Wilhelmina Children's Hospital

# syndromes associated with brain malformation - dysmorphology

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Milano, 2018

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# THE FACE PREDICTS THE BRAIN: DIAGNOSTIC SIGNIFICANCE OF MEDIAN FACIAL ANOMALIES FOR HOLOPROSENCEPHALY (ARHINENCEPHALY)

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*Departments of Neurology, Neuropathology, and Medicine, and the Medical Genetics Program, Indiana University School of Medicine, Indianapolis*

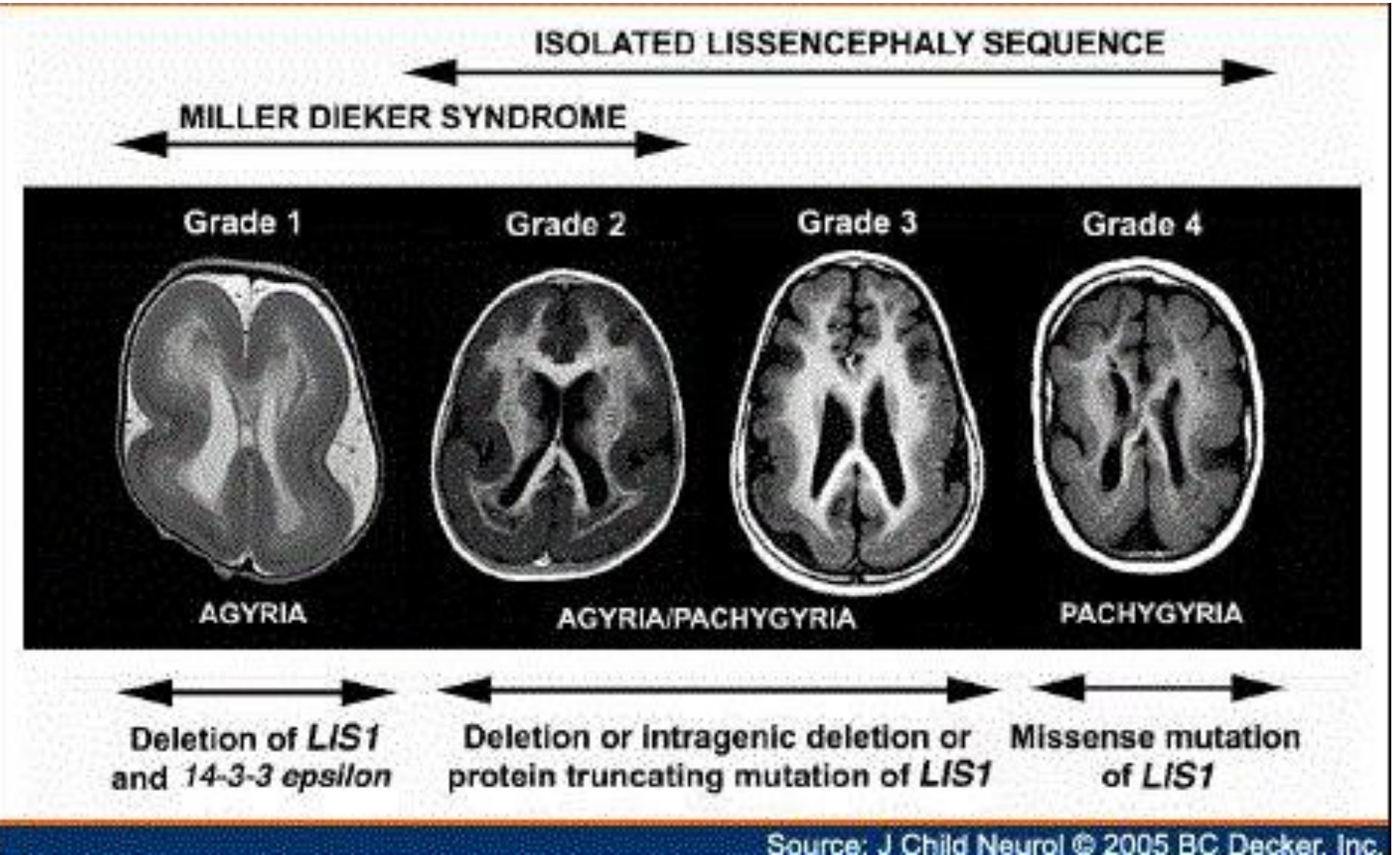
AMONG the more grotesque congenital anomalies is a group characterized by specific types of median facio-cerebral defects. Facial anomalies include a single eye or some lesser degree of orbital hypotelor-

anomaly.[1,2] 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.[1,2] Since the prosenceph-

*J Med Genet* 1998;35:920–923

# Classical lissencephaly syndromes: does the face reflect the brain?

J E Allanson, D H Ledbetter, W B Dobyns




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

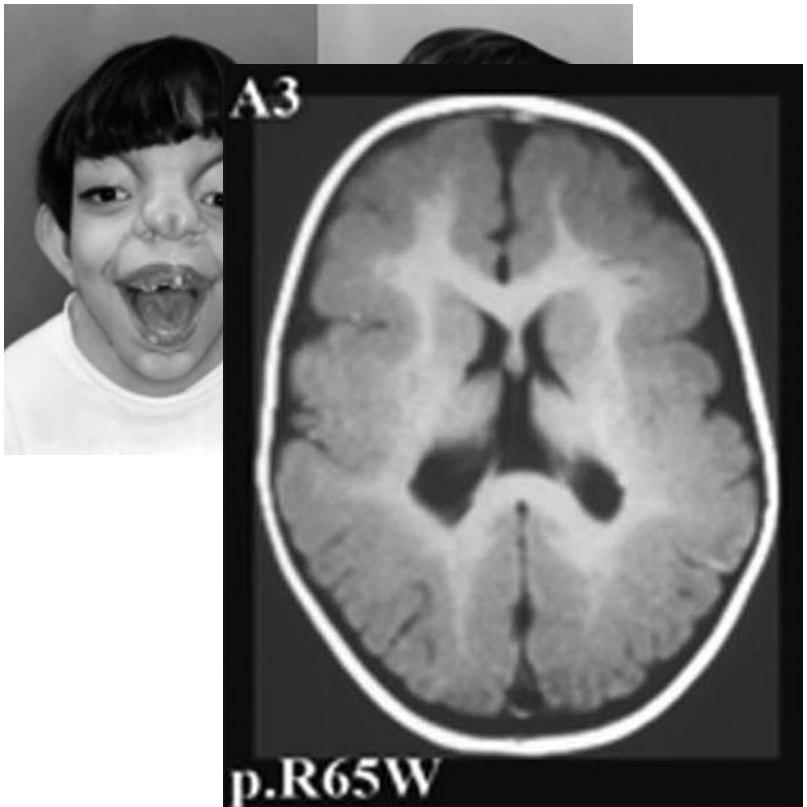
- Prominent forehead 26/26
- Short nose with upturned nares 26/26
- Protuberant upper lip 24/25
- Thin upper lip vermillion border 25/25
- Small jaw 26/27

Vertical furrows

*Dobyns, LMD*

# Baraitser–Winter cerebrofrontofacial syndrome

*Verloes 2015*




ID (variable)

Dysmorphism (variable)

Iris or retinal coloboma, ptosis

Sensorineural deafness

Postnatal microcephaly

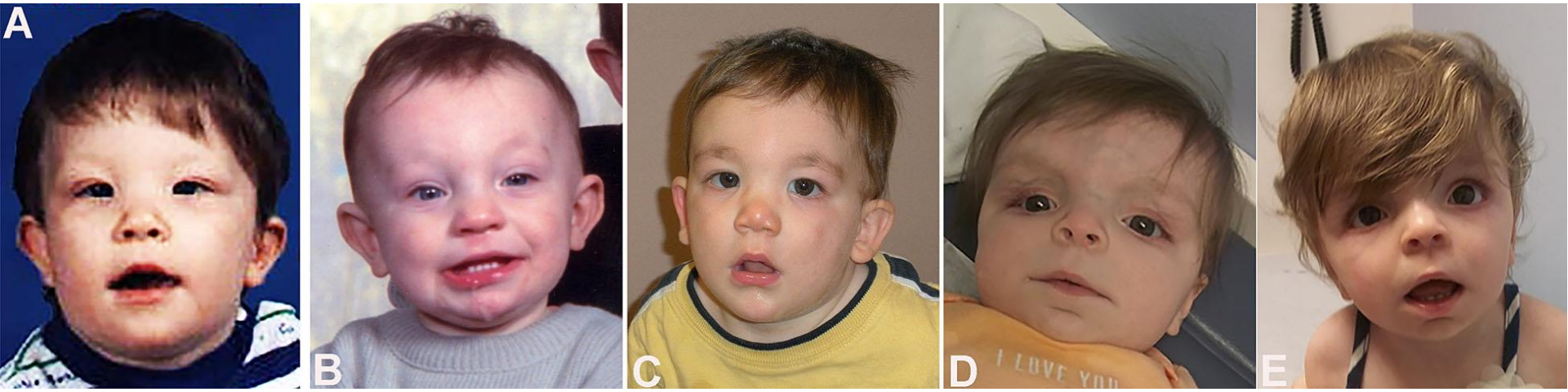
Progressive joint stiffness, congenital arthrogryposis

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

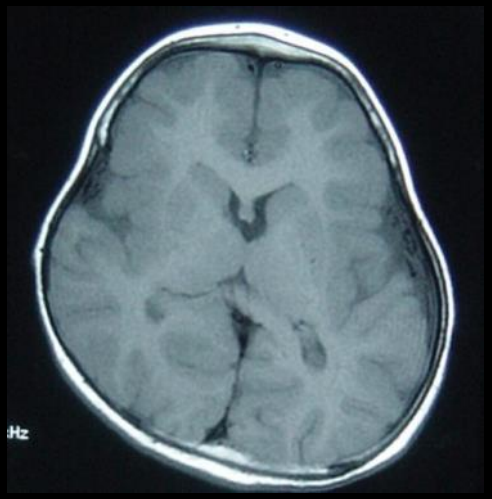
*Di Donato 2016*

# Actin-related MCD: wide phenotypic spectrum

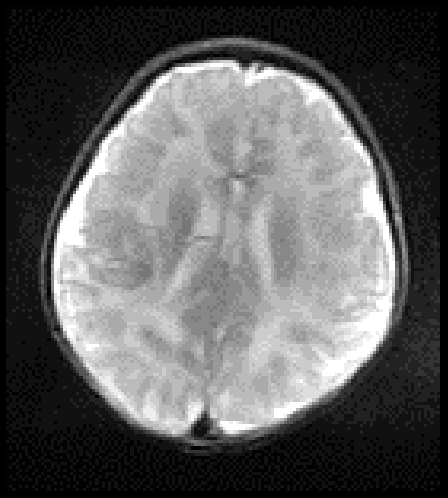
Grazia Mancini

Dominant negative missense mutations

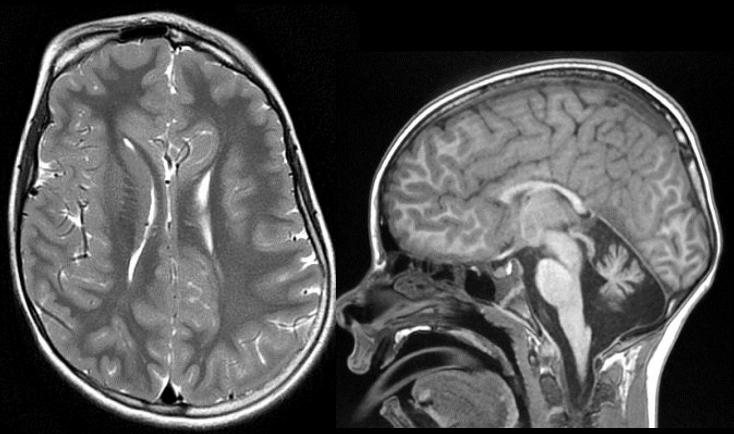
**ACTB**



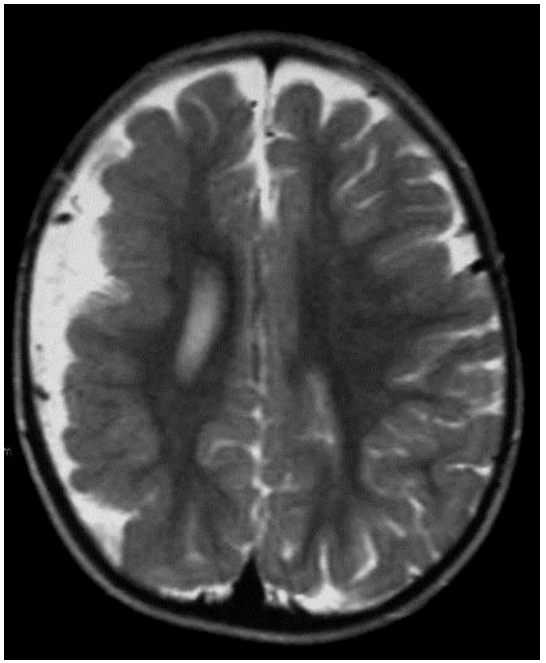
**ACTB**



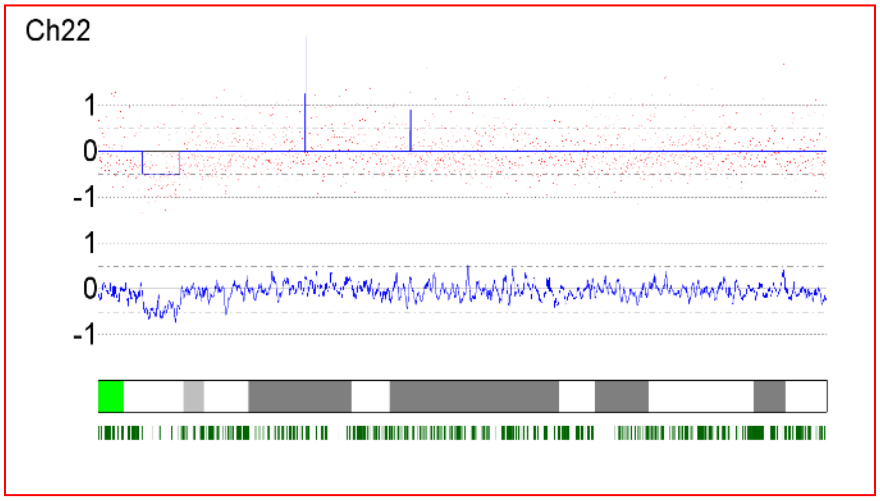
**ACTG1**
**Deafness, ID, epilepsy**



# 22q11.2 microdeletion



Hemiparesis, mild cognitive delay
Unilateral polymicrogyria

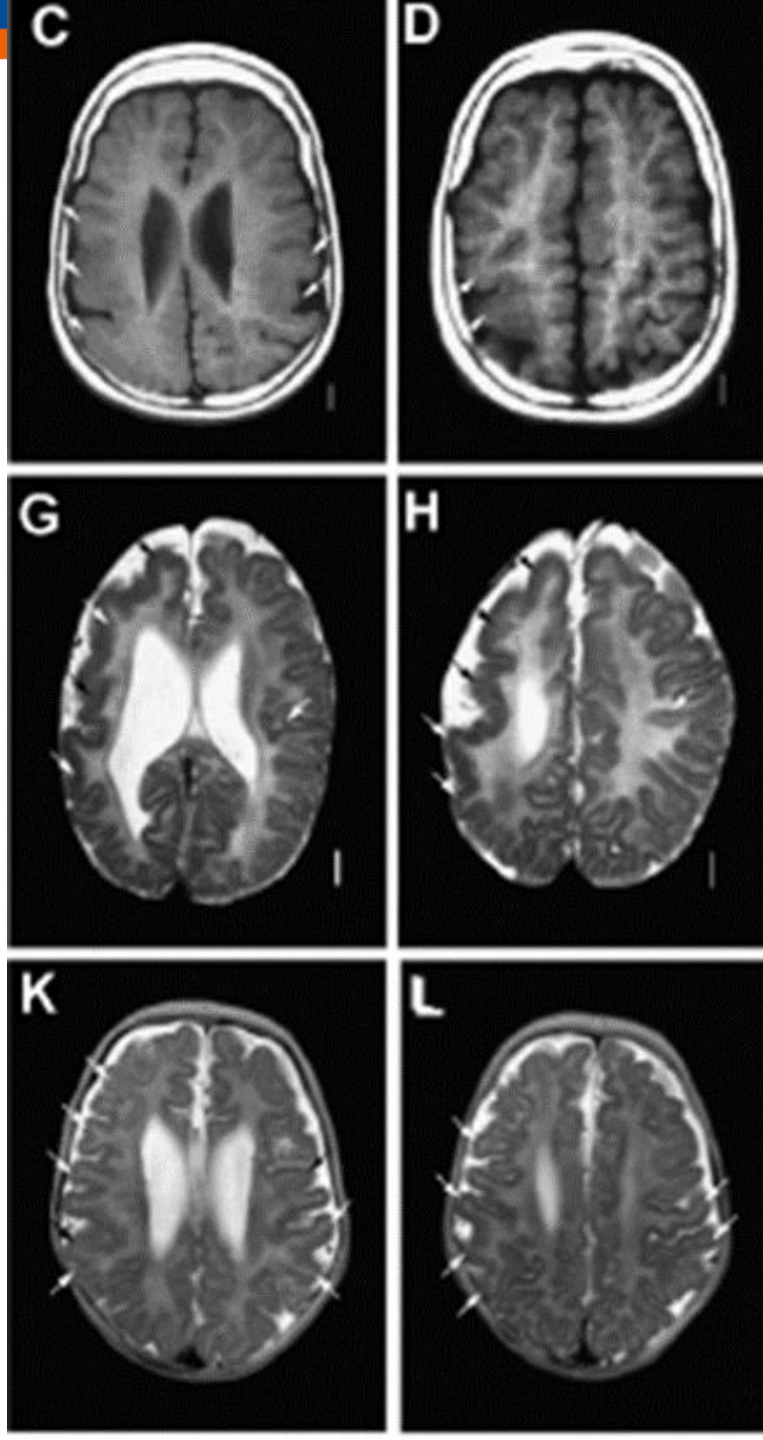


1p36 deletion syndrome

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



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American Journal of Medical Genetics Part A 146A:1637–1654 (2008)

# 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. Shaffer[14,15]**

[1]Department of Human Genetics, The University of Chicago, Chicago, Illinois
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# Periventricular nodular heterotopia

**Broad clinical spectrum**

*ARFGEF2*

ID

Microcephaly

Movement disorder

Cardiomyopathy

*Filamine A*

Cardiovascular

Gastrointestinal

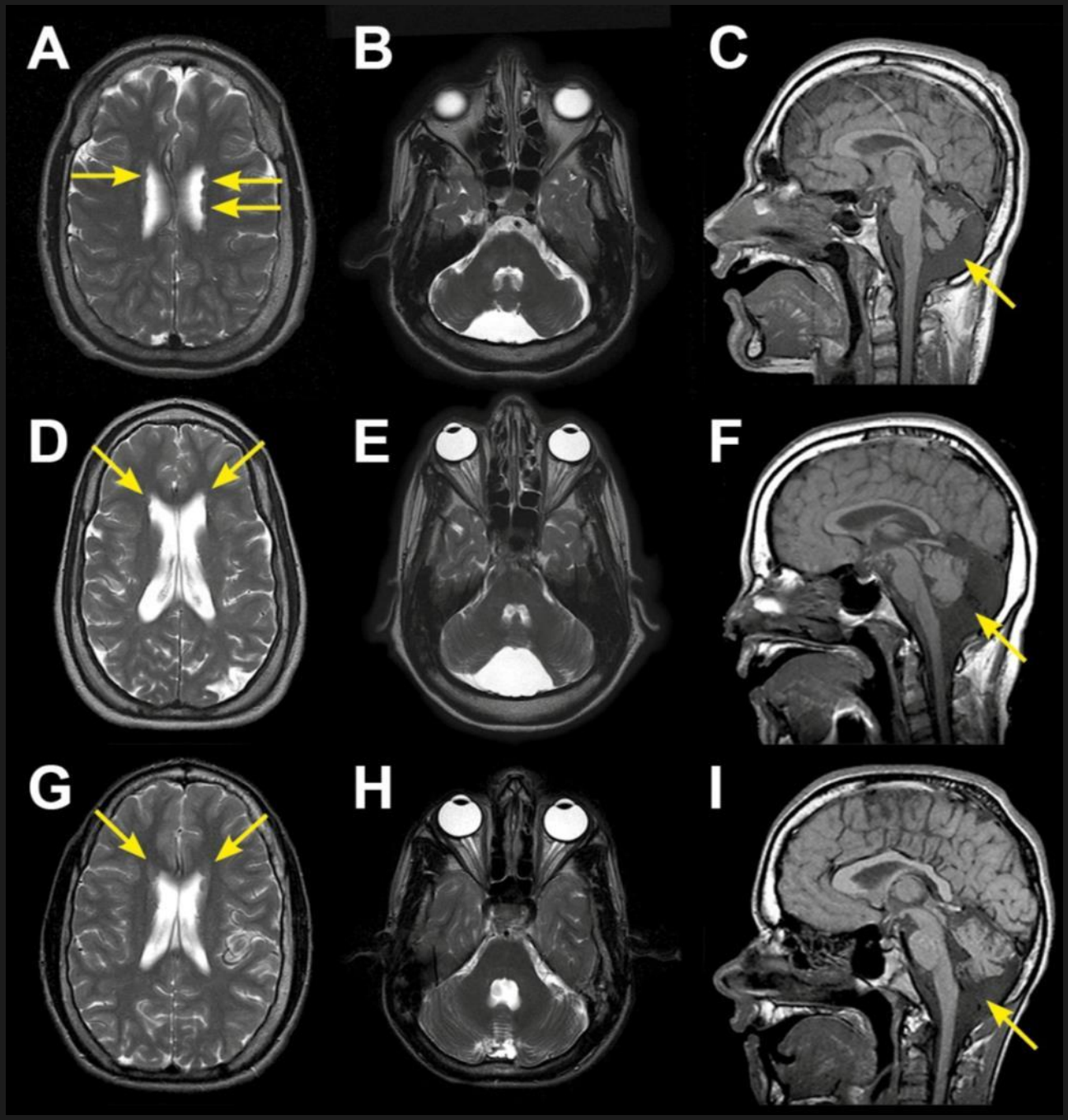
Mild dysmorphism

Skeletal defects

…..

*INTS8*

- Severe ID
- Microcephaly
- Epilepsy
- Cerebral blindness
- Absent speech
- Spastic tetraplegia
- Overlapping toes


A
B
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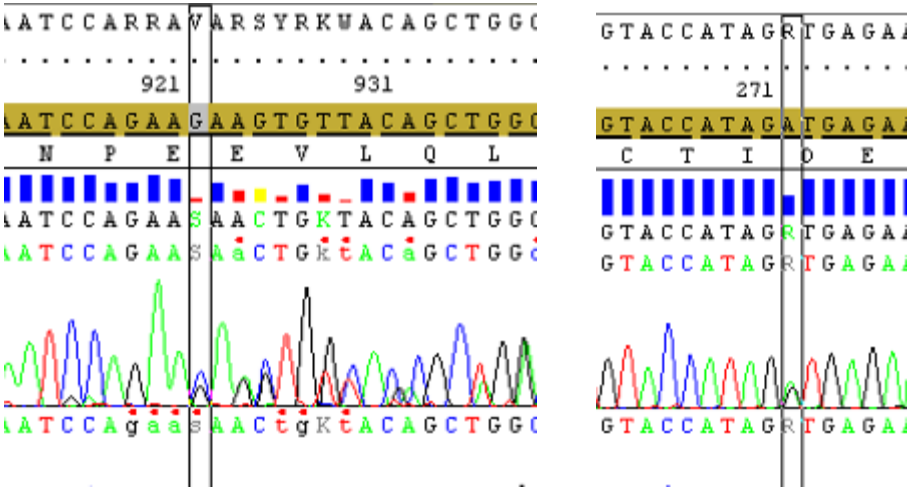
# INTS8 mutations

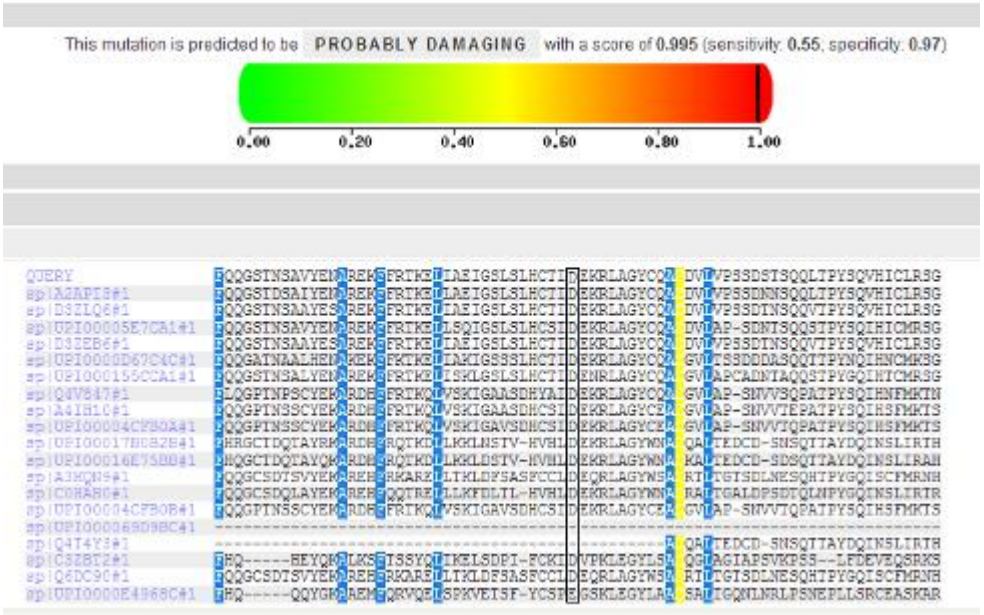
*Oegema et al, Plos Gen 2017*

Compound heterozygous mutations :

*Integrator Complex Subunit 8 (**INTS8**)*

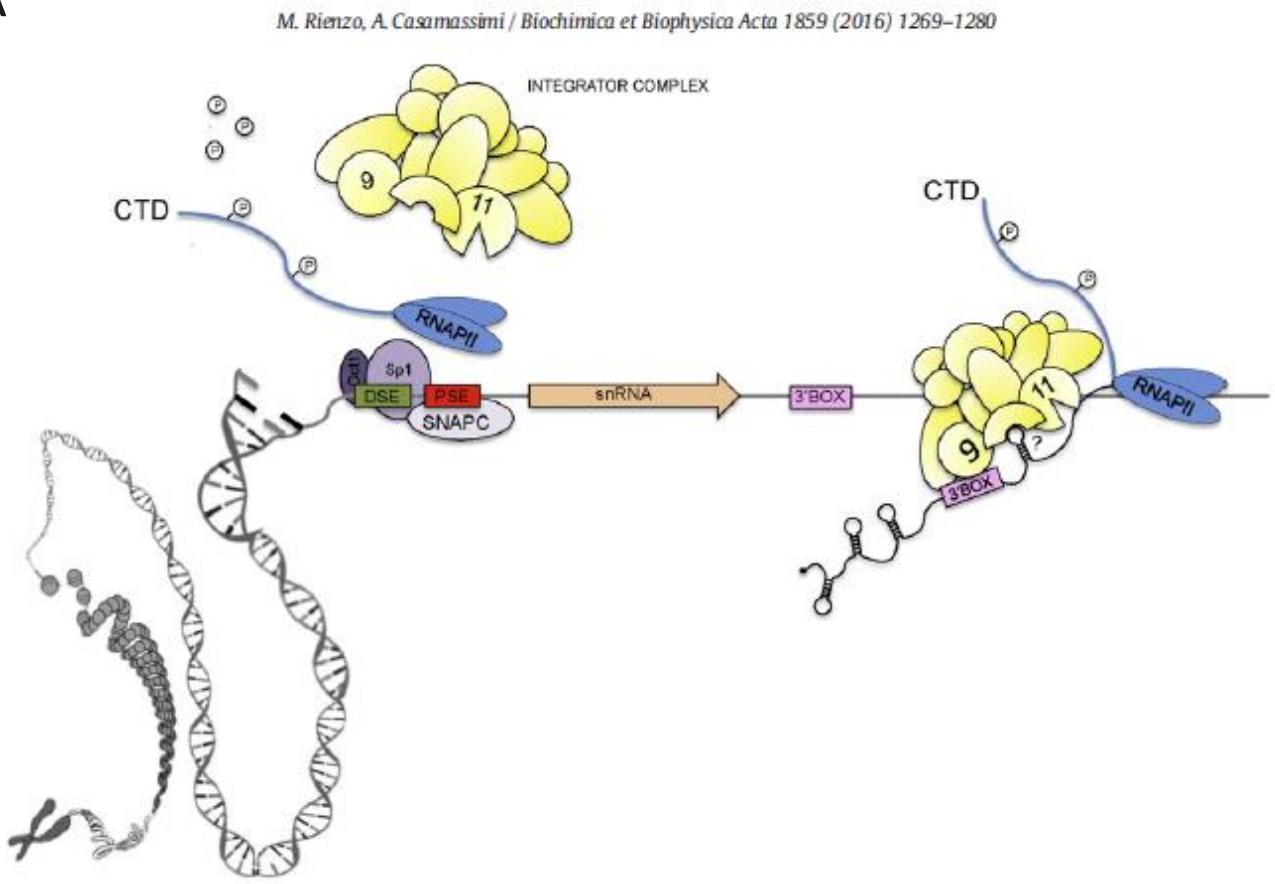
- 1st mutation: p.D297G,pat; exon 7
  - Affects splicing
- 2nd mutation: p.972delEVL,mat; exon 26



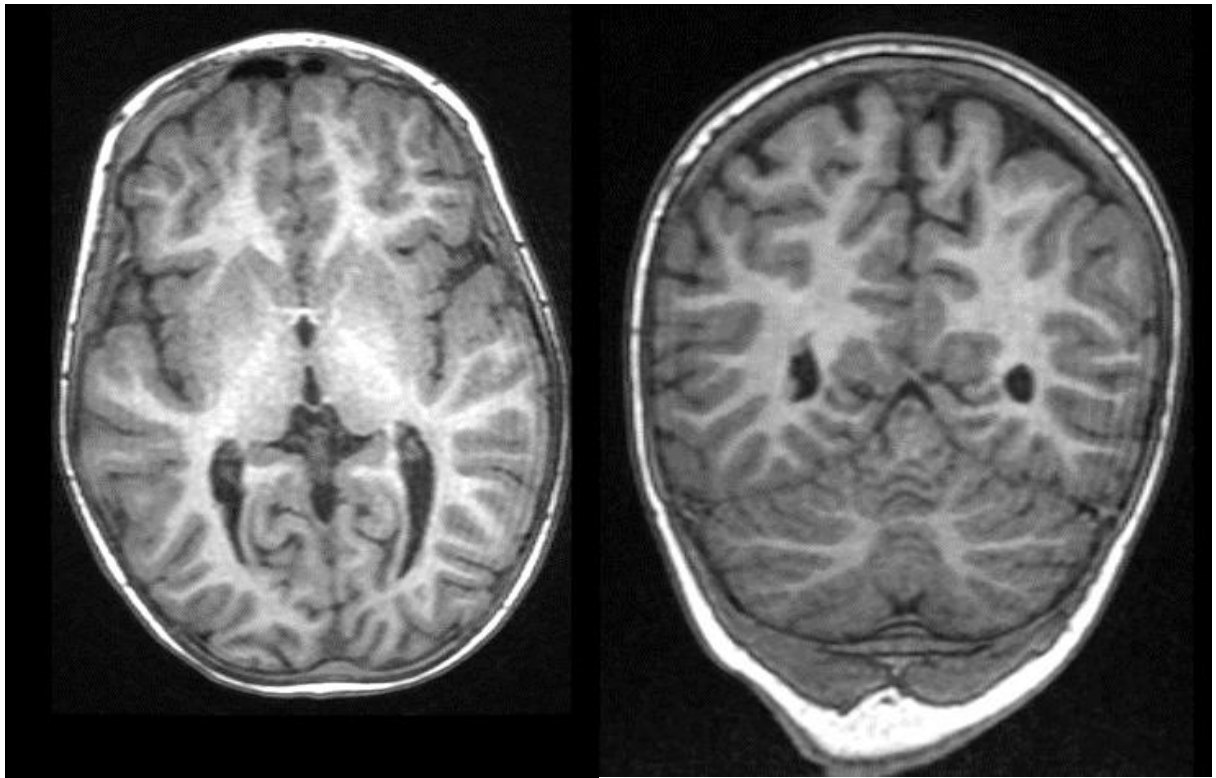
# Integrator Complex

- 14 subunits
- Associates with RNA polymerase II
- Role in
  - Transcription regulation
  - RNA processing
  - Especially non coding RNA's (enhancers, snRNAs)

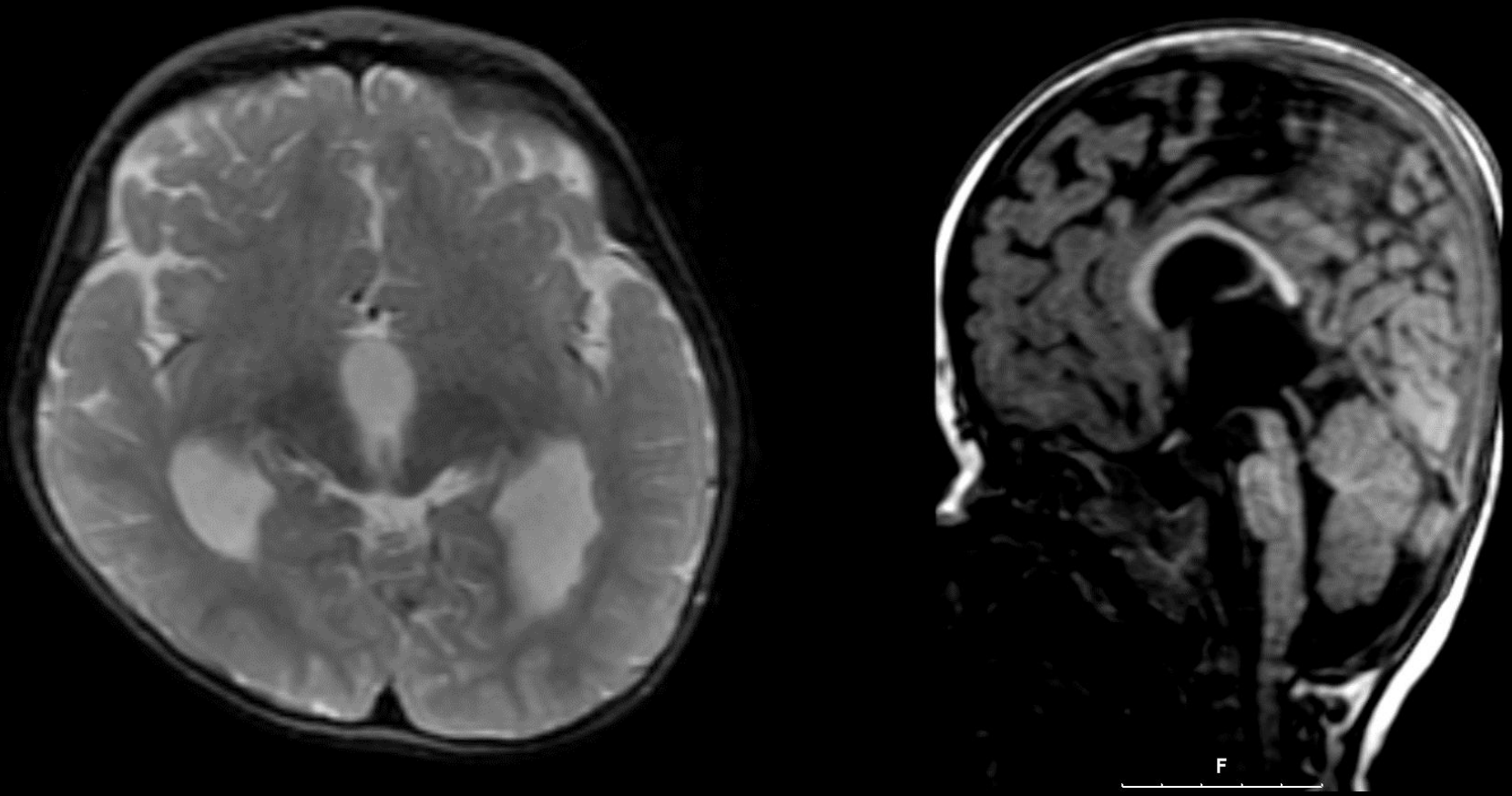


ID, epilepsy, cleft palate, temper tantrums, narcolepsy, autism

- Smith Magenis syndrome
- *RAI1* mutation



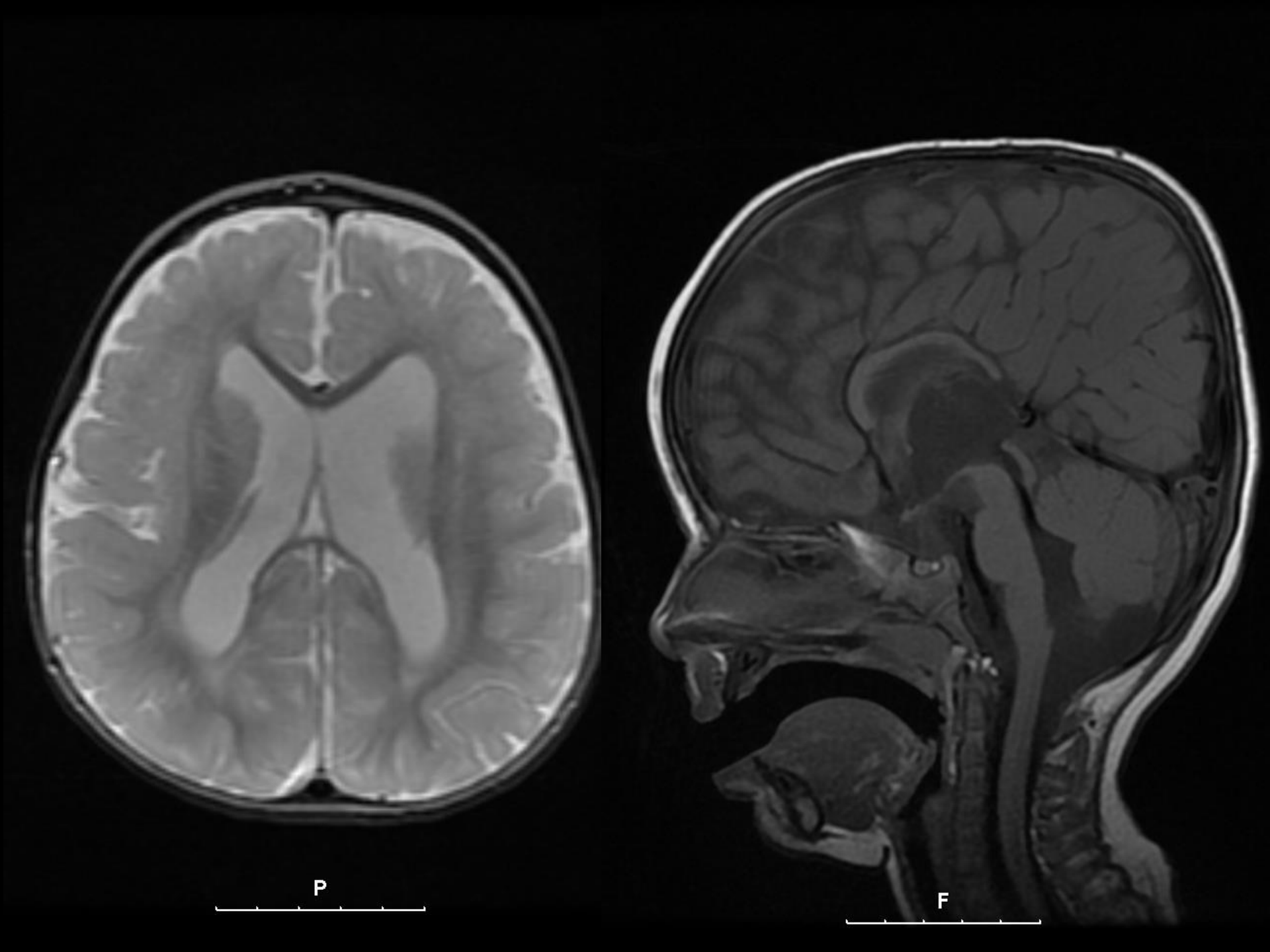
# Del 17p11.2



Last visit at age 9 yr, no walking, no speech, not able to perform simple tasks.

Eating and swalowing 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.


P
F

# 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

Lot Snijders Blok,[1,48] Erik Madsen,[2,48] Jane Juusola,[3,48] Christian Gilissen,[1] Diana Baralle,[4] Margot R.F. Reijnders,[1] Hanka Venselaar,[5] Céline Helsmoortel,[6] Megan T. Cho,[3] Alexander Hoischen,[1] Lisenka E.L.M. Vissers,[1] Tom S. Koemans,[1] Willemijn Wissink-Lindhout,[1] Evan E. Eichler,[7,8] Corrado Romano,[9] Hilde Van Esch,[10] Connie Stumpel,[11] Maaike Vreeburg,[11] Eric Smeets,[11] Karin Oberndorff,[12] Bregje W.M. van Bon,[1,13] Marie Shaw,[13] Jozef Gecz,[13] Eric Haan,[13,14] Melanie Bienek,[15] Corinna Jensen,[15] Bart L. Loeys,[6] Anke Van Dijck,[6] A. Micheil Innes,[16] Hilary Racher,[16] Sascha Vermeer,[17] Nataliya Di Donato,[18] Andreas Rump,[18] Katrina Tatton-Brown,[19] Michael J. Parker,[20] Alex Henderson,[21] Sally A. Lynch,[22] Alan Fryer,[23] Alison Ross,[24] Pradeep Vasudevan,[25] Usha Kini,[26] Ruth Newbury-Ecob,[27] Kate Chandler,[28] Alison Male,[29] the DDD Study, Sybe Dijkstra,[30]

**Table 2. Clinical Features of Females with De Novo *DDX3X* Mutations**

| | Percentage | Number |
|---|---|---|
| **Development** | | |
| Intellectual disability or developmental delay | 100% | 38/38 |
| Mild or mild-moderate disability | 26% | 10/38 |
| Moderate or moderate-severe disability | 26% | 10/38 |
| Severe disability | 40% | 15/38 |
| Developmental delay | 8% | 3/38 |
| **Growth** | | |
| Low weight | 32% | 12/38 |
| Microcephaly | 32% | 12/38 |
| **Neurology** | | |
| Hypotonia | 76% | 29/38 |
| Epilepsy | 16% | 6/38 |
| Movement disorder (including spasticity) | 45% | 17/38 |
| Behavior problems | 53% | 20/38 |
| **Brain MRI** | | |
| Corpus callosum hypoplasia | 35% | 13/37 |
| Cortical malformation | 11% | 4/37 |
| Ventricular enlargement | 35% | 13/37 |
| **Other** | | |
| Skin abnormalities | 37% | 14/38 |
| Hyperlaxity | 37% | 14/38 |
| Visual problems | 34% | 13/38 |
| Hearing loss | 8% | 3/38 |
| Cleft lip or palate | 8% | 3/38 |
| Precocious puberty | 13% | 5/38 |
| Scoliosis | 11% | 4/38 |

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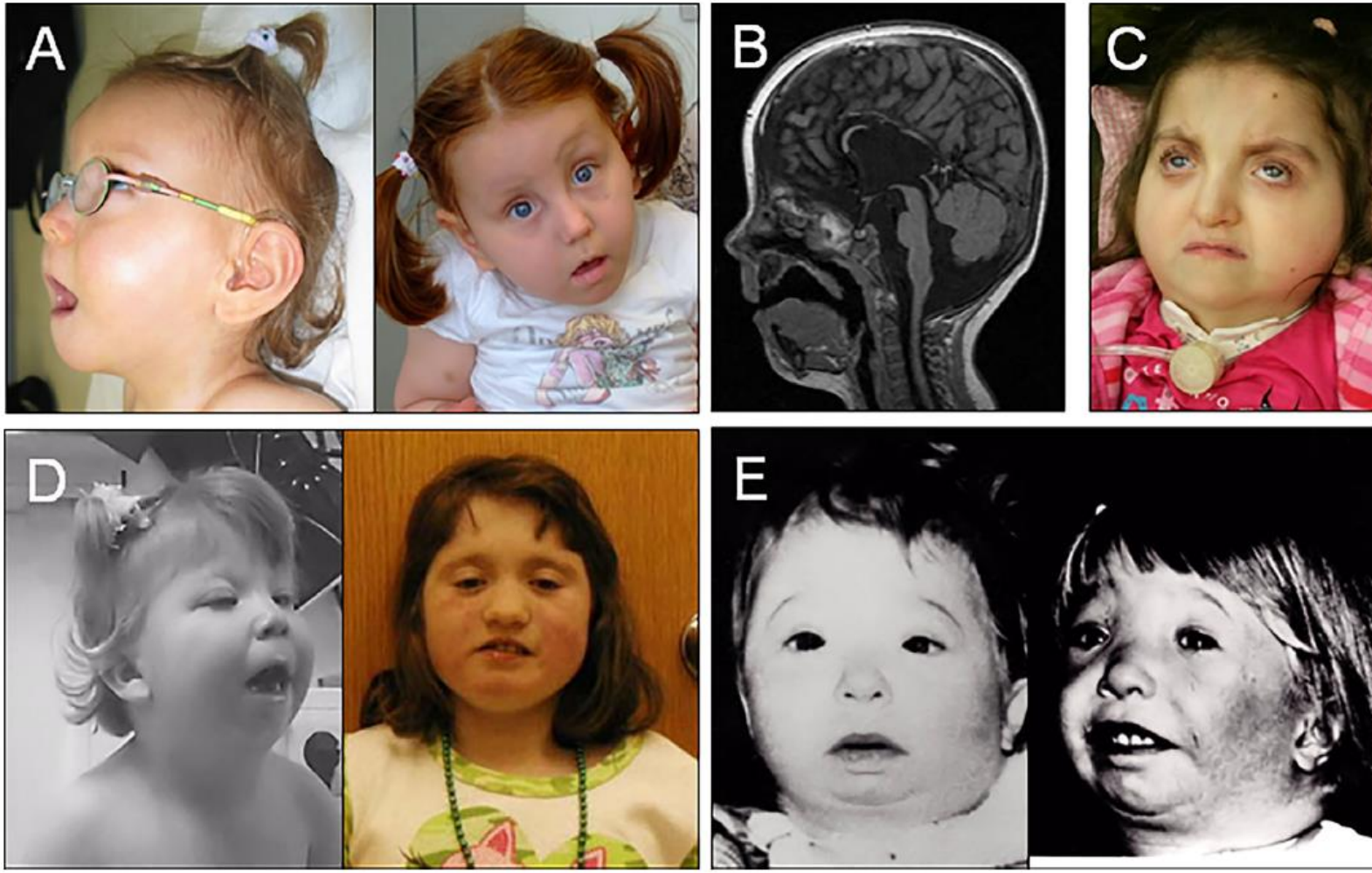
DOI 10.1002/ajmg.a.38164

CLINICAL REPORT

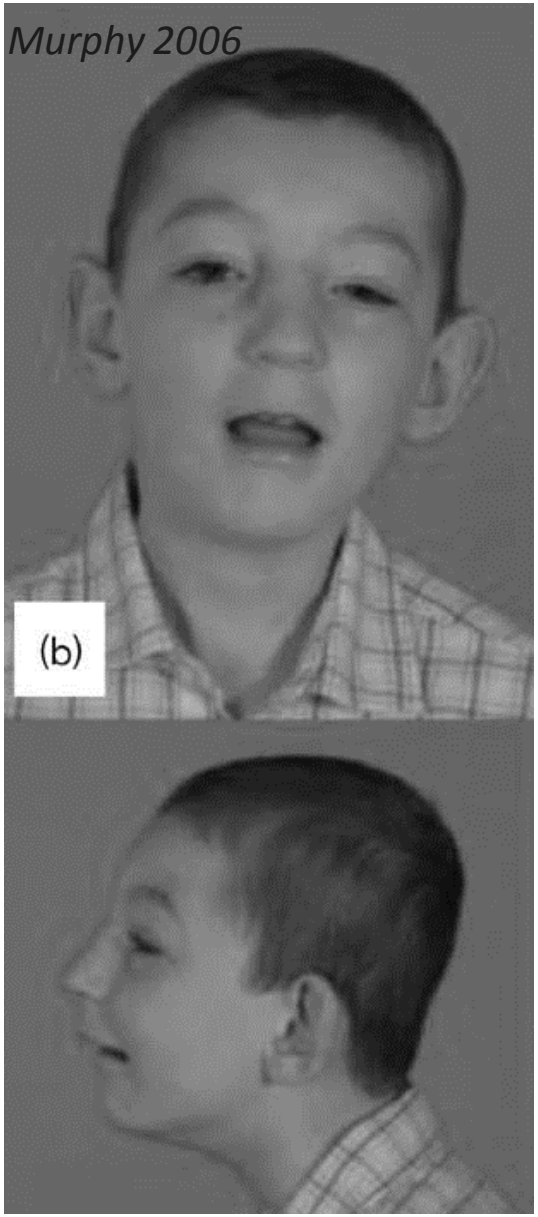
WILEY AMERICAN JOURNAL OF medical genetics PART A

# *DDX3X* mutations in two girls with a phenotype overlapping Toriello–Carey syndrome

Nicola Dikow[1] | Martin Granzow[1] | Luitgard M. Graul-Neumann[2] | Stephanie Karch[3] | Katrin Hinderhofer[1] | Nagarajan Paramasivam[4,5] | Laura-Jane Behl[6] | Lilian Kaufmann[1] | Christine Fischer[1] | Christina Evers[1] | Matthias Schlesner[5] | Roland Eils[5,7] | Guntram Borck[8] | Christiane Zweier[9] | Claus R. Bartram[1] | [illegible]

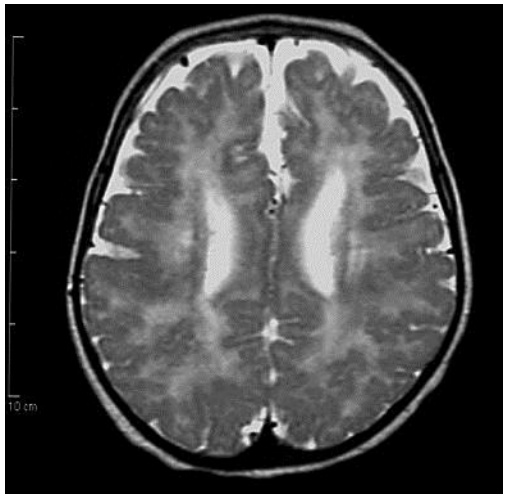


# Goldberg-Shprintzen syndrome




- **Hirschsprung's disease**
- **DD/ ID**
- **Ptosis**
- **Dysmorphic features**

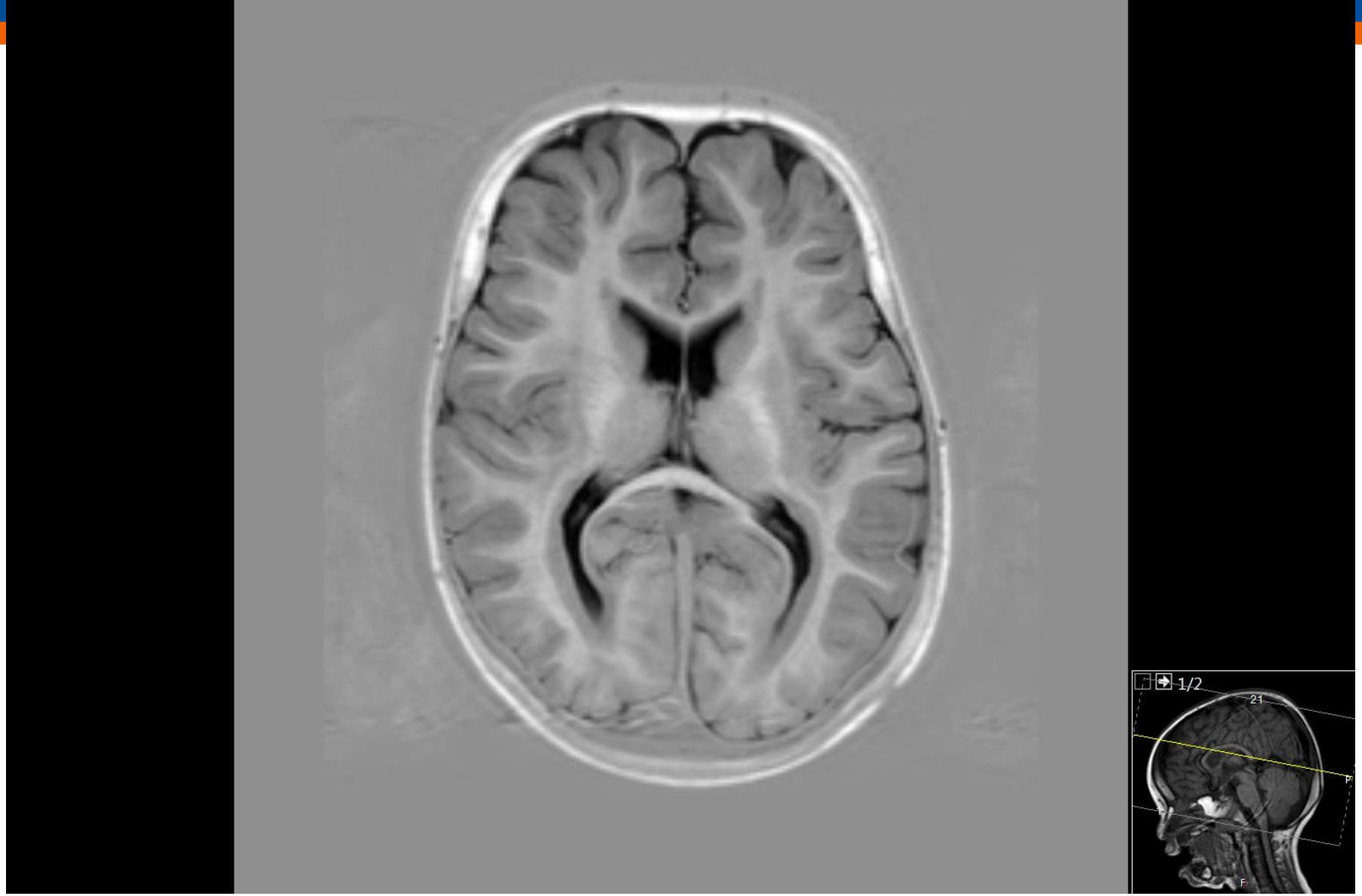
- **Bi-allelic mutations in *KIAA1279* (*KBP*).**



Brooks. AJHG 2005

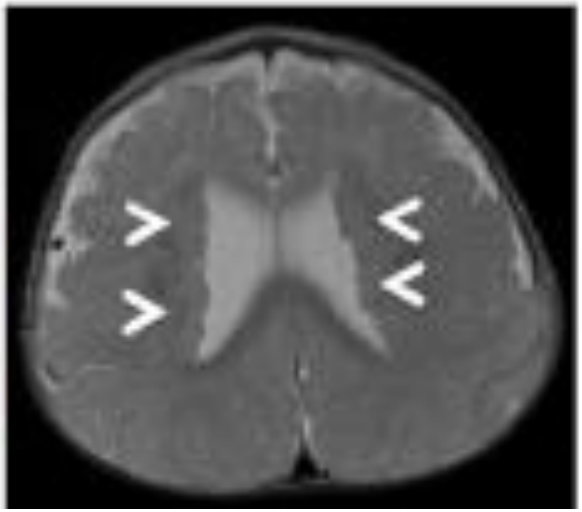
# Van Maldergem syndrome

- ID
- Dysmorphism
- Auditory malformation
- Skeletal/ limb malformations




Van Maldergem syndrome, AR
Laminar periventricular heterotopia
Mutations in DCHS1, FAT4

# *NEDD4L* (AD)



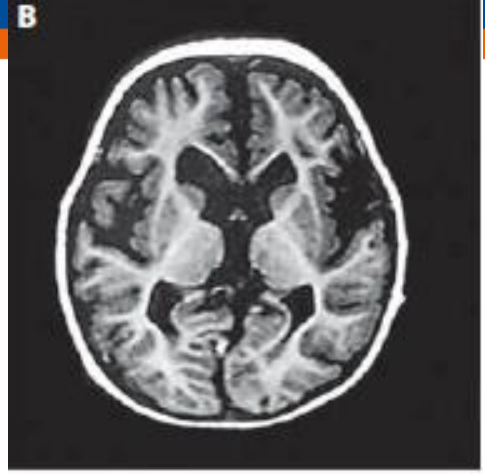
- PNH
- PMG
- 2-3 toe syndactyly
- 3-4(-5) finger syndactyly
- Hypotonia
- ID (can be mild)
- Cleft palate/ bifid uvula

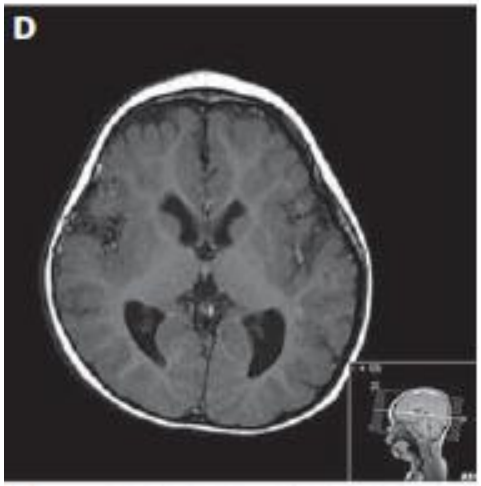
*Broix 2016, Meuwissen personal communication*

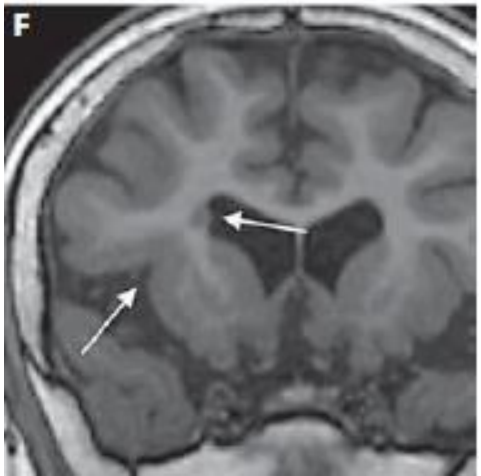
# Distinctive Phenotypic Abnormalities Associated with Submicroscopic 21q22 Deletion Including *DYRK1A*

R. Oegema[a] A. de Klein[a] A.J. Verkerk[b] R. Schot[a] B. Dumee[b] H. Douben[a]
B. Eussen[a] L. Dubbel[a] P.J. Poddighe[a] I. van der Laar[a] W.B. Dobyns[c]
P.J. van der Spek[b] M.H. Lequin[d] I.F.M. de Coo[e] M.-C.Y. de Wit[e] M.W. Wessels[a]
G.M.S. Mancini[a]

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

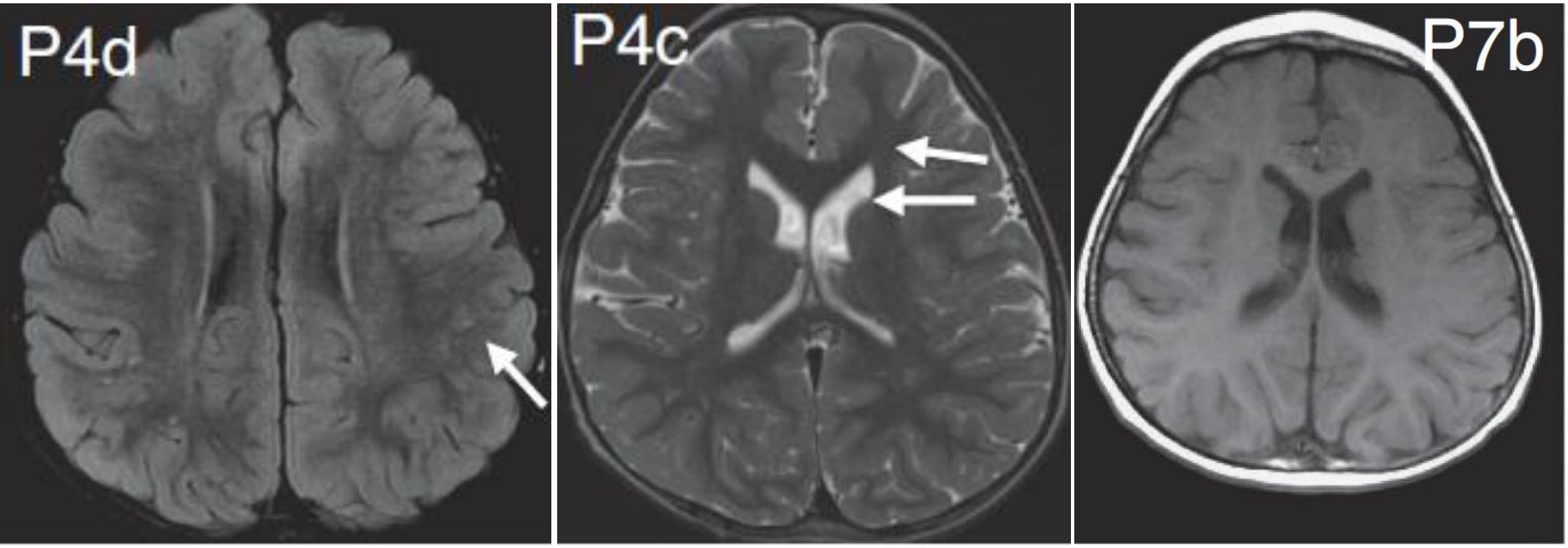
European Journal of Human Genetics (2015) 23, 1473–1481

Jianling Ji[1,2], Hane Lee[1,2], Bob Argiropoulos[3], Naghmeh Dorrani[1,2,4], John Mann[5], Julian A Martinez-Agosto[2,4,6], Natalia Gomez-Ospina[7], Natalie Gallant[4], Jonathan A Bernstein[7], Louanne Hudgins[7], Leah Slattery[7], Bertrand Isidor[8], Cédric Le Caignec[8], Albert David[8], Ewa Obersztyn[9], Barbara Wiśniowiecka-Kowalnik[9], Michelle Fox[2,4], Joshua L Deignan[1,2], Eric Vilain[1,2,4,6], Emily Hendricks[10], Margaret Horton Harr[11], Sarah E Noon[11], Jessi R Jackson[11], Alisha Wilkens[11], Ghayda Mirzaa[10], Noriko Salamon[12], Jeff Abramson[13,14], Elaine H Zackai[11], Ian Krantz[11], A Micheil Innes[3], Stanley F Nelson[1,2,4,6], Wayn biola

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
- Vici syndrome
- Joubert syndrome
- ….

**Remember the non-genetic causes!**

*[Guerrini and Dobyns, Lancet Neurol 2014]*

# Thank you!

The project is supported by

cost
EUROPEAN COOPERATION
IN SCIENCE & TECHNOLOGY

Neuro-MIG