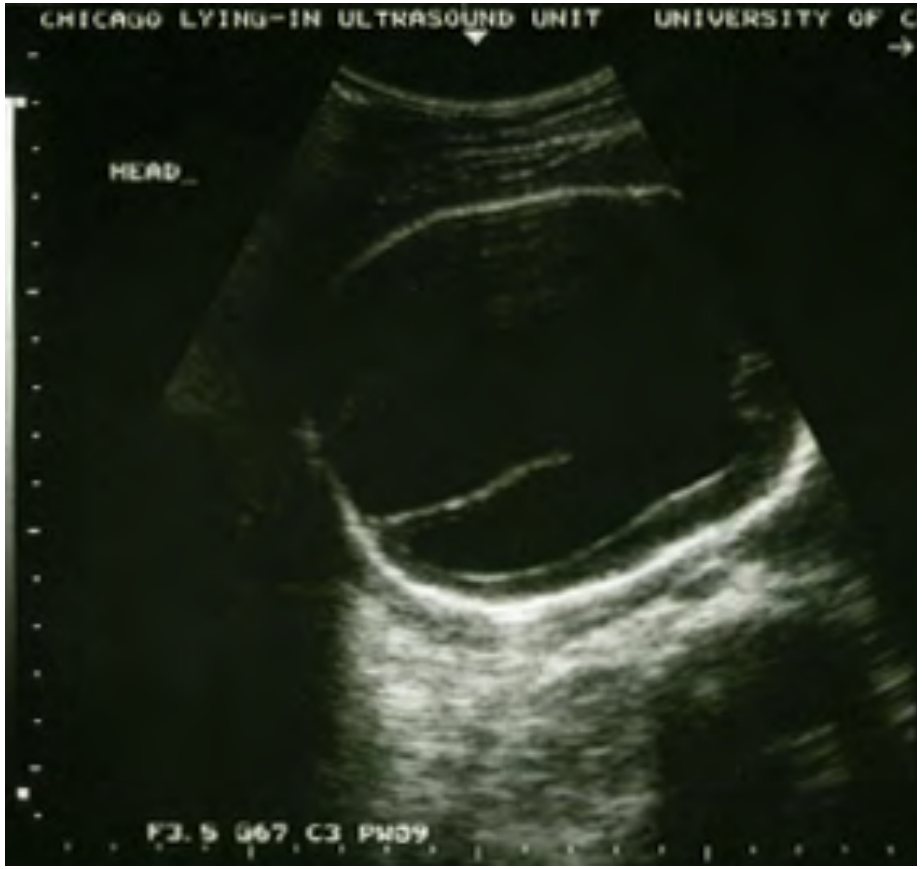
- Simple inheritance
  - AD, AR and XL disorders
  - Chromosome disorders
- Developmental disorders
  - Neural tube disorders
  - Forebrain DEV disorders
  - Mid-hindbrain DEV disorders
  - Brain growth disorders
  - Cortical malformations
- The CSF system
  - Choroid plexus, ependyma
  - Aqueduct and SCO
  - Ventricles and foramina
  - Extra-axial space and “AG”

- Genes and pathways
  - Early pattern formation
    - SHH, ZIC2, other HPE genes
    - FOXC1, ZIC1/4, DWM genes
    - Pax6, Wnt1
    - Msi1, Msx1, Rfx4
  - Neuronal pathfinding
    - L1CAM
  - Cortical development
    - POMT1 and many COB gene
  - Growth regulation
    - PIK3CA, PIK3R2, AKT3

- Where do you start?

The scope of the problem for HYD

- Prenatal HYD
  - N = 286 fetuses
    - 30% (82/286) die
    - 29% (80/286) have intellectual disability
    - 41% (114/286) are normal



The scope of the problem for HYD

- Congenital HYD
  - N = 48 children
    - 33% (16/48) die
    - 19% (09/48) have intellectual disability
    - 48% (23/48) are normal or have mild LD

Inheritance of HYD

- Single gene disorders
  - AD
    - No human genes
  - AR
    - No human genes
  - XL
    - L1CAM
- Chromosome disorders
  - 6p25.3
  - 6q25.3-qter
  - 8q12.2-q21.2
  - Others

ELSEVIER

Journal of the Neurological Sciences 158 (1998) 101–105

JOURNAL OF THE NEUROLOGICAL SCIENCES

Familial congenital hydrocephalus and aqueduct stenosis with probably autosomal dominant inheritance and variable expression

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Abstract

A kindred is reported on with suspected autosomal dominant congenital hydrocephalus and aqueduct stenosis. In contrast to patients with X-linked congenital hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS) our patients were not mentally retarded and they did not show any pyramidal tract dysfunction or clasped thumbs; the pyramids were not affected either, as was confirmed by autopsy, CT or MRI. Molecular genetic studies in our patients have not revealed abnormalities of eight exons of the L1 neural adhesion molecule gene that is related to HSAS. © 1998 Elsevier Science B.V.

Keywords: Congenital hydrocephalus; Aqueduct stenosis; Autosomal dominant inheritance; Molecular genetics; Autopsy

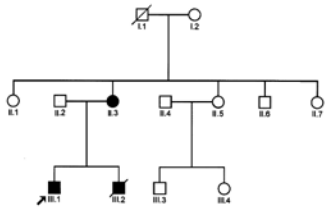

Fig. 1. Pedigree of the family. The arrow marks the proband.

1. Introduction

The cause of hydrocephalus may be genetic or nongenetic. Nongenetic congenital hydrocephalus (CH) can be the result of congenital malformations, infectious diseases, haemorrhage and tumours, but the cause often remains obscure [36]. The overall incidence of fetal hydrocephalus not associated with meningomyelocele has been reported to be 0.2–2.1 per 1000 total births [2,8,15,31,32,40]. Males are more often affected than females [4,36]. A marked increase in the risk of congenital hydrocephalus has been noted with primogeniture, older maternal age and lower social class of the father [10]. Congenital hydrocephalus in successive pregnancies is very uncommon [12,25]. A genetic basis for CH not associated with meningomyelocele has rarely been observed, as the incidence in siblings born after the propositus is estimated to be 0.5%–1.4% [4,10]. We report on a kindred (Fig. 1) in which a hydrocephalic woman gave birth to two hydrocephalic sons.

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PII: S0022-510X(98)00097-5

American Journal of Medical Genetics 31:467–470 (1988)

Letter to the Editor

Autosomal Recessive Nonsyndromal Hydrocephalus

To the Editor:

The report of Willems et al. [1987] on a large kindred with an unusual form of X-linked hydrocephalus without aqueductal stenosis is very interesting and prompts us to describe a consanguineous Arab family with four hydrocephalic children (two males, and two females), one confirmed at autopsy to have the Arnold-Chiari malformation. This family may indicate the existence of an autosomal recessive form, adding further evidence for genetic heterogeneity of familial hydrocephalus.

CLINICAL REPORTS

Family Data (Fig. 1)

The father and mother (III-7 and III-8) were phenotypically normal first cousins of Palestinian Arab origin. They were 35 and 27 years old, respectively, when evaluated in 1983. They have a normal daughter (IV-1) born in 1977 and another (IV-2), who died in infancy from bronchopneumonia. The third child (IV-3) was a male stillborn at term by cesarean section (CS) with hydrocephalus documented from files, with occipitofrontal circumference (OFC) of 42 cm and weight of 3,400 g, with no other reported anomalies.

Patient 1 (IV-4)

A female, the second affected hydrocephalic sib, was born in August 1983 at term. The mother received daily folic acid supplements for 3 months in the preconception and early conception periods. Hydrocephaly was diagnosed prenatally by real-time ultrasound, which showed a progressive increase in the head circumference from the 19th week but, because of religious beliefs, the mother did not wish to terminate the pregnancy, which ended spontaneously at term. CS was done because of cephalopelvic disproportion and shoulder presentation. At birth, the infant showed an apparent hydrocephalus by transillumination with widely open sutures. OFC was 41 cm and weight was 3250 g.

Received for publication December 21, 1987; revision received April 25, 1988.

Address reprint requests to Dr. A.S. Teebi, P.O. Box 36660, Raas, 24757, Kuwait.

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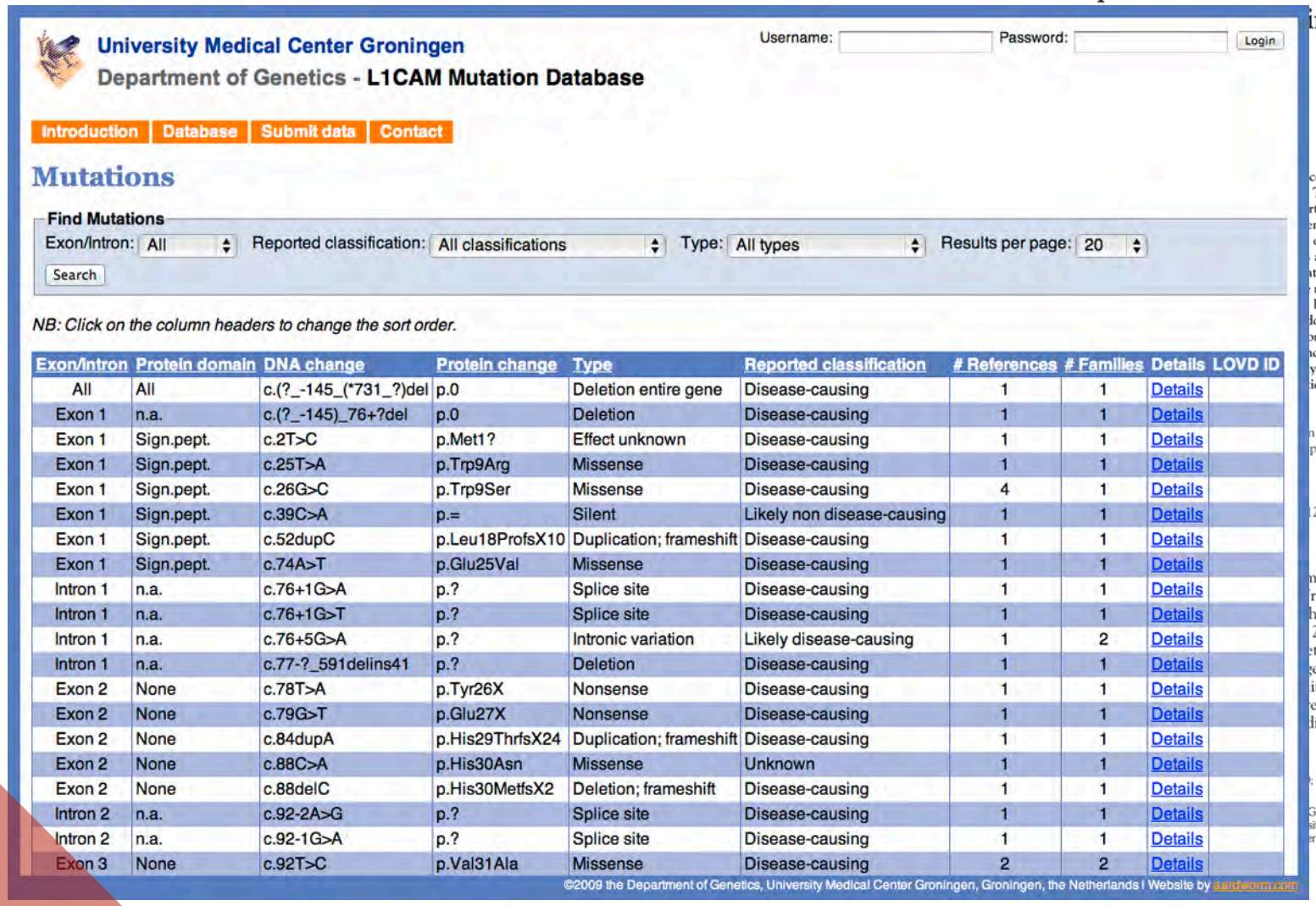
XL-HYD and *L1CAM*



University Medical Center Groningen
Department of Genetics - **L1CAM Mutation Database**

Username: Password: Login

Introduction | Database | Submit data | Contact

Mutations

Find Mutations

Exon/Intron: All | Reported classification: All classifications | Type: All types | Results per page: 20

Search

NB: Click on the column headers to change the sort order.

Exon/Intron	Protein domain	DNA change	Protein change	Type	Reported classification	# References	# Families	Details	LOVD ID
All	All	c.(?_-145_(*731_?)del	p.0	Deletion entire gene	Disease-causing	1	1	Details	
Exon 1	n.a.	c.(?_-145)_76+?del	p.0	Deletion	Disease-causing	1	1	Details	
Exon 1	Sign.pept.	c.2T>C	p.Met1?	Effect unknown	Disease-causing	1	1	Details	
Exon 1	Sign.pept.	c.25T>A	p.Trp9Arg	Missense	Disease-causing	1	1	Details	
Exon 1	Sign.pept.	c.26G>C	p.Trp9Ser	Missense	Disease-causing	4	1	Details	
Exon 1	Sign.pept.	c.39C>A	p.=	Silent	Likely non disease-causing	1	1	Details	
Exon 1	Sign.pept.	c.52dupC	p.Leu18ProfsX10	Duplication; frameshift	Disease-causing	1	1	Details	
Exon 1	Sign.pept.	c.74A>T	p.Glu25Val	Missense	Disease-causing	1	1	Details	
Intron 1	n.a.	c.76+1G>A	p.?	Splice site	Disease-causing	1	1	Details	
Intron 1	n.a.	c.76+1G>T	p.?	Splice site	Disease-causing	1	1	Details	
Intron 1	n.a.	c.76+5G>A	p.?	Intronic variation	Likely disease-causing	1	2	Details	
Intron 1	n.a.	c.77-?_591delins41	p.?	Deletion	Disease-causing	1	1	Details	
Exon 2	None	c.78T>A	p.Tyr26X	Nonsense	Disease-causing	1	1	Details	
Exon 2	None	c.79G>T	p.Glu27X	Nonsense	Disease-causing	1	1	Details	
Exon 2	None	c.84dupA	p.His29ThrfsX24	Duplication; frameshift	Disease-causing	1	1	Details	
Exon 2	None	c.88C>A	p.His30Asn	Missense	Unknown	1	1	Details	
Exon 2	None	c.88delC	p.His30MetfsX2	Deletion; frameshift	Disease-causing	1	1	Details	
Intron 2	n.a.	c.92-2A>G	p.?	Splice site	Disease-causing	1	1	Details	
Intron 2	n.a.	c.92-1G>A	p.?	Splice site	Disease-causing	1	1	Details	
Exon 3	None	c.92T>C	p.Val31Ala	Missense	Disease-causing	2	2	Details	

HUMAN MUTATION 18:1–12 (2001)

MUTATION UPDATE

Genetic and Clinical Aspects of X-linked

in the

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domains or muta-
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ies. Hum Mutat

n spectrum; neural
pastic paraparesis

20133; GenBank:

mbs, spastic paraplegia,
ransen et al., 1995;
he estimated incidence
25,000 to one in every
t al., 1986]. However,
gene mutations on the
ital hydrocephalus in
estimated. Predictions
lies, as well as the over-

: accepted revised manuscript

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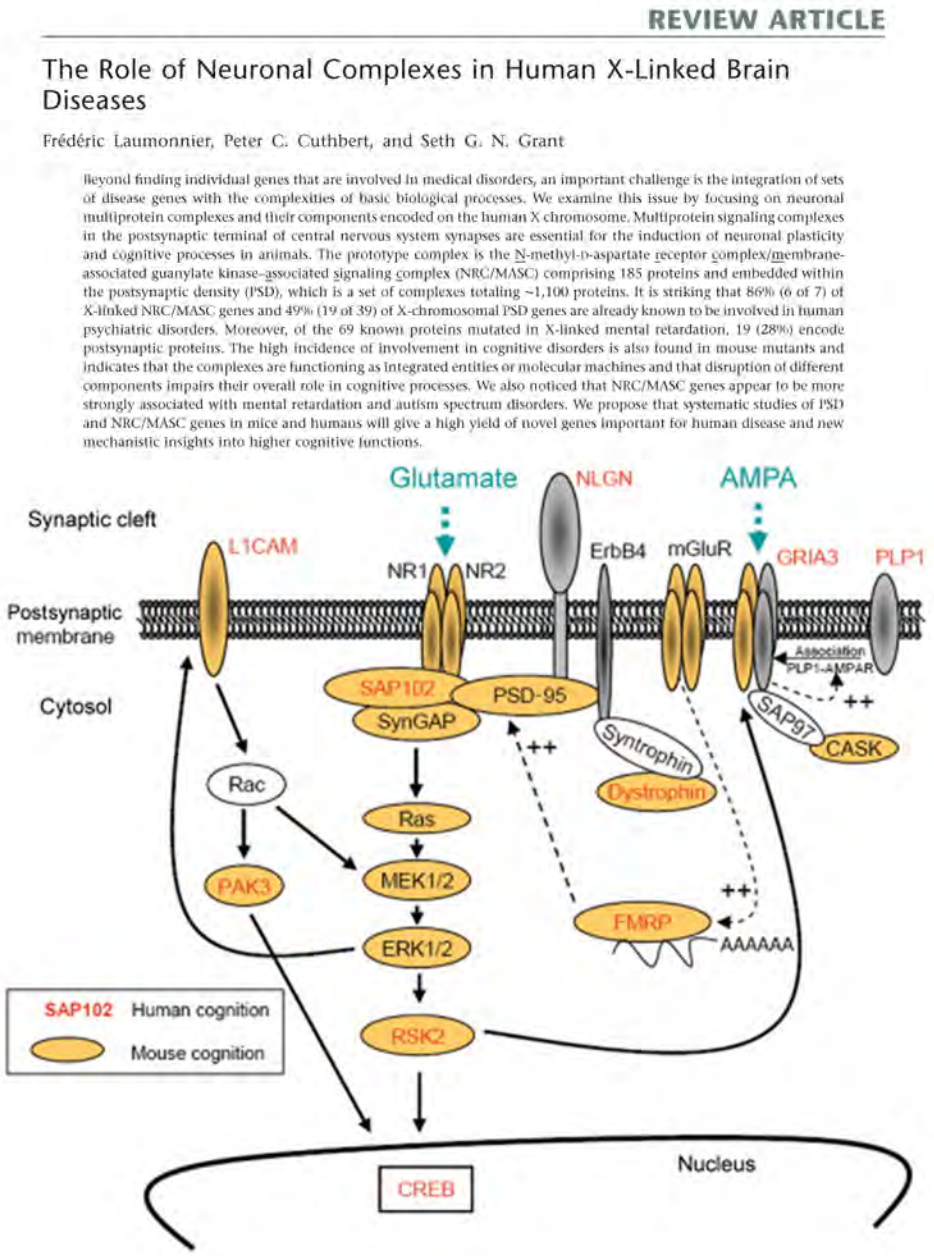
sität, Moorenstrasse 5, D-40225
rtnj@uni-duesseldorf.de

XL-HYD and *L1CAM*

- L1CAM (L1 cell adhesion molecule)
  - Immunoglobulin-like family of cell-adhesion glycoproteins
  - Highly conserved
  - Expressed in neurons throughout the brain during development
  - Controls many processes
    - Neurite outgrowth
    - Axonal guidance
    - Synaptogenesis
    - Myelination
    - Fasciculation
  - Regulated by MAPK pathway, which phosphorylate the protein and modulates its interaction with ankyrin B



REVIEW ARTICLE

The Role of Neuronal Complexes in Human X-Linked Brain Diseases

Frédéric Laumonnier, Peter C. Cuthbert, and Seth G. N. Grant

Beyond finding individual genes that are involved in medical disorders, an important challenge is the integration of sets of disease genes with the complexities of basic biological processes. We examine this issue by focusing on neuronal multiprotein complexes and their components encoded on the human X chromosome. Multiprotein signaling complexes in the postsynaptic terminal of central nervous system synapses are essential for the induction of neuronal plasticity and cognitive processes in animals. The prototype complex is the N-methyl-D-aspartate receptor complex/membrane-associated guanylate kinase–associated signaling complex (NRC/MASC) comprising 185 proteins and embedded within the postsynaptic density (PSD), which is a set of complexes totaling ~1,100 proteins. It is striking that 86% (6 of 7) of X-linked NRC/MASC genes and 49% (19 of 39) of X-chromosomal PSD genes are already known to be involved in human psychiatric disorders. Moreover, of the 69 known proteins mutated in X-linked mental retardation, 19 (28%) encode postsynaptic proteins. The high incidence of involvement in cognitive disorders is also found in mouse mutants and indicates that the complexes are functioning as integrated entities or molecular machines and that disruption of different components impairs their overall role in cognitive processes. We also noticed that NRC/MASC genes appear to be more strongly associated with mental retardation and autism spectrum disorders. We propose that systematic studies of PSD and NRC/MASC genes in mice and humans will give a high yield of novel genes important for human disease and new mechanistic insights into higher cognitive functions.

Genetics of HYD

Genetic testing (clinical labs)

- Most patients with HYD
  - Chromosome microarray
  - L1CAM sequencing and dup/del analysis
- Syndromes
  - Testing selected for the specific syndrome suspected

Recurrence risk data

- Male proband
  - 12 - 15%
- Female proband
  - 05 - 06%

Eur J Pediatr (1999) 158: 474–478

MEDICAL GENETICS

F. Haverkamp · J. Wölfle · M. Aretz
A. Krämer · B. Höhmann · H. Fahnenstich · K. Zerres

Congenital hydrocephalus internus and aqueduct stenosis: aetiology and implications for genetic counselling

Received: 29 May 1998 / Accepted in revised form: 25 August 1998

Abstract Genetic counselling in families with congenital hydrocephalus internus (CHI) in combination with aqueduct stenosis (AS) is often difficult due to an uncertain aetiology. We present a series of 35 patients with CHI and AS focusing on the aetiology and presumed recurrence risk for siblings. In 13 patients (37.1%) a genetic aetiology was identified with an increased recurrence risk for siblings. The relative frequency of patients with X-linked hydrocephalus in our sample was in accordance with the literature (2/35), but was more frequent in other diseases with Mendelian inheritance.

Conclusion In addition to the well-known X-linked and autosomal recessive forms of aqueduct stenosis with hydrocephalus, this malformation can occur in other diseases with Mendelian inheritance. This finding is of considerable importance for genetic counselling and prognosis.

Key words Congenital internal hydrocephalus · Aqueduct stenosis · Inheritance · Aetiology · Genetic counselling

Abbreviations *AS* aqueduct stenosis · *CHI* congenital hydrocephalus internus · *XLC* X-linked congenital hydrocephalus internus

Introduction

The frequency of congenital hydrocephalus internus (CHI) varies between 0.5 and 2.5 per 1000 newborns for different populations [4, 11, 13, 22, 25]. Retrospective studies report a low overall recurrence risk (0.6–1.4%) of CHI [4, 7].

In 22.5–42.9% of patients, CHI is associated with aqueduct stenosis (AS) [4, 13]. The most common causes of AS are intra-uterine infections or intracerebral haemorrhage. There are also cases compatible with Mendelian inheritance [4]. The most common monogenetic type with a frequency of 4.5–14.2% is X-linked CHI (XLC) [4, 13, 20]. In male patients with CHI and AS, it is assumed that XLC may be present in up to 23%–25% [4, 13]. The overall recurrence risk for male siblings of a male index patient has been reported to be about 12%; for female siblings the recurrence risk is 2%–6% [4, 13]. If the index patient is female, the empiric recurrence risk is usually 2% or less, indicating that autosomal-recessive inheritance is rare [2, 5, 13, 14, 23]. However, specific subgroups of infants with CHI bear a higher recurrence risk, e.g. in patients suffering from a specific genetic disease [1]. With respect to the underlying aetiology, epidemiological data on patients with CHI and AS are lacking. The aim of our study was to determine the specific aetiology as well as the relative frequency of conditions leading to CHI and AS in a series of 35 patients.

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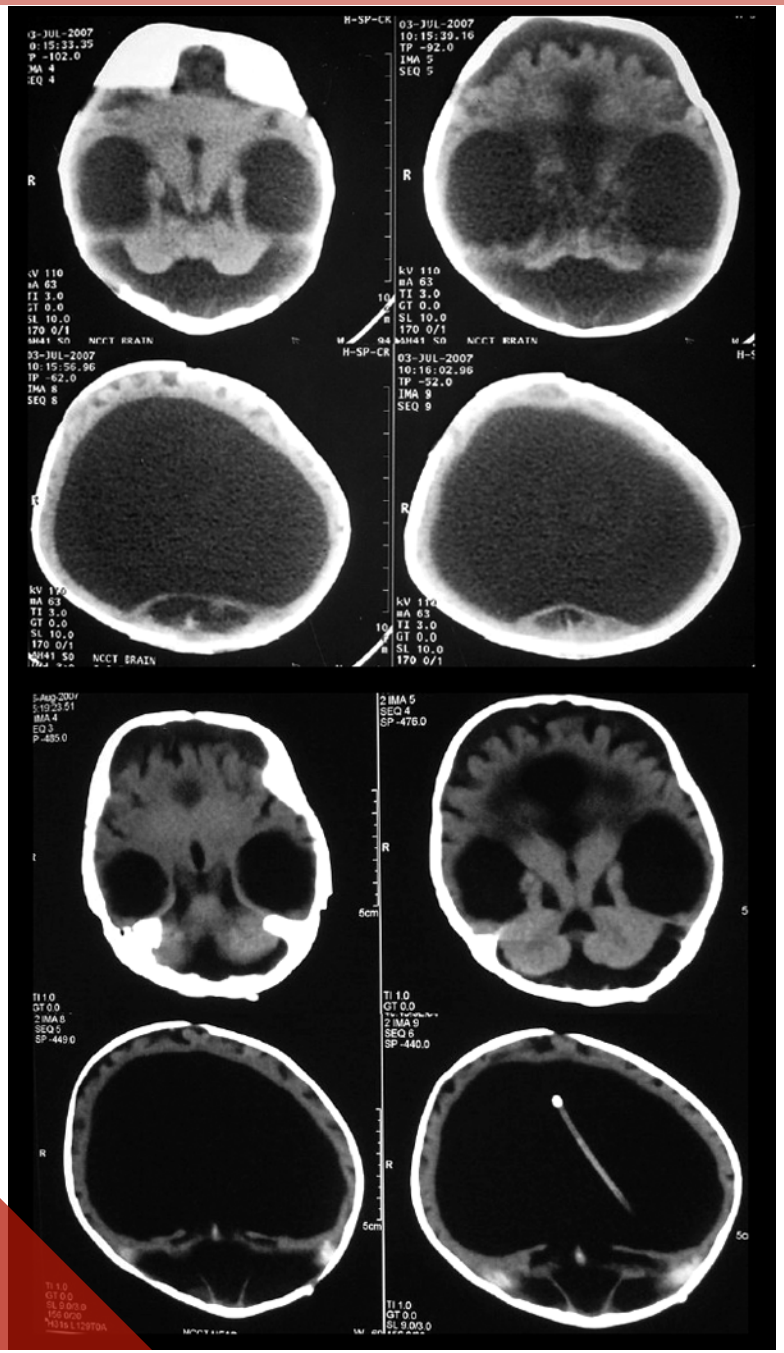
HYD in developmental brain disorders

- Neural tube disorders
  - Myelomeningocele
  - Cephaloceles
- Forebrain DEV disorders
  - Holoprosencephaly
  - Corpus callosum agenesis
- Mid-hindbrain DEV disorders
  - Dandy-Walker spectrum
  - Rhombencephalosynapsis
  - Pontine tegmental cap dysplasia
  - Others
- MCD: brain growth
  - Microcephaly (rare)
  - Megalencephaly
- MCD: neuronal migration
  - Heterotopia
  - Lissencephaly
  - Cobblestone malformation
- MCD: post-migrational
  - Polymicrogyria



HPE and HYD

Journal of Pediatric Neurosciences

J Pediatr Neurosci. 2009 Jan-Jun; 4(1): 41–43. PMCID: PMC3162837
doi: 10.4103/1817-1745.49108

Hydrocephalic holoprosencephaly: An oxymoron? Insights into etiology and management

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Abstract

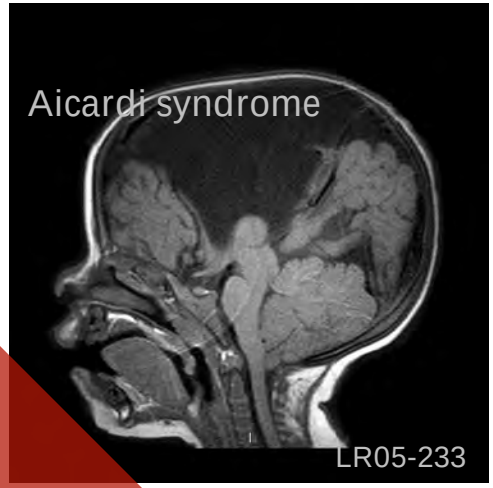
Holoprosencephaly is usually associated with microcephaly, although macrocephaly is not uncommonly seen. However, the cause of hydrocephalus in holoprosencephaly remains ill-defined. Here, the authors report a case of CSF ascites following ventriculoperitoneal shunt placement in a five month-old child with alobar holoprosencephaly, and hypothesize that the excessive CSF production which occurs in this condition may be responsible for the formation of CSF ascites. Further research is required to assess whether the gene responsible for holoprosencephaly is also responsible for upregulating CSF production in patients with concomitant hydrocephalus.

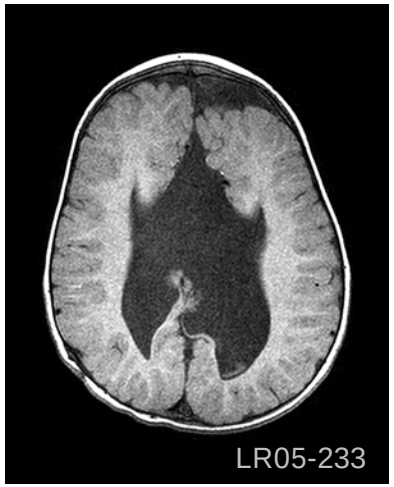
Keywords: Complication, CSF ascites, holoprosencephaly, hydrocephalus, shunt

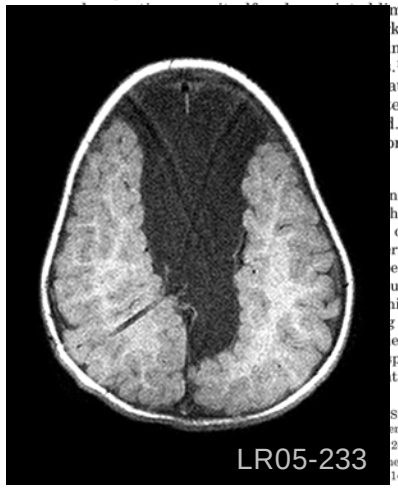
SHH, SIX3, ZIC2 , ~15 others

ACC/cysts and HYD

- Type I cysts communicates with LV
  - Ia with frequent HYD
  - Ib with frequent HYD
- Type 2 no communication with LV
  - IIa with frequent HYD (M>F)
  - IIb with frequent HYD (Aicardi)







CME

Callosal agenesis with cyst

A better understanding and new classification

A. James Barkovich, MD; Erin M. Simon, MD; and Christopher A. Walsh, MD, PhD

Article abstract—*Objective:* To analyze imaging studies of 25 cases of agenesis of the corpus callosum with interhemispheric cyst to assess this malformation itself and associated anomalies. *Methods:* CT (6 patients) and MRI (19 patients) were retrospectively reviewed. The patients were categorized according to morphologic and clinical characteristics. *Results:* Based on morphology, the patients were separated into two major types, each with subtypes. Type 1 cysts appear to be an extension or diverticulation of the third or lateral ventricles, whereas Type 2 are loculated and do not communicate with the ventricular system. Type 1a were associated with presumed communicating hydrocephalus but no other cerebral malformations. Type 1b were associated with hydrocephalus secondary to diencephalic malformations prohibiting egress of CSF from the third ventricle into the aqueduct of Sylvius. Type 1c were associated with small head size and apparent cerebral hemispheric dysplasia or hypoplasia. Type 2a (multiloculated cysts) were associated with no abnormalities other than callosal agenesis/hypogenesis. Type 2b were associated with deficiencies of the falx cerebri, subependymal heterotopia, and polymicrogyria (and were almost all in patients diagnosed with Aicardi syndrome). Type 2c were associated with subcortical heterotopia. Type 2d consists of interhemispheric arachnoid cysts. Other than those with Type 2b cysts, gender predominance was overwhelmingly male. *Conclusion:* Agenesis of the corpus callosum with interhemispheric cyst appears to consist of a heterogeneous group of disorders that have in common callosal agenesis and extraparenchymal cysts, both of which are among the commonest CNS malformations. This article proposes a classification system, based primarily on morphology, by which this complex group of disorders might begin to be better understood.

NEUROLOGY 2001;56:220–227

The ability of MRI to show the gross morphology of the brain in vivo using thin sections in multiple planes has allowed the identification of previously unknown malformations,[1,2] a new appreciation of the frequency of malformations that were previously thought extremely rare,[3,4] and differentiation of malformations that were previously combined.[5] Although MR has been utilized to assess the agenetic/

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cephaly with seizures in 1 patient, microcephaly with infantile spasms in 1 patient, and partial motor seizures with right spastic hemiparesis in 1 patient.

Imaging consisted of MR in 17 patients, X-ray CT in 6, and both MR and CT in 2. MR studies varied in technique, as they were performed at multiple institutions over a period of 16 years. However, all studies included sagittal T1 images, axial T1-weighted images, axial T2-weighted images, and coronal T1- or T2-weighted images. All CT scans included both axial and coronal images, although in three patients the coronal images were reformatted from 5-mm–thick axial sections. Paramagnetic contrast was administered in five of the MR scans and iodinated contrast was administered in two of the CT scans.

All of the scans were reviewed with particular attention to the degree of callosal abnormality (agenesis versus hypogenesis, severity of hypogenesis), character of the cyst (unilocular versus multilocular, intensity or attenuation as compared to CSF of the ventricles and subarachnoid space, location, communication with the ventricular system), and the presence and type of associated malformations. Clinical information was limited, as most of the patients were imaged as neonates because of macrocephaly or ultrasound findings of ventricular enlargement or cyst. When information from later in infancy or childhood was available, it was examined to determine neurologic status, developmental status, the presence or absence of seizures, type of seizures, and whether any anomalies were present outside of the nervous system. Based on these characteristics and

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2000.

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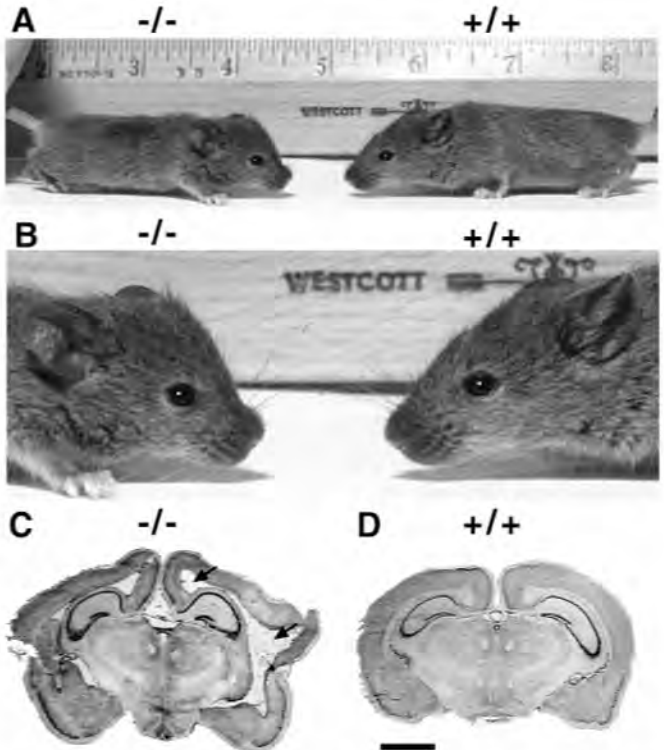
Disruption of the murine nuclear factor I-A gene (*Nfia*) results in perinatal lethality, hydrocephalus, and agenesis of the corpus callosum

Liomar das Neves*, Cynthia S. Duchala†, Fatima Godinho‡, Musa A. Haxhiu‡, Clemencia Colmenares*, Wendy B. Macklin†, Christine E. Campbell*, Kenneth G. Butz*, and Richard M. Gronostajski*§¶



- Phenotype
  - Intellectual disability, ACC, HYD or VMEG
  - Chiari 1, tethered cord
  - Urinary tract anomalies
- Gene
  - Nuclear Factor I (NFI) family of transcription factors

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NFIA Haploinsufficiency Is Associated with a CNS Malformation Syndrome and Urinary Tract Defects

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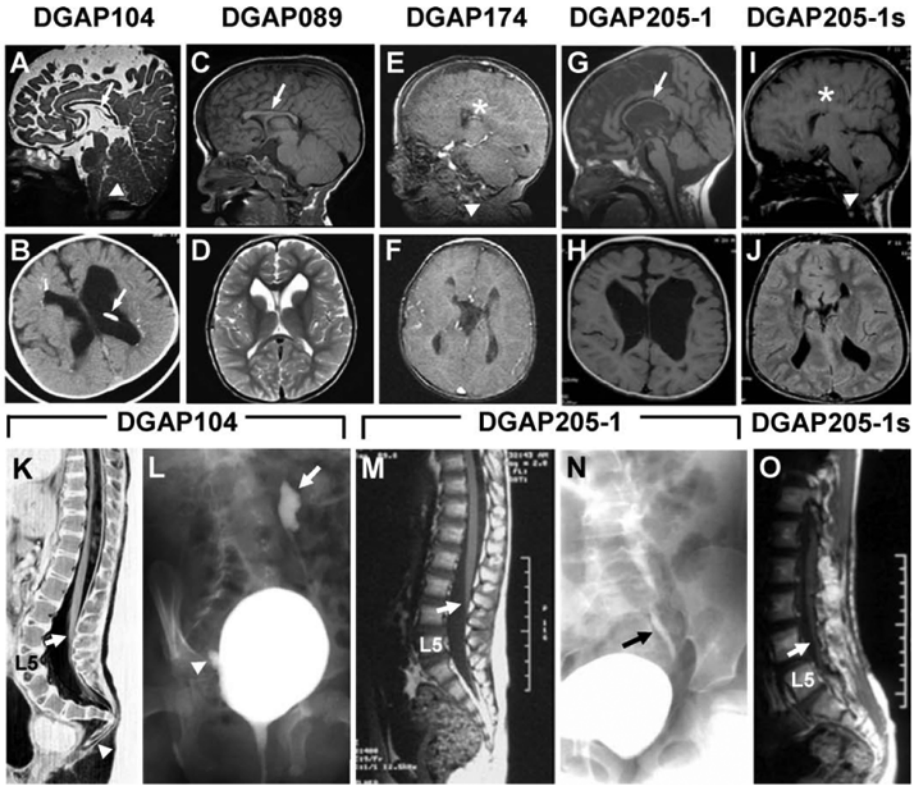
ACC and HYD or VMEG



Tetherd cord and urinary tract anomalies

nature genetics

Heterozygous deletion of the linked genes *ZIC1* and *ZIC4* is involved in Dandy-Walker malformation

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Dandy-Walker malformation (DWM; OMIM #220200) is a common but poorly understood congenital cerebellar malformation in humans. Through physical mapping of 3q2 interstitial deletions in several individuals with DWM, we defined the first critical region associated with DWM, encompassing two adjacent Zinc finger in cerebellum genes, *ZIC1* and *ZIC4*. Mice with a heterozygous deletion of these two linked genes have a phenotype that closely resembles DWM, providing a mouse model for this malformation.

DWM is defined by hypoplasia and upward rotation of the cerebellar vermis and cystic dilation of the fourth ventricle[1,2]. Affected individuals often have motor deficits such as delayed motor development, hypotonia and ataxia; about half have mental retardation; and some have hydrocephalus. Many other abnormalities have been described in DWM, such as agenesis of the corpus callosum, visual deficits and epilepsy, but these are uncommon[3]. DWM is a heterogeneous disorder that has been associated with several malformation syndromes and cytogenetic abnormalities, although no specific genes have yet been implicated in its pathogenesis[4]. The low empiric recurrence rate of ~1–2% for nonsyndromic DWM suggests that mendelian inheritance is unlikely and that a polygenic model may be more appropriate[5].

We identified seven individuals with *de novo* interstitial deletions of chromosome 3q. Magnetic resonance imaging or computed tomography scans of these individuals show that they all have isolated DWM with hypoplasia and upward rotation of the cerebellar vermis and a posterior fossa cyst, although with variable expressivity (**Fig. 1a** and **Supplementary Table 1** online). Typical of DWM, the cerebellar hemispheres are less affected than the vermis. Three of these individuals also have hydrocephalus. All seven have substantial cognitive deficits owing to the size of their deletions. Three have large deletions that include 3q22.2 and have facial changes of the blepharophimosis-ptosis-epicanthus inversus syndrome, presumably due to codeletion of the gene *FOXL2* (ref. 6). Six of the seven individuals were initially recruited into this study because of their cytogenetic abnormalities and were then found to have DWM. The other individual (LR03-317) presented with signs of DWM and, on further analysis, was found to have a small 3q deletion. We mapped the sizes and locations of the seven deletions by extensive fluorescence *in situ* hybridization analysis on metaphase chromosomes and identified a 7-Mb critical region for DWM (**Fig. 1b–g**). BACs RP11-635I23 at 3q24 and RP11-167H9 at 3q25.1 define the centromeric and telomeric boundaries of this critical region, respectively.

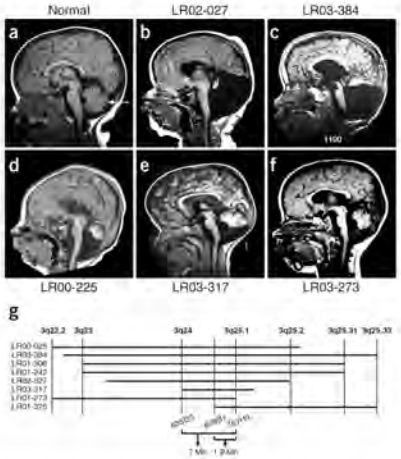

Figure 1 Midline sagittal T1-weighted magnetic resonance images of the brains of a child with a normal cerebellum (**a**, arrow) and of five of the eight individuals with deletions of 3q (**b**–**f**), ordered by decreasing severity. All five have hypoplasia of the cerebellar vermis (most severe in **b**; least severe in **f**), large fluid collections in the posterior fossa and widely open communication between the 4th ventricle and the fluid collection. The severity of the malformation does not correlate with the size of the deletion. (**g**) Diagram of the eight interstitial deletions. Data from individuals LR03-317 and LR01-273 established the centromeric and telomeric boundaries, respectively, of the 7-Mb critical region. Data from individual LR01-325 defined the centromeric boundary of the smaller, 1.9-Mb critical region.

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nature genetics

FOXC1, ZIC1 and ZIC4

FOXC1 is required for normal cerebellar development and is a major contributor to chromosome 6p25.3 Dandy-Walker malformation

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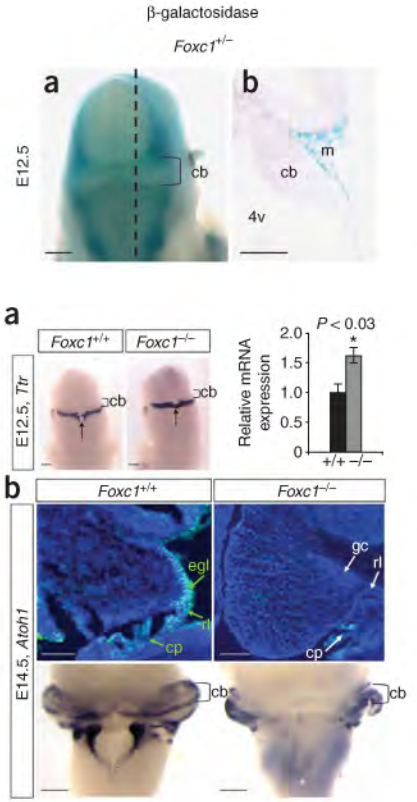
Dandy-Walker malformation (DWM), the most common human cerebellar malformation, has only one characterized associated locus[1,2]. Here we characterize a second DWM-linked locus on 6p25.3, showing that deletions or duplications encompassing *FOXC1* are associated with cerebellar and posterior fossa malformations including cerebellar vermis hypoplasia (CVH), megacisterna magna (MCM) and DWM. *Foxc1*-null mice have embryonic abnormalities of the rhombic lip due to loss of mesenchyme-secreted signaling molecules with subsequent loss of Atoh1 expression in vermis. *Foxc1* homozygous hypomorphs have CVH with medial fusion and foliation defects. Human *FOXC1* heterozygous mutations are known to affect eye development, causing a spectrum of glaucoma-associated anomalies (Axenfeld-Rieger syndrome, ARS; MIM no. 601631). We report the first brain imaging data from humans with *FOXC1* mutations and show that these individuals also have CVH. We conclude that alteration of *FOXC1* function alone causes CVH and contributes to MCM and DWM. Our results highlight a previously unrecognized role for mesenchyme-neuroepithelium interactions in the mid-hindbrain during early embryogenesis.

Malformations of the cerebellum are common, heterogeneous human birth defects with chromosomal, single-gene and complex inheritance[1–3]. CVH, MCM and DWM are generally classified as separate disorders, but they overlap in appearance, and it remains unclear whether they represent distinct entities or share a common pathogenesis[1,3,4]. We found reports supporting four classic DWM-associated loci, including chromosome 3q24 and 6p25.3, with brain imaging documentation (**Supplementary Table 1**). We



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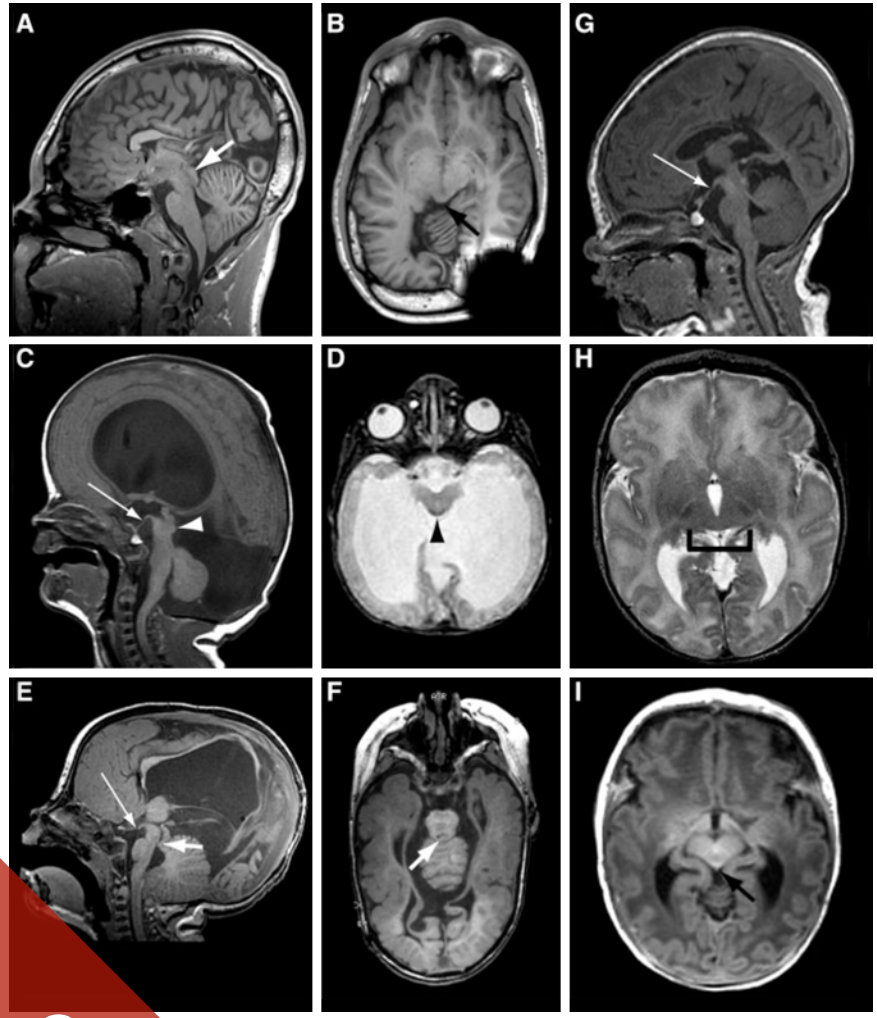

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BRAIN
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Rhombencephalosynapsis: a hindbrain malformation associated with incomplete separation of midbrain and forebrain, hydrocephalus and a broad spectrum of severity

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- Rhombencephalosynapsis: review of brain imaging 42 patients
  - HYD in 45% (19/42)
  - *Links to VACTERL-H and maternal DM*
- Congenital obstructive HYD
  - RES in 9%