syndromes associated with brain malformation - dysmorphology

Renske Oegema, MD, PhD
clinical geneticist UMC Utrecht, NL
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THE FACE PREDICTS THE BRAIN: DIAGNOSTIC SIGNIFICANCE OF MEDIAN FACIAL ANOMALIES FOR HOLOPROSENCEPHALY (ARHINENCEPHALY)

William DeMyer, M.D., Wolfgang Zeman, M.D., and Catherine Gardella Palmer, Ph.D.
Departments of Neurology, Neuropathology, and Medicine, and the Medical Genetics Program, Indiana University School of Medicine, Indianapolis

Among the more grotesque congenital anomalies is a group characterized by specific types of median facio-cerebral defects. Facial anomalies include a single eye or some lesser degree of orbital hypotelorism. In its various gradations, the brain anomaly links the severely malformed and the nearly normal members and consists of some degree of arrested prosencephalic cleavage. Since the prosenceph-

Classical lissencephaly syndromes: does the face reflect the brain?

J E Allanson, D H Ledbetter, W B Dobyns
ISOLATED LISSENCEPHALY SEQUENCE

MILLER DIEKER SYNDROME

Grade 1: AGYRIA
Grade 2: AGYRIA/PACHYGYRIA
Grade 3: PACHYGYRIA

Deletion of LIS1 and 14-3-3 epsilon
Deletion or intragenic deletion or protein truncating mutation of LIS1
Missense mutation of LIS1

Source: J Child Neurol © 2005 BC Decker, Inc.
Miller Dieker syndrome, del 17p13.3 incl LIS1 en YWHAE

- Postnatal mild hypotonia, feeding difficulties can be present
- Progressive DD, hypotonia
- Progressive microcephaly
- Within first months onset intractable seizures
- Limited life expectancy
MDS facial phenotype

- Prominent forehead 26/26
- Short nose with upturned nares 26/26
- Protuberant upper lip 24/25
- Thin upper lip vermilion border 25/25
- Small jaw 26/27

Vertical furrows

Dobyns, LMD
Baraitser–Winter cerebrofrontofacial syndrome

ID (variable)
Dysmorphism (variable)
Iris or retinal coloboma, ptosis
Sensorineural deafness
Postnatal microcephaly
Progressive joint stiffness, congenital arthrogryposis
Cleft lip and palate, hallux duplex, congenital heart defects and renal tract anomalies are reported.

MRI: pachygyria with anteroposterior severity gradient, SBH, prominent perivascular spaces
De novo mutations in ACTB or ACTG1

- Mutational hotspot: p.Arg196
- Encoding non-muscle specific actins
- ACTG1- milder facial phenotype
- ACTG1 – pachy/LIS more frequent

ACTG1

Di Donato 2016
Actin-related MCD: wide phenotypic spectrum

Dominant negative missense mutations

ACTB

ACTB

ACTG1
Deafness, ID, epilepsy
22q11.2 microdeletion

Hemiparesis, mild cognitive delay
Unilateral polymicrogyria
1p36 deletion syndrome

Heilstedt 2003
1p36 neuroimaging

- microcephaly
- ventriculomegaly
- cerebral atrophy
- abnormal patchy signal in white matter, delayed myelination
- **polymicrogyria (13/64 Dobyns)**
- PNH
- hypoplasia or agenesis of the corpus callosum
- holoprosencephaly
- cerebellar hypoplasia
- choroid plexus hyperplasia
Consistent Chromosome Abnormalities Identify Novel Polymicrogyria Loci in 1p36.3, 2p16.1–p23.1, 4q21.21–q22.1, 6q26–q27, and 21q2

William B. Dobyns,1,2,3* Ghayda Mirzaa,1,4 Susan L. Christian,1 Kristin Petras,1 Jessica Roseberry,1,16 Gary D. Clark,5 Cynthia J.R. Curry,6 Donna McDonald-McGinn,7 Livija Medne,7 Elaine Zackai,7 Julie Parsons,8 Dina J. Zand,9 Fuki M. Hisama,10 Christopher A. Walsh,10,11 Richard J. Leventer,12 Christa L. Martin,13 Marzena Gajecka,14 and Lisa G. Shaffer14,15

1Department of Human Genetics, The University of Chicago, Chicago, Illinois
2Department of Neurology, The University of Chicago, Chicago, Illinois
Periventricular nodular heterotopia

**Broad clinical spectrum**

**ARFGEF2**
- ID
- Microcephaly
- Movement disorder
- Cardiomyopathy

**Filamine A**
- Cardiovascular
- Gastrointestinal
- Mild dysmorphism
- Skeletal defects
- 

**INTS8**
Severe ID
Microcephaly
Epilepsy
Cerebral blindness
Absent speech
Spastic tetraplegia
Overlapping toes
INTS8 mutations

Compound heterozygous mutations:

*Integrator Complex Subunit 8 (INTS8)*

- 1\(^{st}\) mutation: p.D297G, pat; exon 7
  - Affects splicing
- 2\(^{nd}\) mutation: p.972delEVL, mat; exon 26

Oegema et al, Plos Gen 2017
Integrator Complex

- 14 subunits
- Associates with RNA polymerase II
- Role in
  - Transcription regulation
  - RNA processing
  - Especially non coding RNA's (enhancers, snRNAs)
ID, epilepsy, cleft palate, temper tantrums, narcolepsy, autism

- Smith Magenis syndrome
- $RAI1$ mutation
Last visit at age 9 yr, no walking, no speech, not able to perform simple tasks. Eating and swallowing ok, uses the fork; not toilet trained; constipation; anxious behavior, stereotypic hand clapping.

Examination: height 130 cm (- 2 SD), HC 54,0 cm (+1 SD). Facial features with small chin, small mouth, mild hypertelorism, broad forehead, thin long fingers and toes, no eye contact. High DTR, no clonus.
DDX3X

- De novo DDX3X variant (c.1492A>G, Thr498Ala)
- "Mental retardation, X-linked 102", OMIM 300958
- Prevalence 1-3% in females with ID
- Ref Sneijders-Blok: 4/37 cortical malformation

Mutations in DDX3X Are a Common Cause of Unexplained Intellectual Disability with Gender-Specific Effects on Wnt Signaling

<table>
<thead>
<tr>
<th>Development</th>
<th>Percentage</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual disability or developmental delay</td>
<td>100%</td>
<td>38/38</td>
</tr>
<tr>
<td>Mild or mild-moderate disability</td>
<td>26%</td>
<td>10/38</td>
</tr>
<tr>
<td>Moderate or moderate-severe disability</td>
<td>26%</td>
<td>10/38</td>
</tr>
<tr>
<td>Severe disability</td>
<td>40%</td>
<td>15/38</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>8%</td>
<td>3/38</td>
</tr>
<tr>
<td>Growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low weight</td>
<td>32%</td>
<td>12/38</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>32%</td>
<td>12/38</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotonia</td>
<td>76%</td>
<td>29/38</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>16%</td>
<td>6/38</td>
</tr>
<tr>
<td>Movement disorder (including spasticity)</td>
<td>45%</td>
<td>17/38</td>
</tr>
<tr>
<td>Behavior problems</td>
<td>53%</td>
<td>20/38</td>
</tr>
<tr>
<td>Brain MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corpus callosum hypoplasia</td>
<td>35%</td>
<td>13/37</td>
</tr>
<tr>
<td>Cortical malformation</td>
<td>11%</td>
<td>4/37</td>
</tr>
<tr>
<td>Ventricular enlargement</td>
<td>35%</td>
<td>13/37</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin abnormalities</td>
<td>37%</td>
<td>14/38</td>
</tr>
<tr>
<td>Hyperlaxity</td>
<td>37%</td>
<td>14/38</td>
</tr>
<tr>
<td>Visual problems</td>
<td>34%</td>
<td>13/38</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>8%</td>
<td>3/38</td>
</tr>
<tr>
<td>Cleft lip or palate</td>
<td>8%</td>
<td>3/38</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td>13%</td>
<td>5/38</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>11%</td>
<td>4/38</td>
</tr>
</tbody>
</table>
DDX3X mutations in two girls with a phenotype overlapping Toriello–Carey syndrome

Nicola Dikow | Martin Granzow | Luitgard M. Graul-Neumann
Stephanie Karch | Katrin Hinderhofer | Nagarajan Paramasivam
Laura-Jane Behl | Lilian Kaufmann | Christine Fischer | Christina Evers
Matthias Schlesner | Roland Eils | Guntram Borck | Christiane Zweier
Claus R. Bartram
Goldberg-Shprintzen syndrome

- Hirschsprung’s disease
- DD/ ID
- Ptosis
- Dysmorphic features

- Bi-allelic mutations in \textit{KIAA1279} (\textit{KBP}).
Van Maldergem syndrome

ID
Dysmorphism
Auditory malformation
Skeletal/ limb malformations
Van Maldergem syndrome, AR
Laminar periventricular heterotopia
Mutations in DCHS1, FAT4
**NEDD4L (AD)**

- PNH
- PMG
- 2-3 toe syndactyly
- 3-4(-5) finger syndactyly
- Hypotonia
- ID (can be mild)
- Cleft palate/ bifid uvula

Broix 2016, Meuwissen personal communication
Severe ID
Absent speech
Microcephaly
Seizures
Autistic features
Dysmorphism
DYRK1A haploinsufficiency causes a new recognizable syndrome with microcephaly, intellectual disability, speech impairment, and distinct facies.

100%: ID, poor speech, microcephaly, short stature, dysmorphism

66%: brain abn, eye defects, seizures, ataxia, IUGR, feeding difficulties
Brain MRI was performed on 11 individuals. The most common abnormalities found were small brain stem (9/11), enlarged ventricles (7/11), microcephaly (3/11), hypoplastic pituitary stalk (6/11), white matter hypomyelination (5/11), hypoplastic corpus callosum (3/11), cortical atrophy/ frontal lobe atrophy (3/11), gliosis (3/11), and thin optic chiasm (2/11) (Figure 2). These findings are indicative of global cerebral underdevelopment or hypomyelination.
PNH- syndromal

**Chromosomal**
- Del 1p36
- Del 17p11.2 (Smith Magenis)
- Del 16q24.3 (incl ANKRD11/KBG)
- Del 11q (Jacobsen syndrome)
- del 17q21.31 (Koolen-De Vries syndrome)
- 5p/5q
- ..

**Monogenic**
- Smith –Magenis (RAI1)
- Van Maldergem syndrome (DCHS1, FAT4)**
- NEDD4L
- FLNA (non-syndromal + syndromal)
- ARFGEF2
- CRB2 (ventriculomegaly with cystic kidney disease)
- MPPH syndrome (AKT3)
- TARP syndrome (RBM10)
- BWS (ACTG1, ACTB)
Polymicrogyria

“Individuals classified as having polymicrogyria have such diverse clinical courses and outcomes, causes and recurrence risks, associated malformations and syndromes, and imaging and neuropathological abnormalities as to render the term no more specific than that of intellectual disability.”

[Guerrini and Dobyns, Lancet Neurol 2014]
Polymicrogyria

Chromosomal

- Del 1p36.3
- Dupl 2p13p23
- Del 4q21q22
- Dele 6q26q27
- Dele 13q3
- Del 18p11
- Del 21q2
- Del 22q11.2

Monogenic

- Microcephaly syndromes
- Micro syndrome (RAB3GAP1, RAB3GAP2, RAB18)
- Megalencephaly syndromes
- DDX3X
- Chudley-McCullough (GPSM2)
- Goldberg-Shprintzen (KIAA1279)
- Fumaric aciduria
- Zellweger syndrome
- Aicardi syndrome
- Knobloch syndrome
- Vic syndrome
- Joubert syndrome

Remember the non-genetic causes!

[Guerrini and Dobyns, Lancet Neurol 2014]
Thank you!

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COST
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IN SCIENCE & TECHNOLOGY

Neuro-MIG