The project is supported by

Wilhelmina Children's Hospital

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EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Neuro-MIG

Heterotopia

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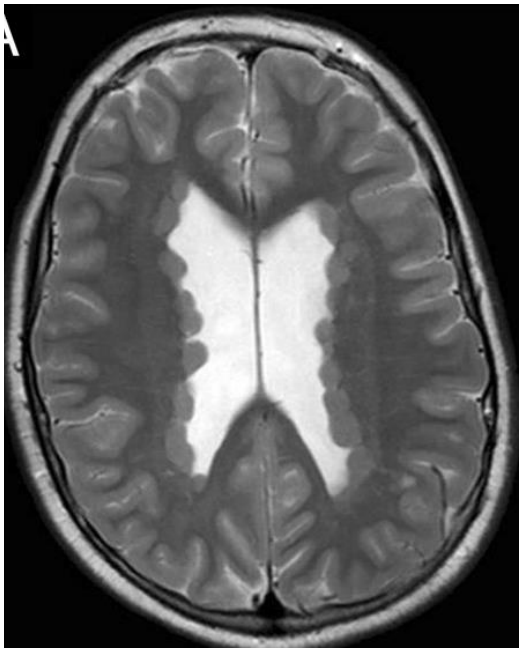
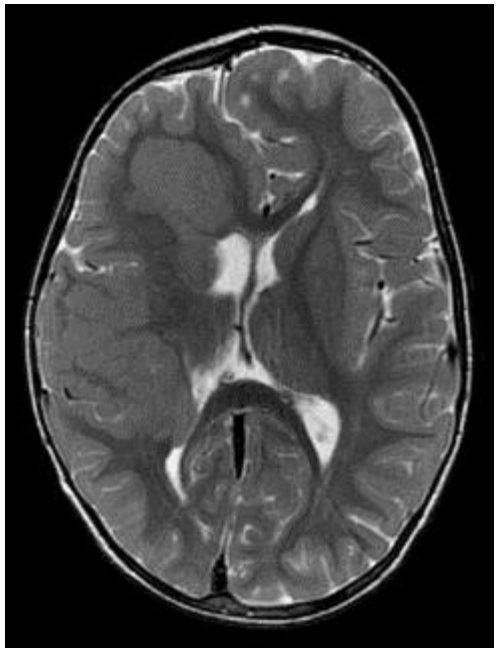
clinical geneticist UMC Utrecht WKZ, the Netherlands

EPNS satellite 2019

Overview

- Periventricular nodular heterotopia (PVNH)
  - FLNA and others
- Other heterotopia





PVNH - broad clinical spectrum

ARFGEF2

ID

Microcephaly

Movement disorder

Cardiomyopathy

[De Wit 2009]

Filamine A

Cardiovascular

Gastrointestinal

Mild dysmorphism

Skeletal defects

.....

[Oegema 2013]

INTS8

Severe ID

..

They are not rare

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Incidental Findings on Brain Imaging in the General Pediatric Population

Table 1. Incidental Findings in the Generation R Study Population (3966 Children).*

Finding	Finding Present	Prevalence
	no. of children	*% (95% CI)*
Migration disorders		
Subependymal gray-matter heterotopia	19	0.48 (0.30–0.76)
Transmantle dysplasia	1	0.03 (0.01–0.16)
Focal cortical dysplasia	1	0.03 (0.01–0.16)

PVNH -etiology

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)

Monogenic

- Smith –Magenis (*RAI1*)
- Van Maldergem syndrome (*DCHS1, FAT4*)**
- *NEDD4L*
- *FLNA*
- *ARFGEF2*
- *CRB2* (ventriculomegaly with

Multiple genomic copy number variants associated with periventricular nodular heterotopia indicate extreme genetic heterogeneity

Elena Cellini[1] · Annalisa Vetro[1] · Valerio Conti[1] · Carla Marini[1] · Viola Doccini[1] · Cla
Elena Parrini[1] · Sabrina Giglio[2] · Matteo Della Monica[2] · Marco Fichera[3,4] ·
Sebastiano Antonino Musumeci[4] · Renzo Guerrini[1,5]

...

Germline and mosaic mutations of FLN1 in men with periventricular heterotopia
R. Guerrini, D. Mei, S. Sisodiya, F. Sicca, B. Harding, Y. Takahashi, T. Dorn, A. Yoshida, J. Campistol, G. Krämer, F. Moro, W. B. Dobyns and E. Parrini
Neurology 2004;63;51-56

Elena Parrini · Davide Mei · Micheal Wright ·
Thomas Dorn · Renzo Guerrini

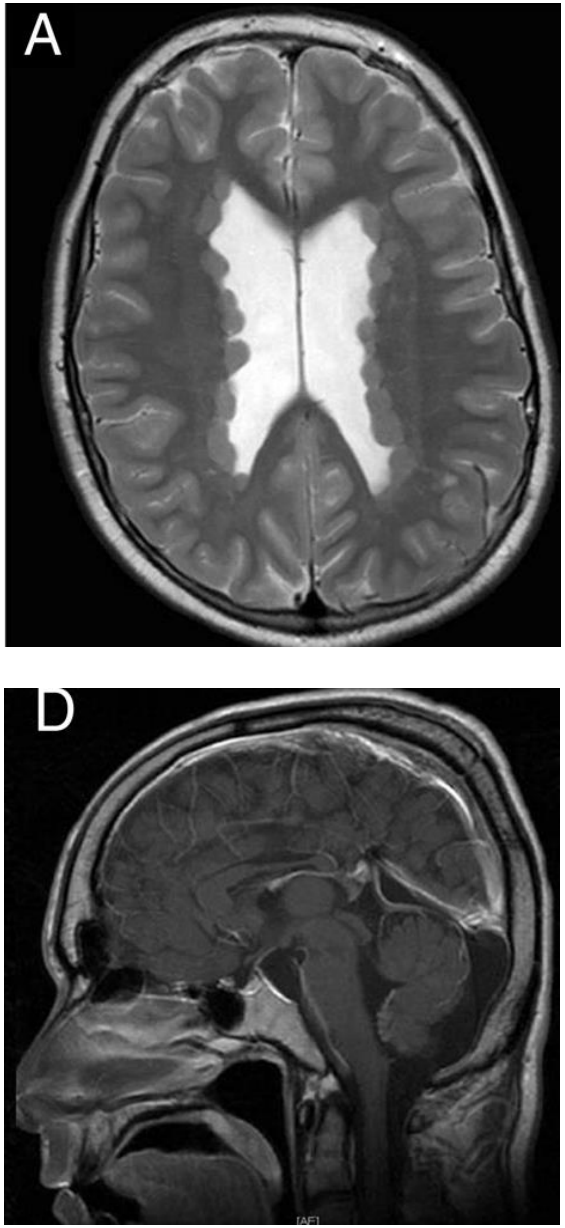
Mosaic mutations of the *FLN1* gene cause a mild phenotype in patients with periventricular heterotopia

A somatic mutation in *MEN1* gene detected in periventricular nodular heterotopia tissue obtained from depth electrodes

Laura Montier[1] | Zulfi Haneef[1] | Jay Gavvala[1] | Daniel Yoshor[2] | Robert North[2] | Terence Verla[2] | Paul C. Van Ness[1] | Janice Drabek[1] | Alica M. Goldman[1]

FLNA mutations

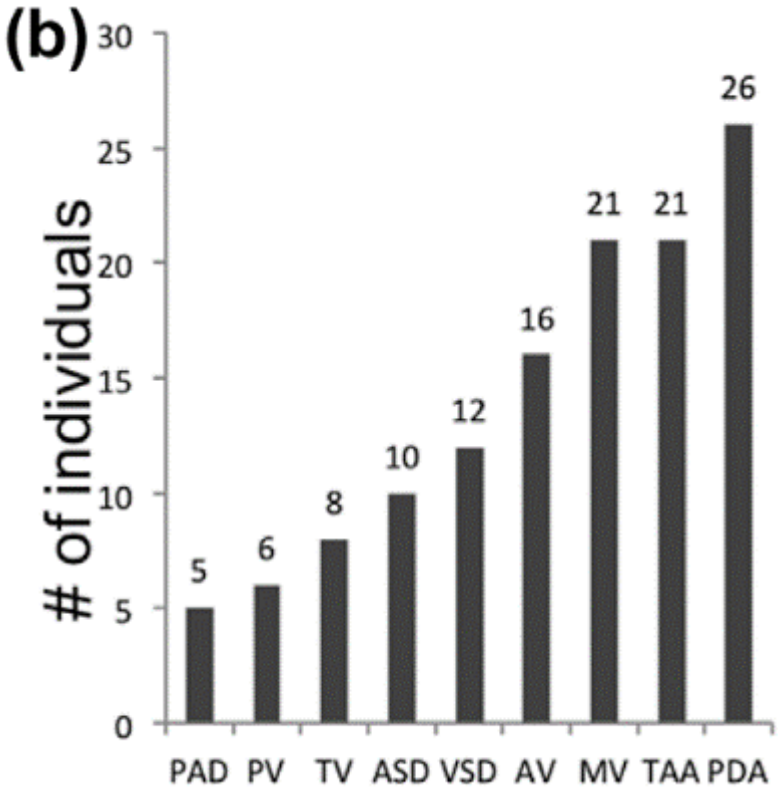
- X-linked PVNH
- Missense and truncating variants
- High diagnostic yield in
  - Females
  - Familial cases
  - Multiple PVNH, frontal predominant
  - Cerebellar hypoplasia/cyst /mega cisterna magna
- Seizures
- Normal intelligence/ LD



Lange 2015

FLNA- systemic disorder

- Cardiovascular
  - 80.8% of males and 60.2% of females



- Congenital heart disease:
  - ASD, VSD, PDA
  - Valvular dysplasia
- Aortic aneurysms
  - Premature rupture

Chen 2019, GeneReviews

FLNA- systemic disorder

- Cardiovascular
- Gastrointestinal
- Respiratory

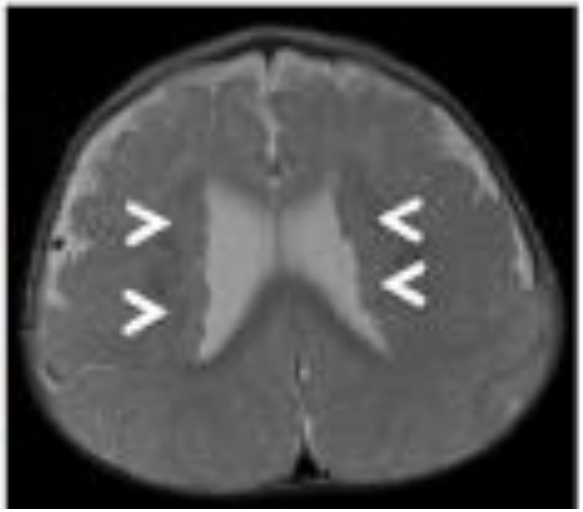
- Connective tissue
- Platelet abnormalities

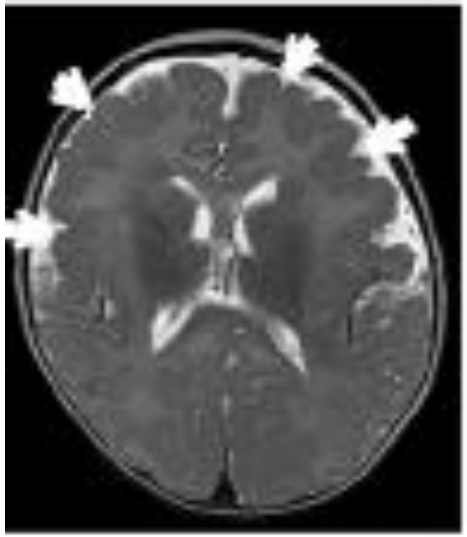
- bronchopulmonary dysplasia
- Chronic obstructive lung disease

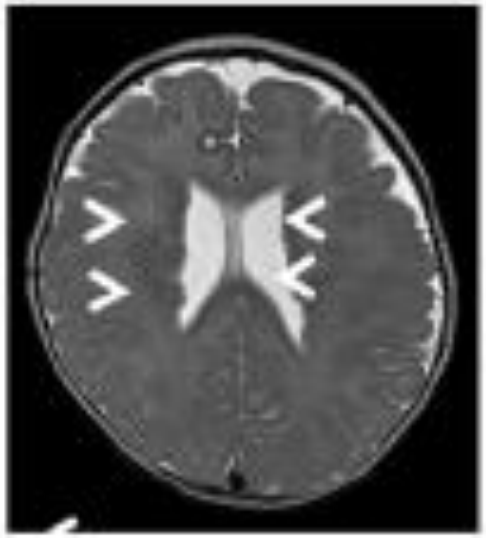
- Constipation
- Pseudoobstruction, malrotation

Chen 2019, Lange, GeneReviews

NEDD4L (AD)

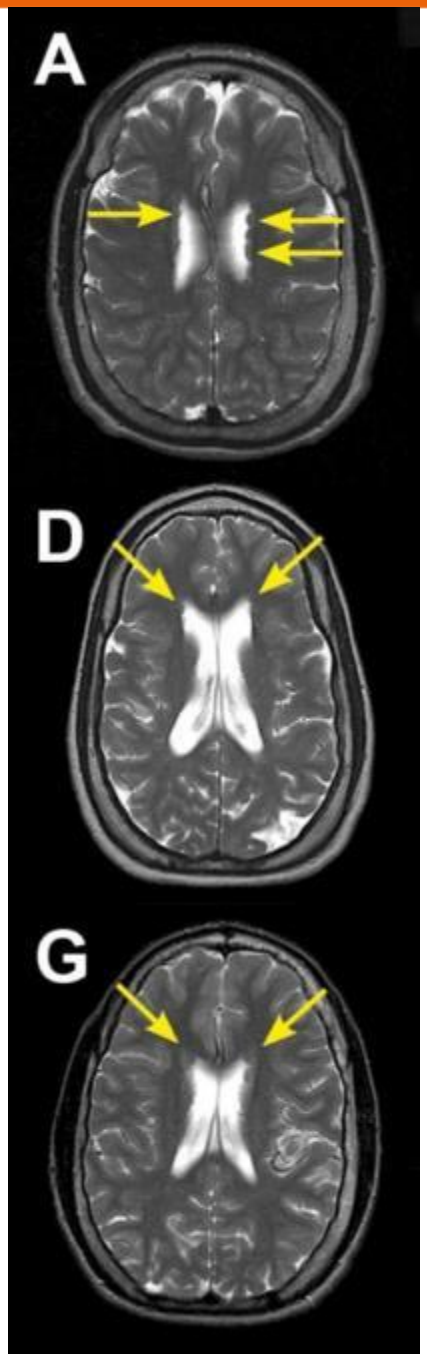






- PVNH
- PMG
- 2-3 toe syndactyly
- 3-4(-5) finger syndactyly
- Hypotonia
- ID (can be mild)
- Cleft palate/ bifid uvula

Broix 2016, Meuwissen personal communication



Severe ID

Absent speech

Spastic tetraplegia

Microcephaly

Epilepsy

Cerebral VI

Overlapping toes

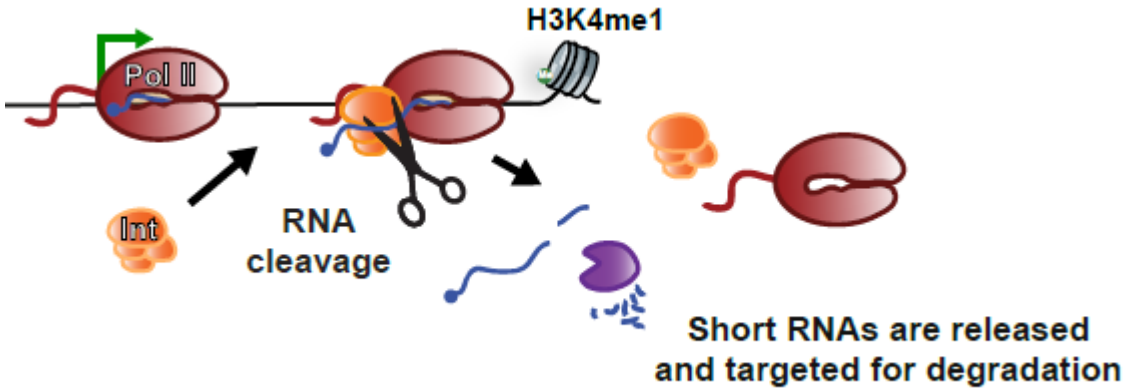
Bi-allelic *INTS8* mutations

INTS1

1 *INTS8* family

Integrator Complex:

- Associates with RNA polymerase II
- Role in
  - Transcription regulation
  - RNA processing

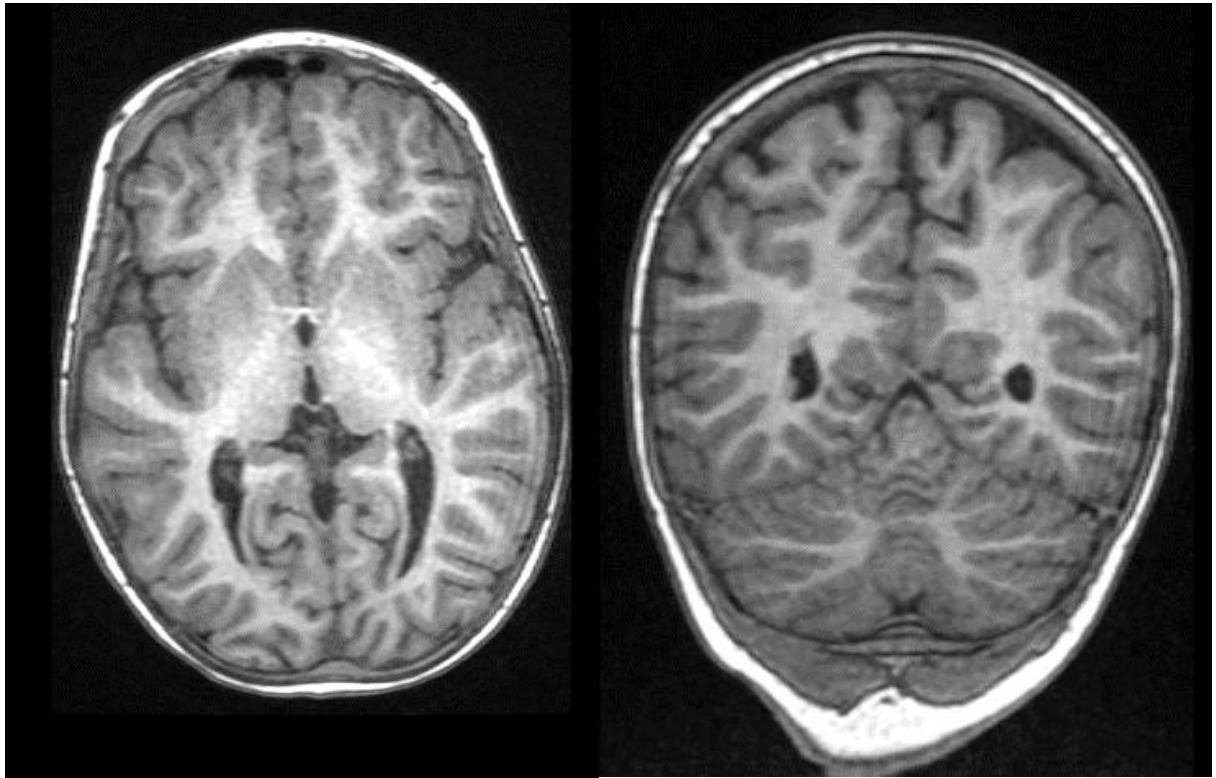


Oegema 2017, Krall 2019, Elrod unpub.

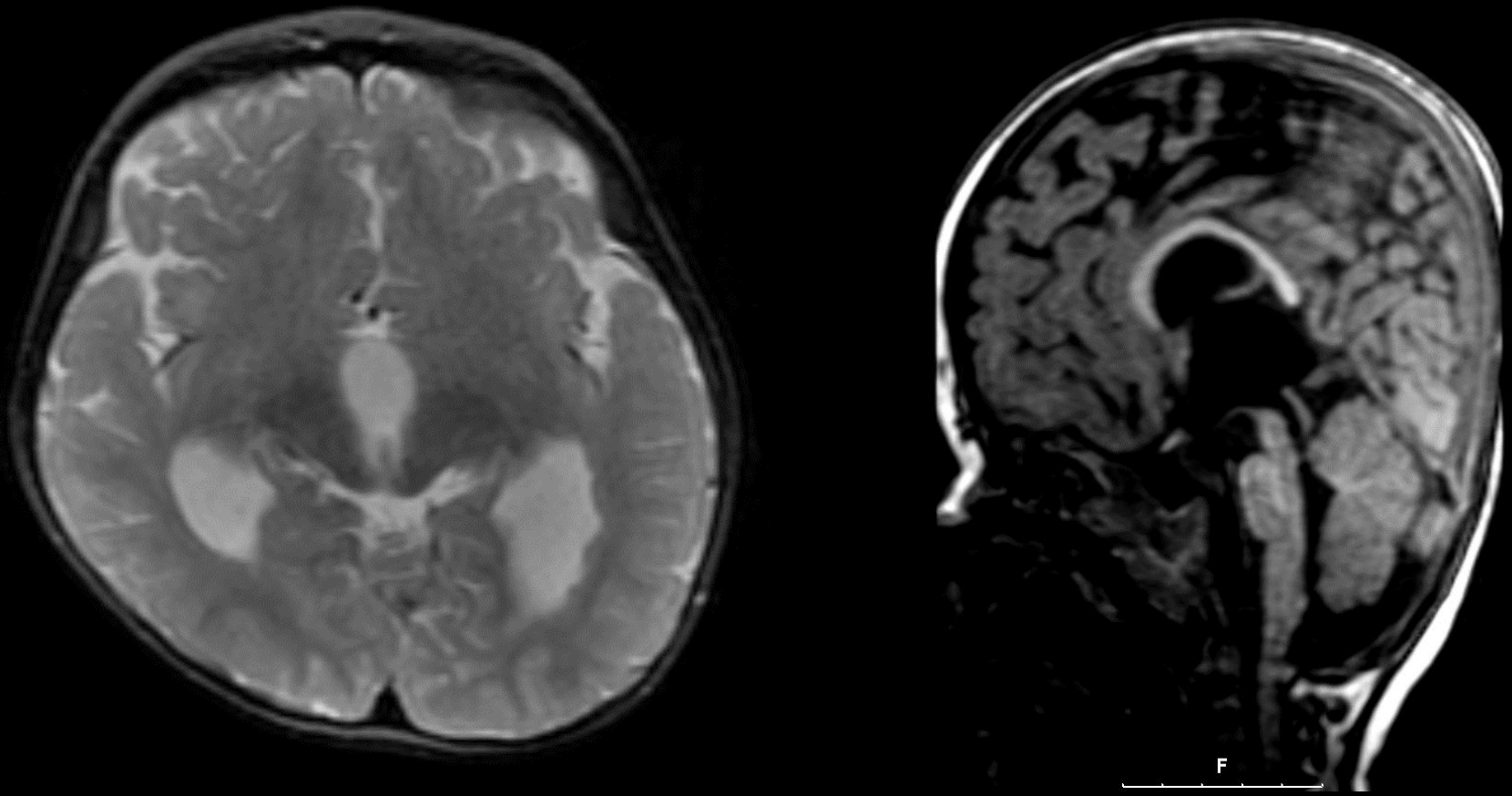
ID, epilepsy, cleft palate, temper tantrums, narcolepsy, autism, PNH

- Smith Magenis syndrome

due to *RAI1* mutation

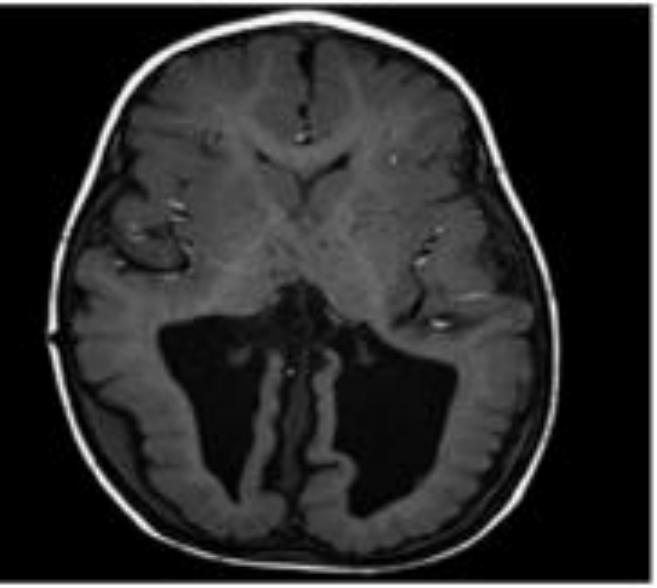


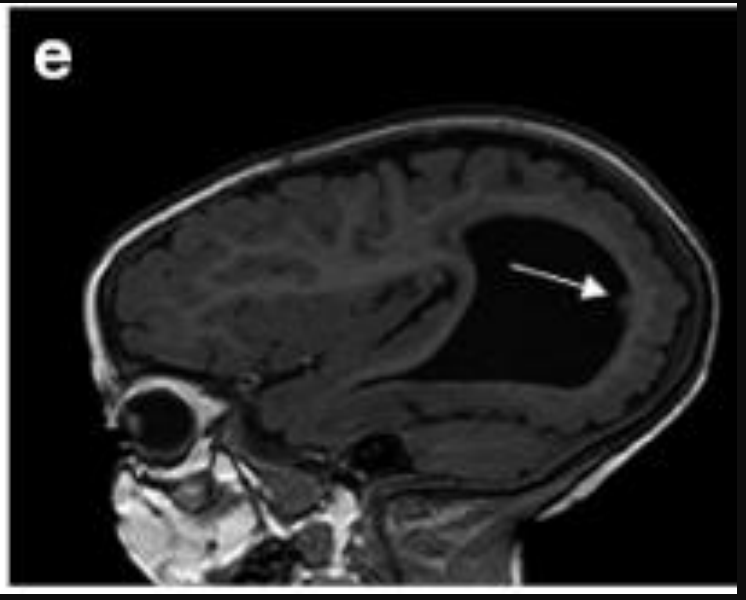
Smith Magenis syndrome due to 17p11.2 deletion



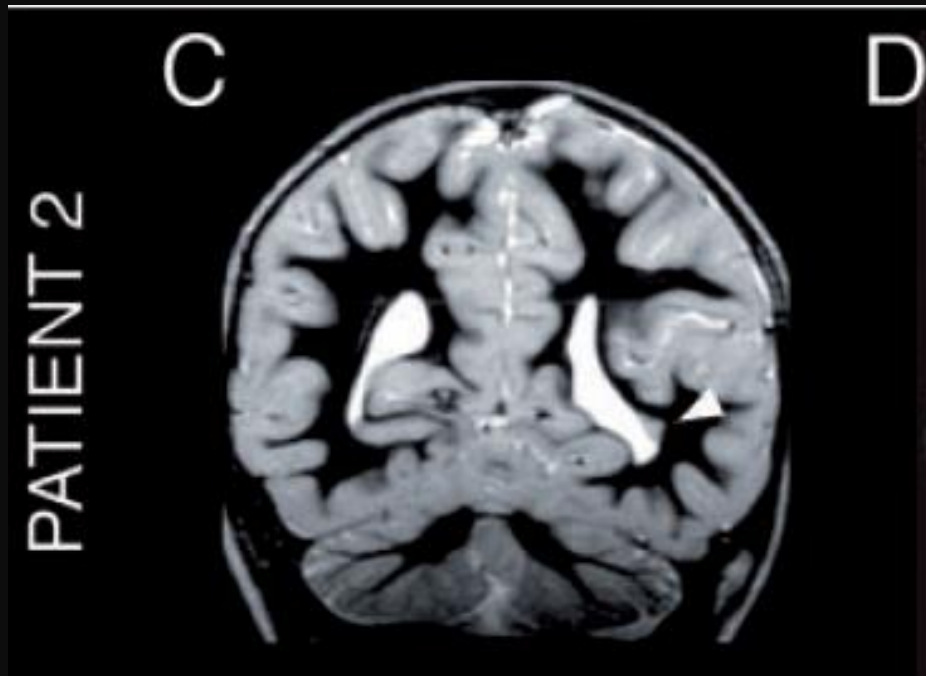
6q25q27 deletions

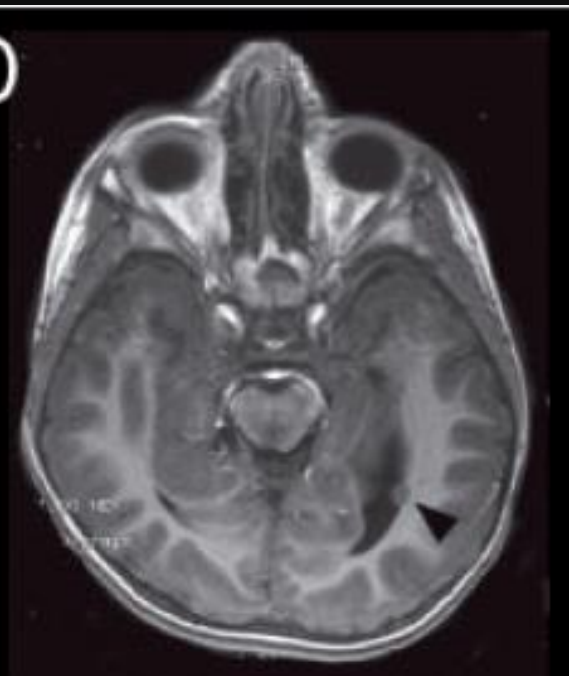
Peddibhotla 2015





Conti 2013



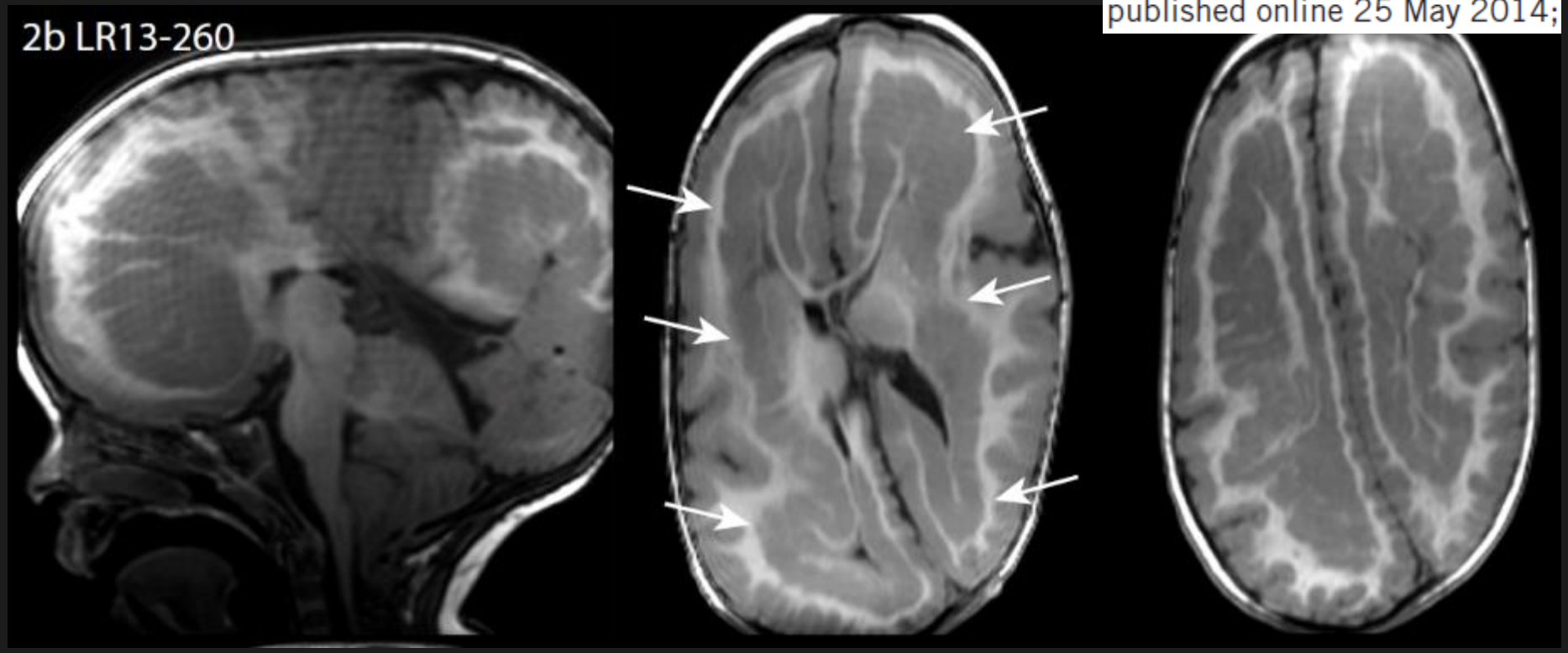


Ribbon

Mutations in Eml1 lead to ectopic progenitors and neuronal heterotopia in mouse and human

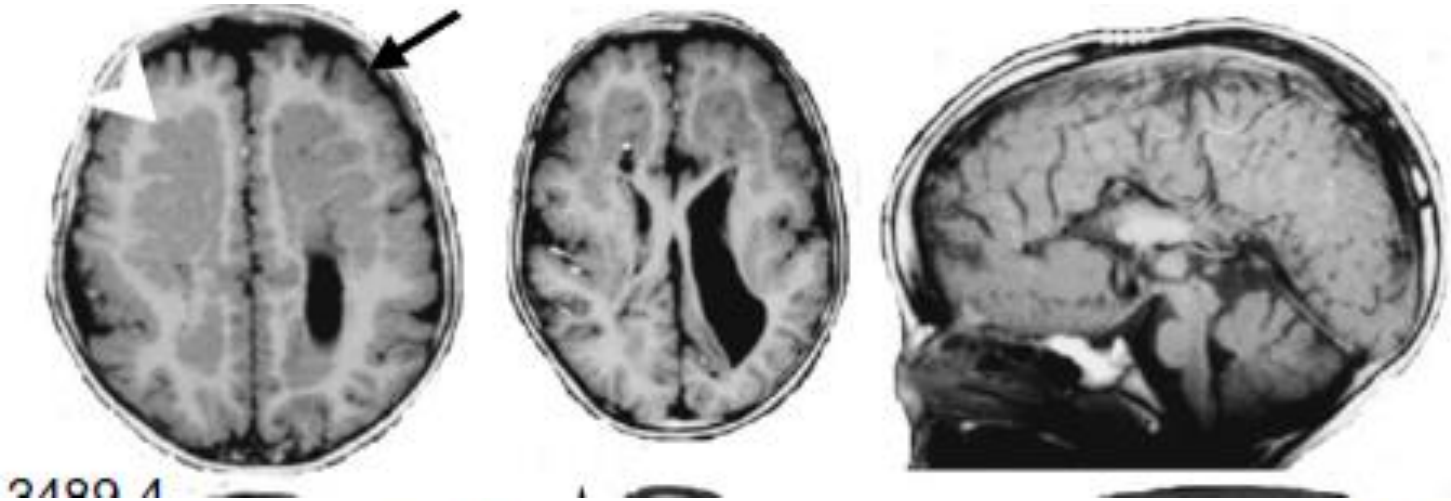
Michel Kielar[1,2,14], Françoise Phan Dinh Tuy[3–5,14], Sara Bizzotto[3–5,14], Cécile Lebrand[2,14], Camino de Juan Romero[6], Karine Poirier[7], Renske Oegema[8], Grazia Maria Mancini[8], Nadia Bahi-Buisson[9], Robert Olaso[10], Anne-Gaëlle Le Moing[11], Katia Boutourlinsky[3–5], Dominique Boucher[4,12], Wassila Carpentier[13], Patrick Berquin[11], Jean-François Deleuze[10], Richard Belvindrah[3–5], Victor Borrell[6], Egbert Welker[2], Jamel Chelly[7], Alexandre Croquelois[1,2,15] & Fiona Francis[3–5,15]

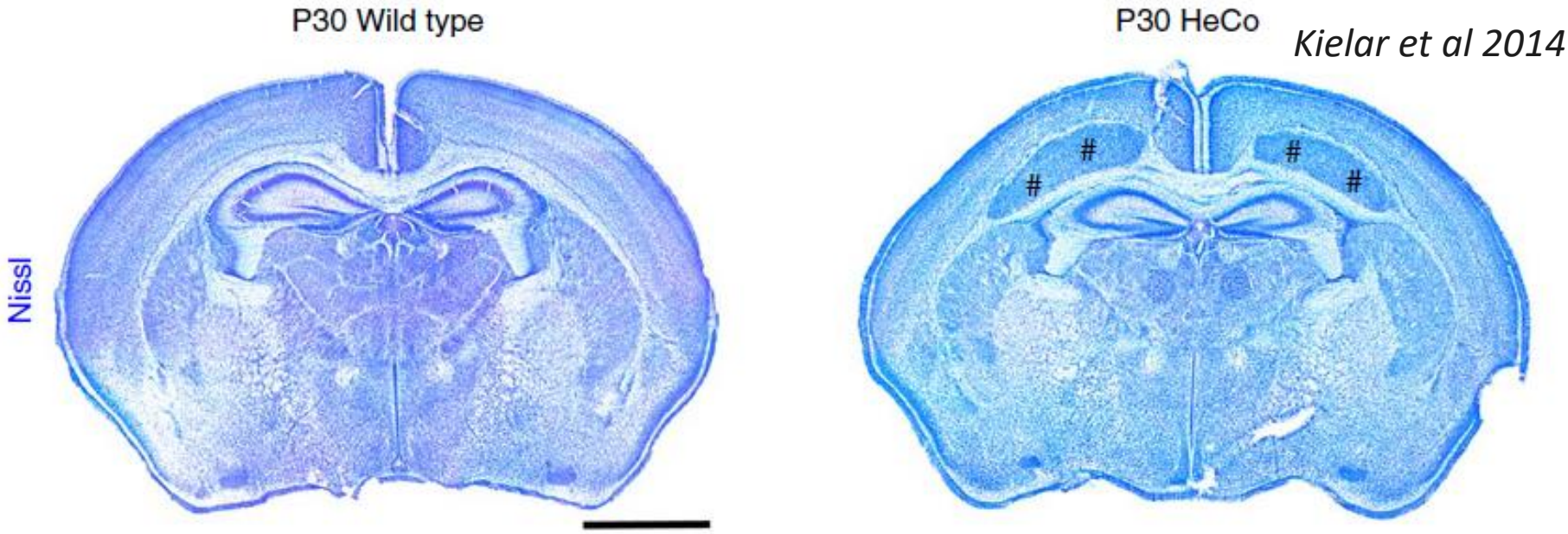
published online 25 May 2014;



Megalencephaly, hydrocephalus, polymicrogyria-like cortex, agenesis corpus callosum, small and fused thalami

Spontaneous mutant HeCo mouse



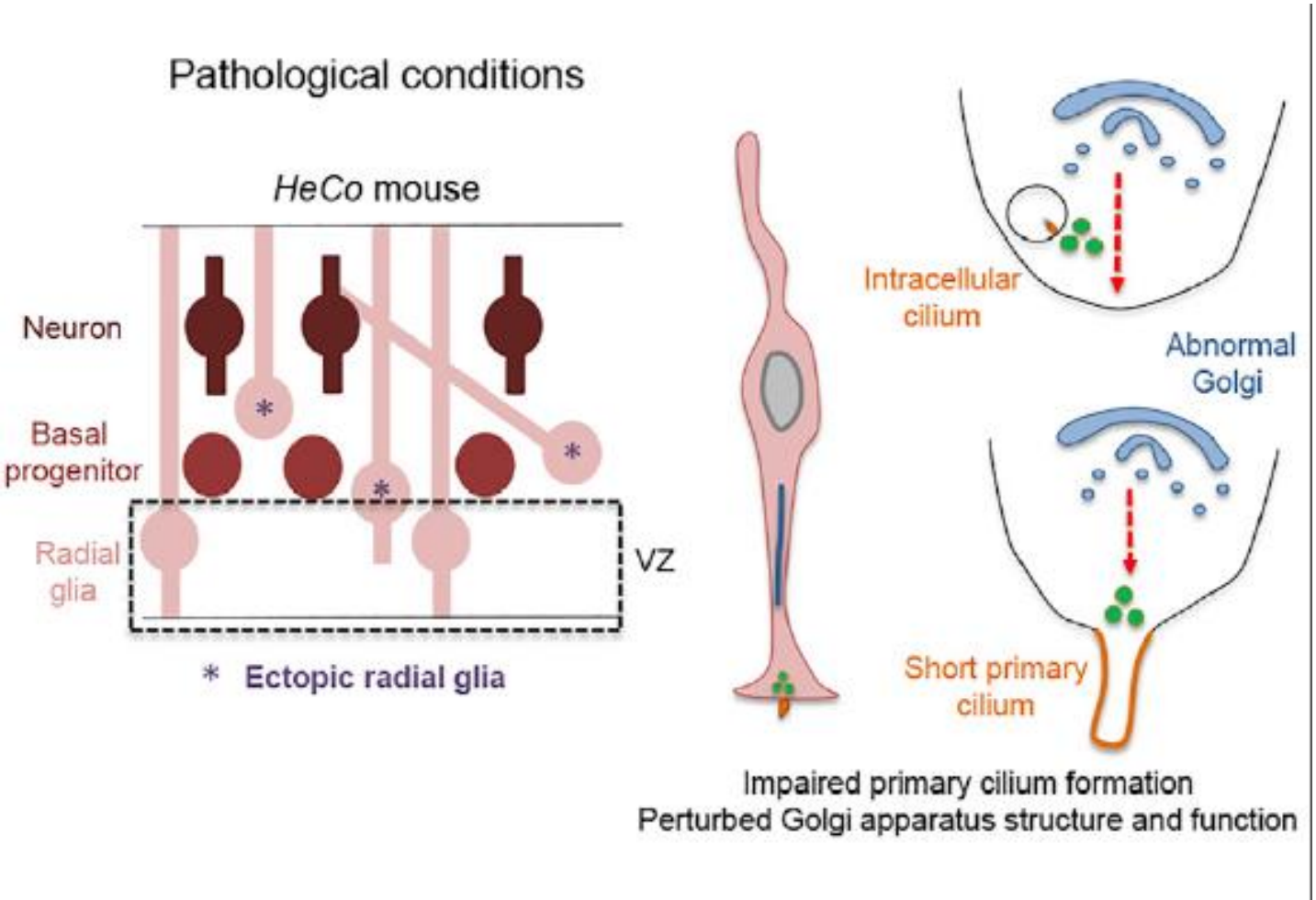


Kielar et al 2014

ectopic proliferating cells in the intermediate zone (IZ) and cortical plate (CP) at E13

EML1

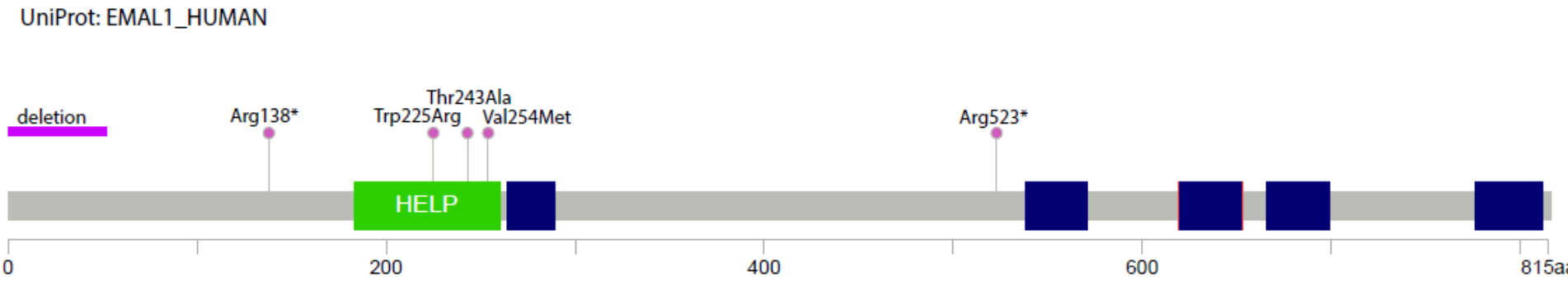
- Echinoderm microtubule-associated protein-like 1
- Mouse mutants show abnormal mitotic spindles and short primary cilia in RGCs



Uzquiano et al

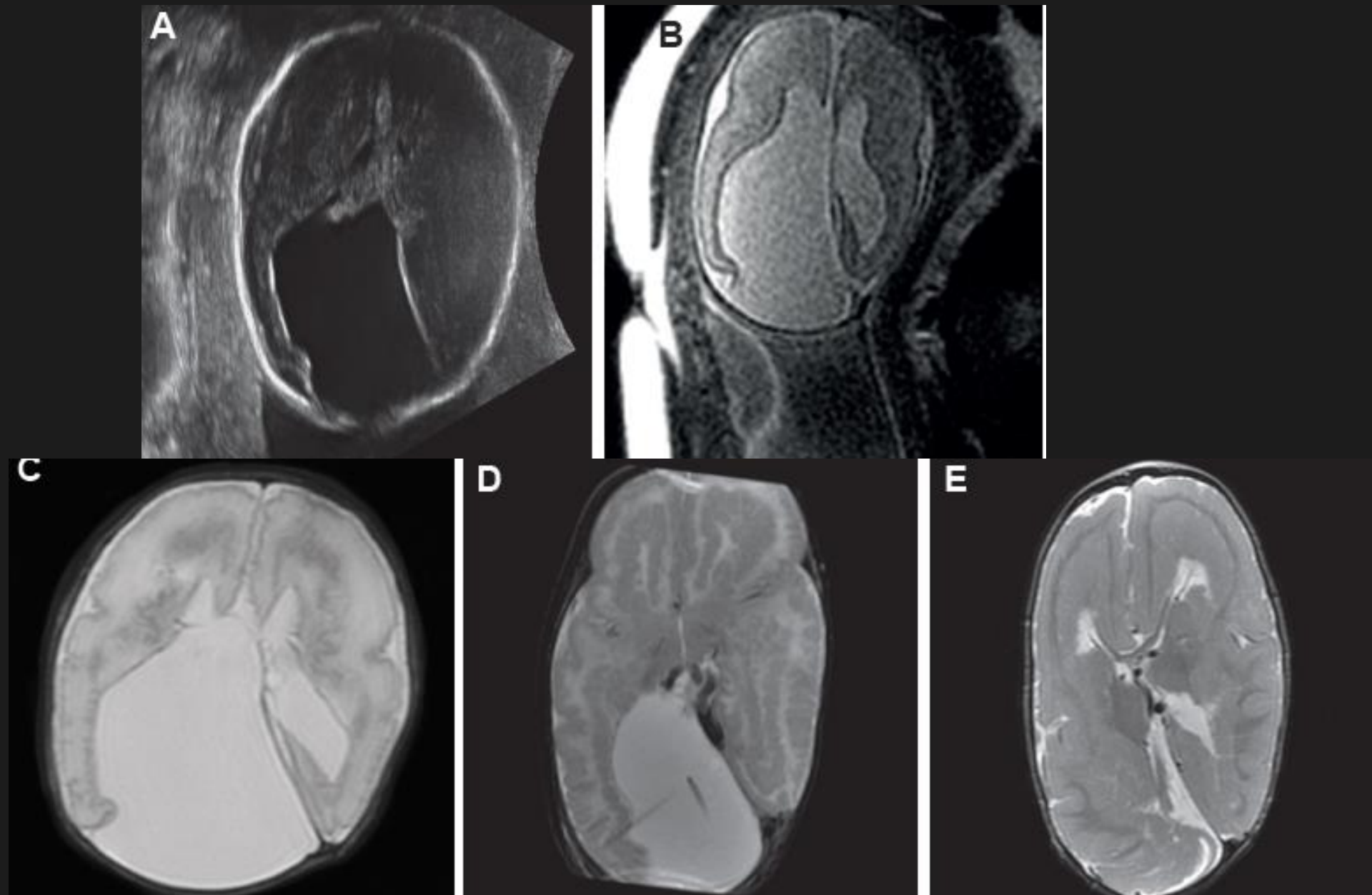
EML1

- Autosomal recessive
- 9 individuals from 6 families (+1 possible)
- DD, seizures, visual impairment, hydrocephalus (3/9)
- Mutations LoF or missense, with 3 clustering in the HELP domain
- Thr243Ala impairs the association of Eml1 with microtubules (Kielar et al., 2014)



Oegema et al, submitted

Pre- and postnatal imaging

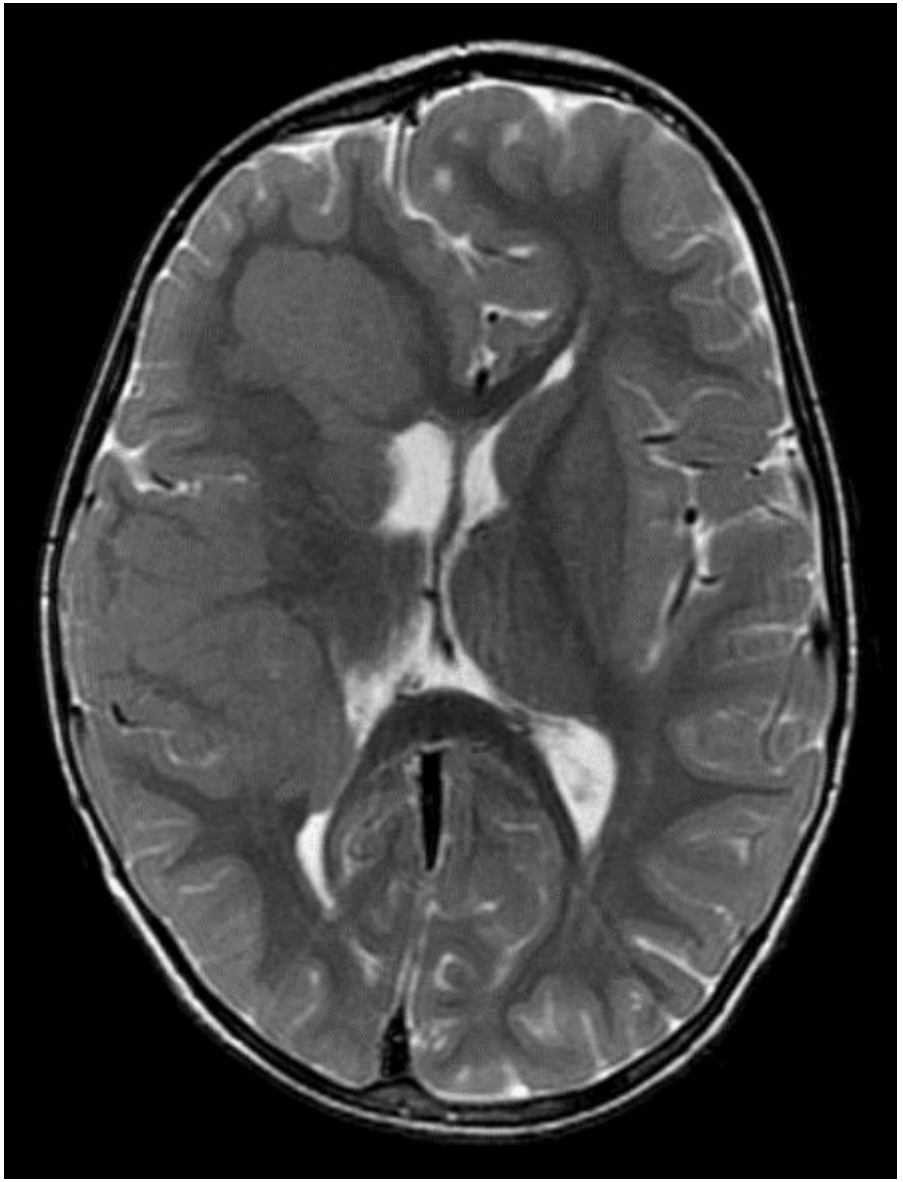


♂ 2 jaar, febrile seizure

- TC, 15 min

- Motor delay
- L hemiplegia
- Drooling
- MR:

Curvilinear heterotopia



Follow-up

- 3y: focal to bilat generalized seizure 45 min
- Medication resistant epilepsy
- Difficulty writing, concentrating
- 4y10m: IQ 120 (pIQ 112, vIQ 127)

Subcortical heterotopia study

- Aim: study imaging of non-PVNH; non-SBH heterotopia
- Methods: search 4 databases
  - Bill Dobyns, Renzo Guerrini, Jim Barkovich, Grazia Mancini
- Results
  - 107 individuals, 66 curvilinear, 41 others

- Curvilinear
  - ¾ seizures, ¾ DD/ ID, 1/3 abnormal behavior
  - 1/3 another congenital abnormality

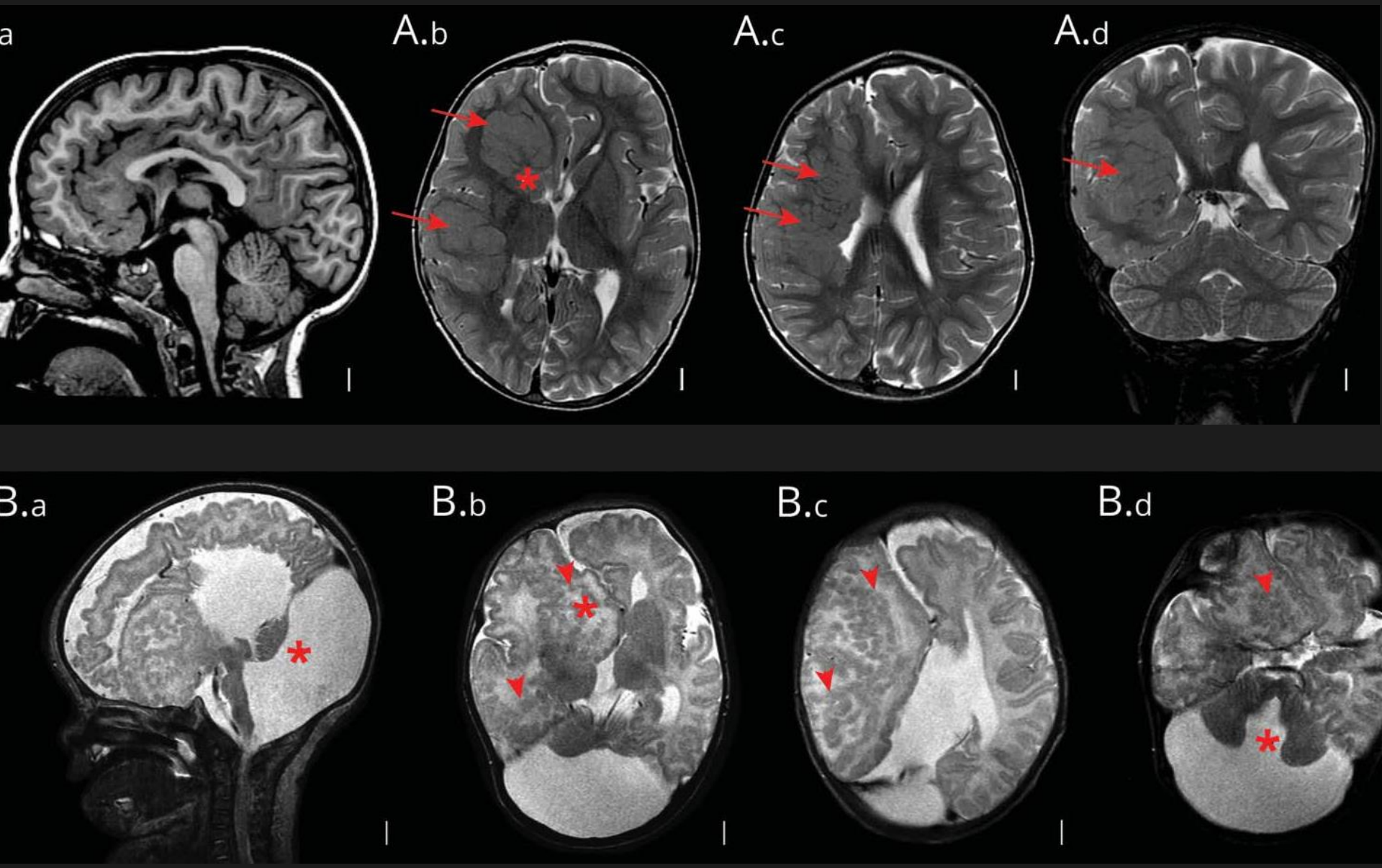
Subcortical heterotopic gray matter brain malformations

Classification study of 107 individuals

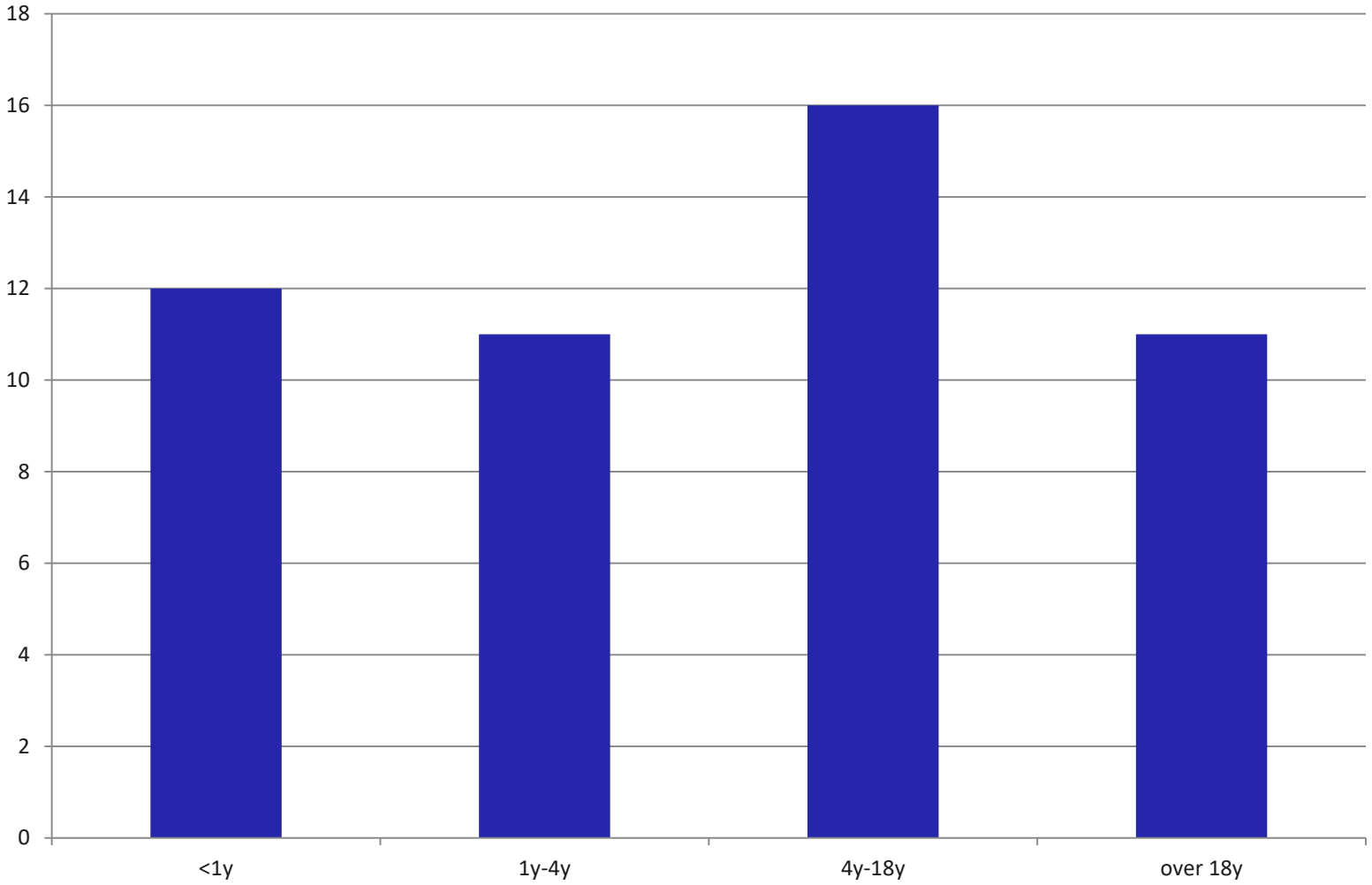
Renske Oegema, MD, PhD, A. James Barkovich, MD, Grazia M.S. Mancini, MD, PhD, Renzo Guerrini, MD, FRCP, and William B. Dobyns, MD

Corresponde
Dr. Oegema
r.oegema@um

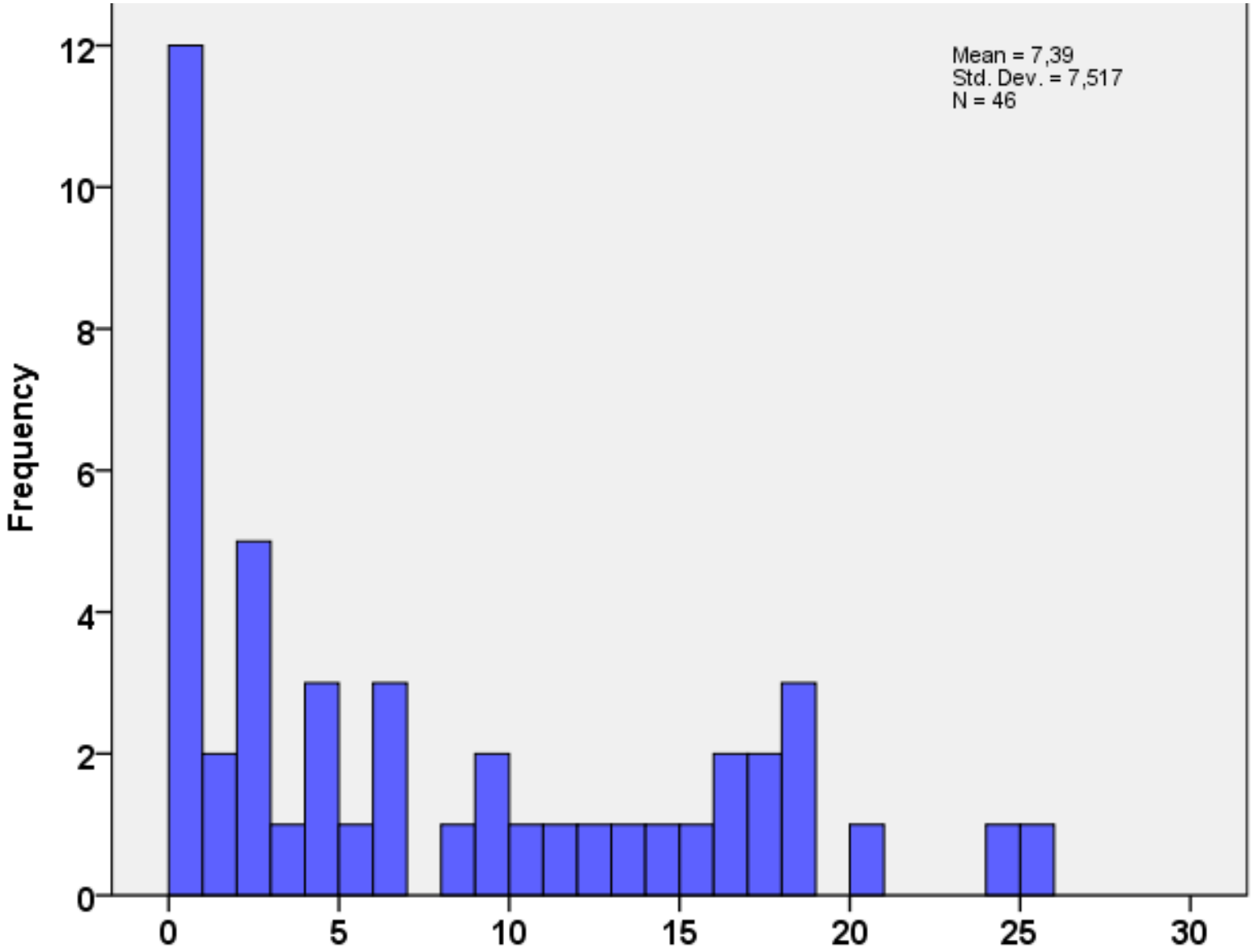
Neurology® 2019;93:e1-e14. doi:10.1212/WNL.0000000000008200


a
A.b
A.c
A.d
B.a
B.b
B.c
B.d

Age first scan



Age onset seizures



Literature prenatal history

Reference	N	Prenatal history	Genetics
Kuzniecky 1995	1	Disconcordant monozygotic twins	-
Dubeau 1995	13	1x twin deceased, 1x 3 miscarriages, FH: 3x epilepsy (non-sibs)	-
Battaglia 1996	1	-	-
Preul 1997	1	Fall early 2nd trimester, no fetal movements for two days	
Barkovich 2000	24	-	-
Eccles 2003	1	Disconcordant dizygotic twins	BRCA1 mutation
Eccles 2005	1	Disconcordant monozygotic twins	BRCA1 mutation
Poduri 2005	3	UK	-
Raghavendra 2006	2	“normal birth”	-
Novegno 2009	3	1. Twin monochorial pregnancy. Caesarean delivery for pre-eclampsia 2. Miscarriage threat 3rd month 3. Miscarriage threat 6th-8th sixth GW	-
Baas 2013	1	Mismatch repair syndrome	MLH1

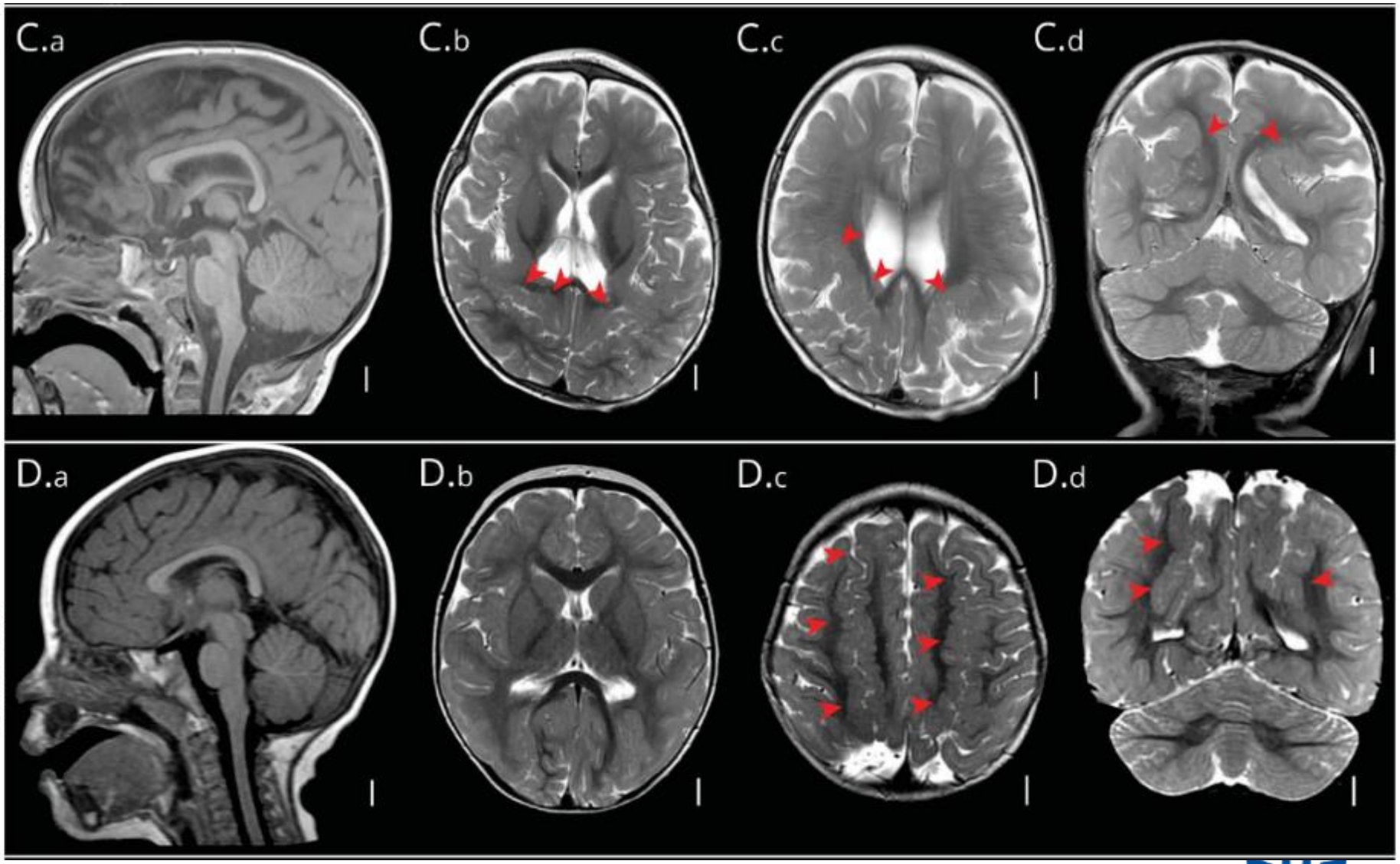
Literature

- 26 patients
  - Sporadic
  - 5x twin pregnancy
  - 3x trauma/ threat of miscarriage

This study

- 61 patients
  - 2x twinning
  - 2x transverse limb defect
  - 1x absent a. carotis interna
- (Limited data)

Others types: Deeply infolded

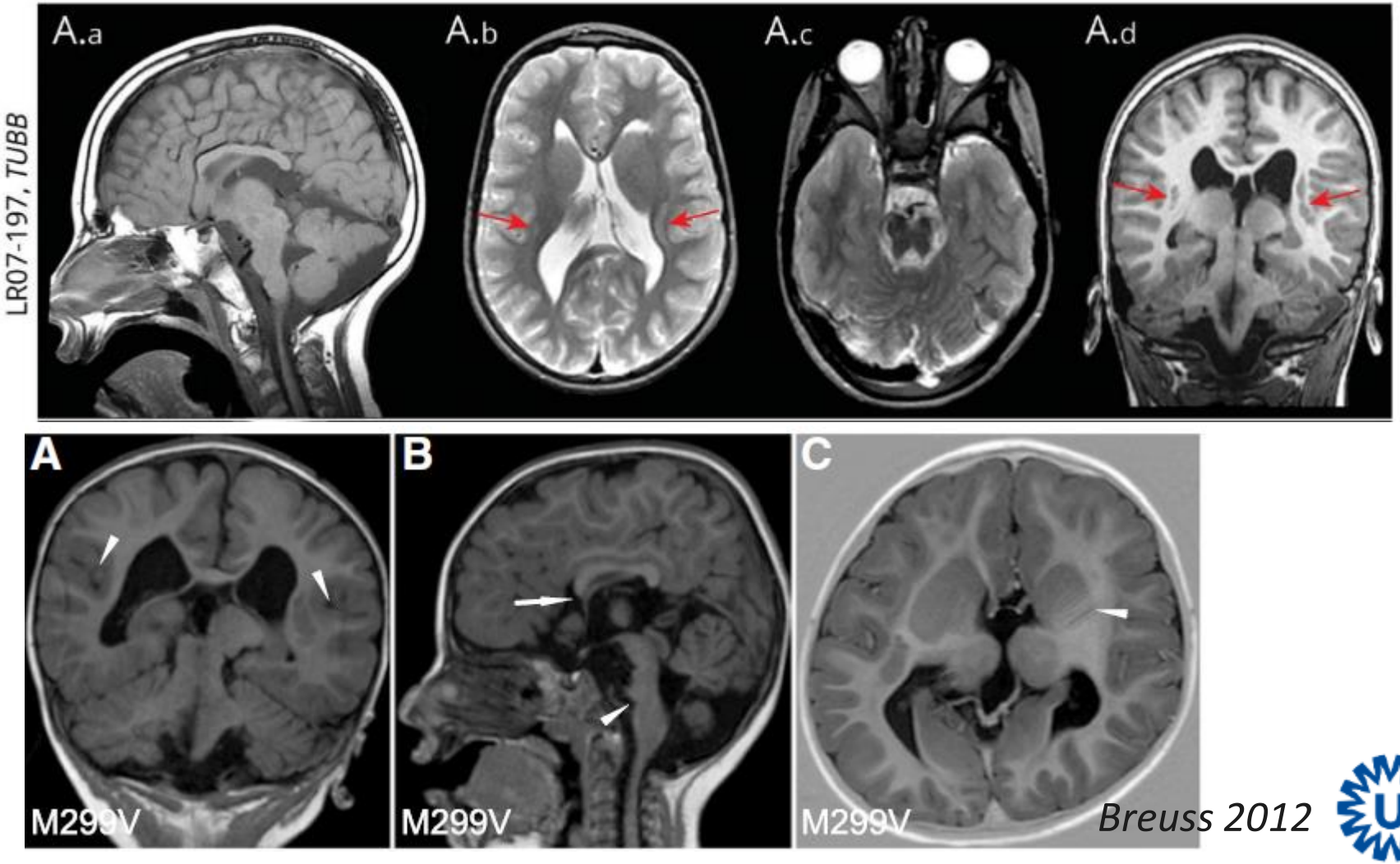


6 deeply infolded –parasagittal

3x twins, 1x jejunal atresia

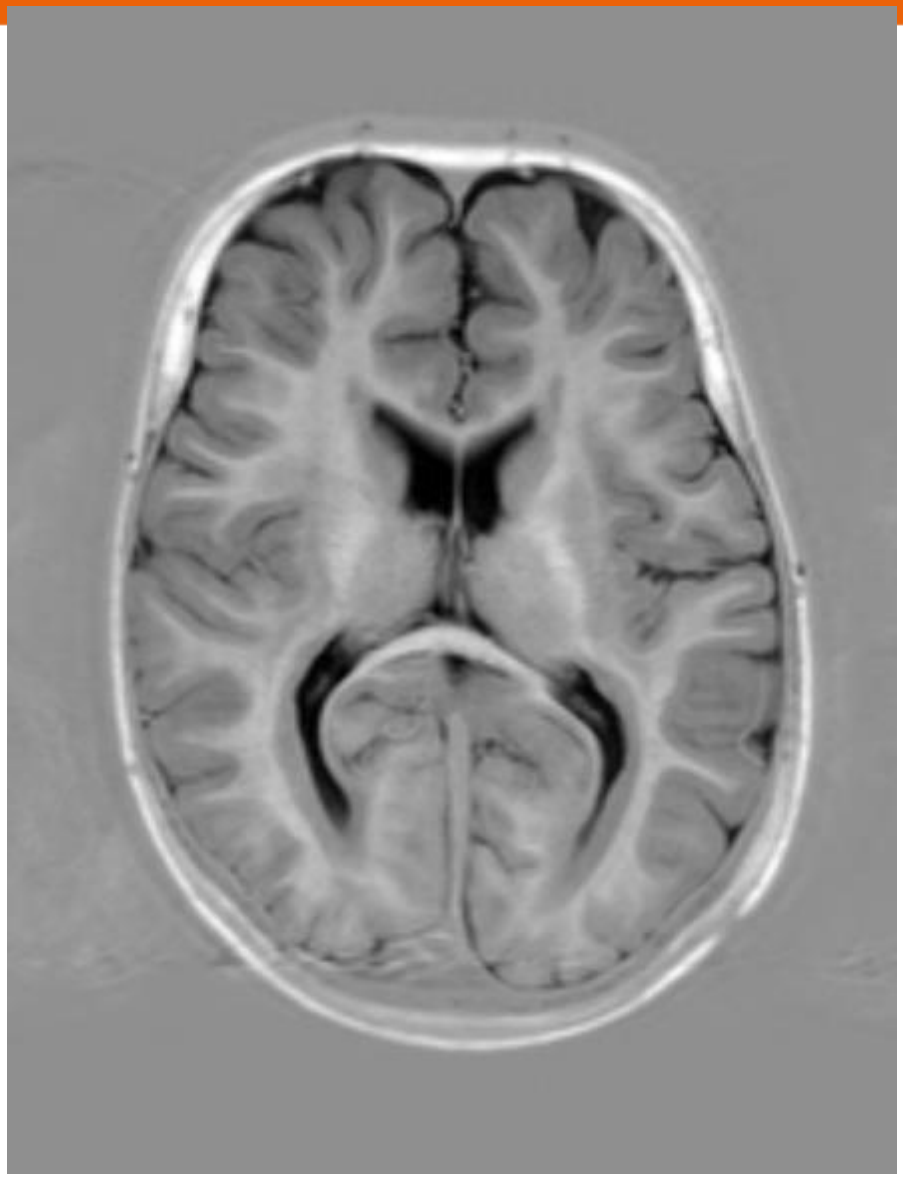
Other types: TUBB / KATNB1

peritrigonal optic pathway heterotopic gray matter brain malformations



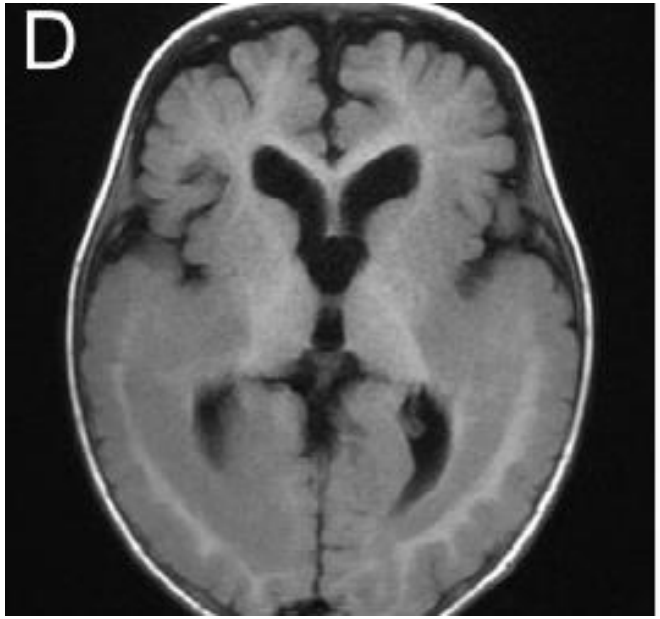
Breuss 2012

- Van Maldergem syndrome, AR
- Laminar periventricular heterotopia
- Mutations in DCHS1, FAT4
- ID
- Dysmorphism
- Auditory malformation
- Skeletal/ limb malformations

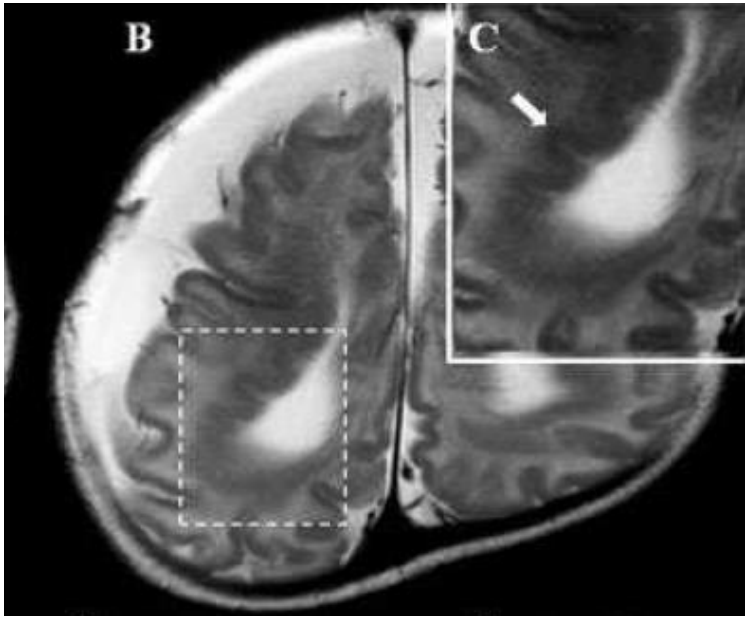


Take home message

- Heterotopia are not rare
- Extremely wide spectrum of clinical outcome
- Diverse etiology
- Several forms are poorly described



Kobayashi et al



Tsurubaya et al

Thank you!

The project is supported by

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Neuro-MIG

UMC Utrecht - WKZ