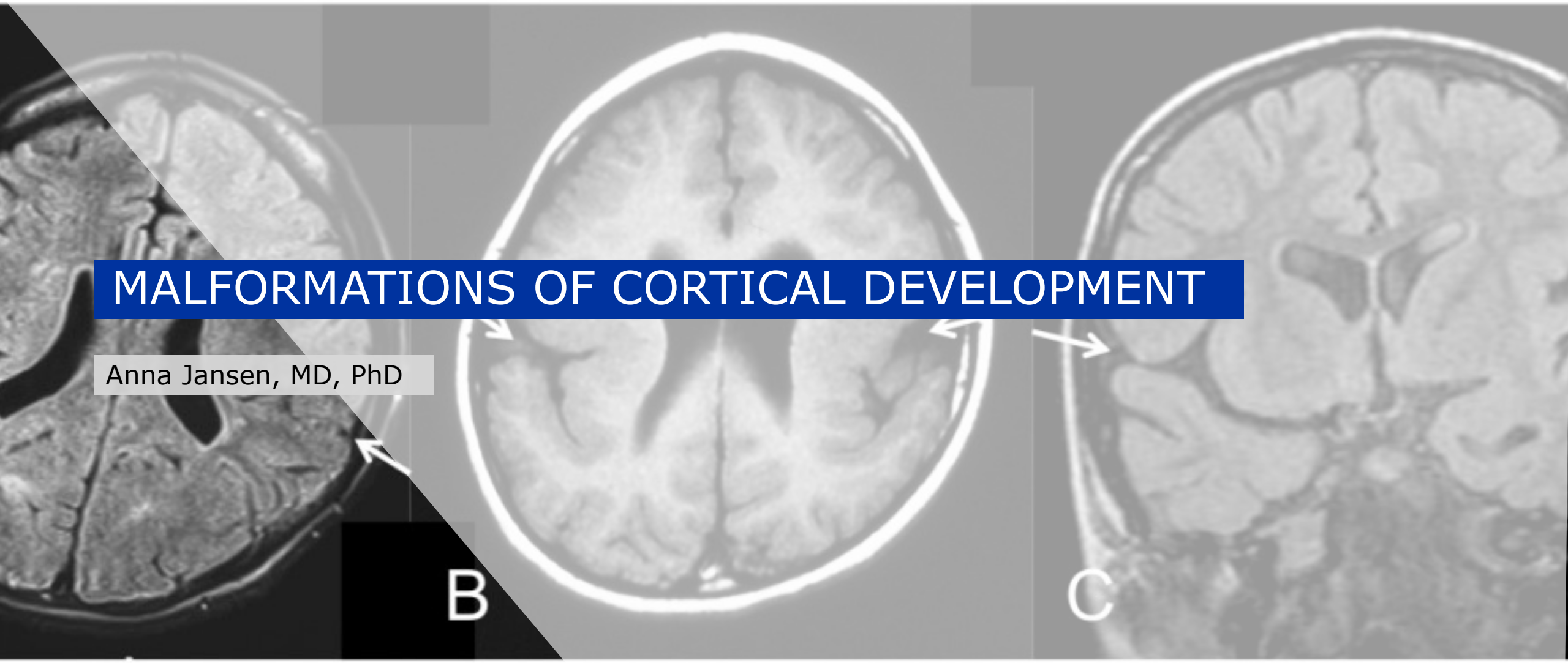


MALFORMATIONS OF CORTICAL DEVELOPMENT

Anna Jansen, MD, PhD

VUB VRIJE UNIVERSITEIT BRUSSEL

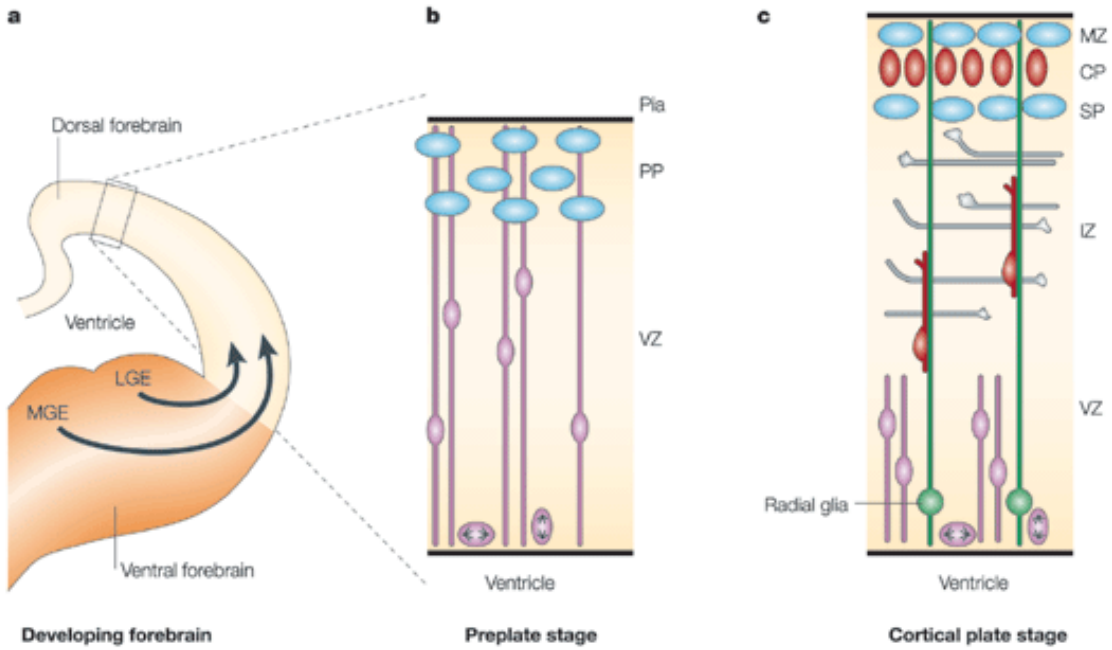
Universitair Ziekenhuis Brussel

UZA

Universiteit Antwerpen

INTRODUCTION TO MCD

PROCESS AND TIMING DURING DEVELOPMENT

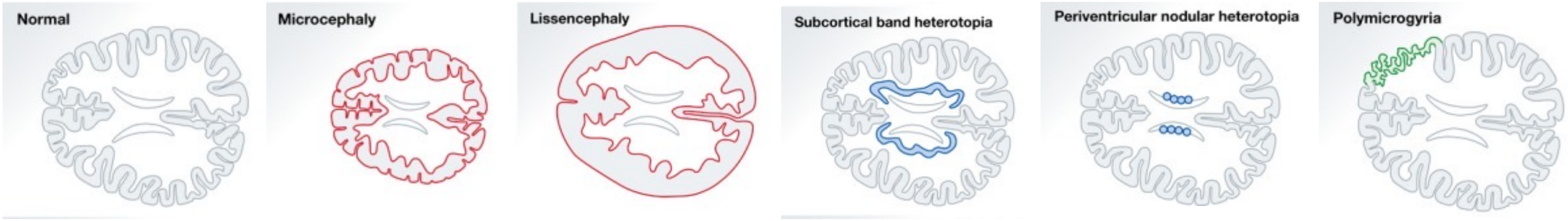


Nadarajah & Parnavelas, Nature Reviews Neuroscience, 2002

Process	**Anomalies**	**Time**
1. Neuronal Glial Proliferation	Micro/Macrocephaly	8-16 weeks gestation
2. Migration	Lissencephaly/Heterotopia	12-20 weeks gestation
3. Organization	Polymicrogyria	>24 weeks gestation

INTRODUCTION TO MCD

PROCESS AND TIMING DURING DEVELOPMENT



V. Fernandez, C. Llinares-Benadero, V. Borrell, Embo J, 35 (2016) 1021-1044

Process	**Anomalies**	**Time**
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3. Organization	Polymicrogyria	>24 weeks gestation

CLASSIFICATION OF MCD

Based upon the earliest developmental step at which the developmental process was disturbed

1. **Malformations secondary to abnormal neuronal and glial proliferation or apoptosis**
   - Severe congenital microcephaly (+/- CNS or extra-CNS abnormalities)
   - Megalencephaly (+/- CNS abnormalities)
   - Hemimegalencephaly / FCD type II / cortical tubers in TSC
   - Ganglioglioma / DNET
2. **Malformations due to abnormal neuronal migration**
   - Periventricular heterotopia
   - Lissencephaly / subcortical band heterotopia
   - Subcortical heterotopia
   - Malformations due to abnormal terminal migration and defects in pial limiting membrane (cobblestone malf)
3. **Malformations due to abnormal post-migrational development**
   - Polymicrogyria
   - Cortical dysgenesis secondary to inborn errors of metabolism (mito, peroxysomal)
   - FCD type 1
   - Postmigrational developmental microcephaly (*FOXG1, MECP2, UBE3A, CASK*, …)

Barkovich et al. 2012

CLASSIFICATION OF MCD

Pathway-based

1. **Lissencephaly spectrum**
   - Centrosome-expressed microtubule
   - Microtubule motor proteins (DYNC1
   - Actins and actin associated MAPs (
   - Complex MAP (CDK5)
   - Tubulinopathies (mainly TUBA1A)
   - Other

2. **Polymicrogyria**
   - mTORopathies (AKT3, CCND2, mT
   - RABopathies (RAB18, RAB3GAP1, I
   - NMDARopathies (GRIN1, GRIN2B)
   - Tubulinopathies (TUBA1A, TUBB, T
   - Other (DDX3X, OCLN, RTTN, SCN3A, WDR62…)

3. **Cobblestone malformation**
   - Alpha-dystroglycanopathies
   - Laminopathies & other congenital disorders of glycosylation

Published in final edited form as:
Am J Med Genet A. 2017 June ; 173(6): 1473–1488. doi:10.1002/ajmg.a.38245.

Lissencephaly: expanded imaging and clinical classification

Nataliya Di Donato[1,2], **Sara Chiari**[3], **Ghayda M. Mirzaa**[2,4], **Kimberly Aldinger**[2], **Elena Parrini**[3], **Carissa Olds**[2], **A. James Barkovich**[5], **Renzo Guerrini**[3,6], and **William B. Dobyns**[2,4,7]

[1]Institute for Clinical Genetics, TU Dresden, Dresden, Germany

Polymicrogyria Overview

Chloe A Stutterd, MBBS, FRACP, William B Dobyns, MD, Anna Jansen, MD, PhD, Ghayda Mirzaa, MD, and Richard J Leventer, MBBS, BMedSci, PhD, FRACP.

DEFINITIONS OF MCD

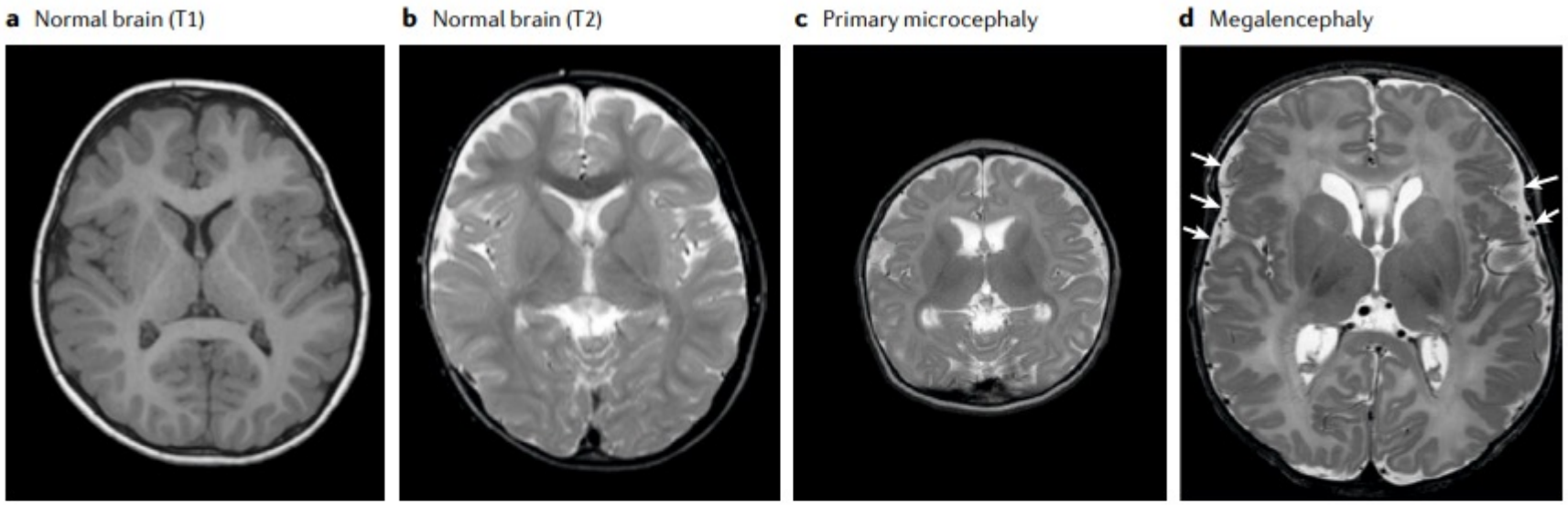
Table 1 | **Consensus definitions of the main MCD types**

Phenotype	HPO ID	Description
Microcephaly	HP:0000252	A significant reduction in OFC by ≥2 s.d. [a]compared with controls matched for age and sex[9,10]
Megalencephaly	HP:0001355	A significant increase in OFC, and specifically brain size, by ≥3 s.d. compared with controls matched for age and sex[b]
Periventricular nodular heterotopia (PVNH)	HP:0032388	Grey matter nodules along the ventricular walls[1]
Lissencephaly spectrum	HP:0001339	Includes agyria, pachygyria and subcortical band heterotopia
Agyria, pachygyria	HP:0031882, HP:0001302	Abnormal gyral pattern with absent or broad gyri in combination with an abnormally thick cortex[18]
Subcortical band heterotopia (SBH)	HP:0032409	A band of grey matter separated from the cortex and lateral ventricles by zones of white matter[18]
Cobblestone malformation (COB)	HP:0007260	An irregular and 'pebbled' cerebral surface with moderately thick cortex and jagged grey–white matter border with frequent vertical (perpendicular to the cortex–white matter border) striations[22,23]
Polymicrogyria	HP:0002126	An excessive number of abnormally small cerebral gyri with cortical overfolding, irregular 'pebbled' cortical surface and a 'stippled' grey–white matter boundary[28]
Schizencephaly	HP:0010636	A full-thickness cerebral cleft lined with grey matter, which extends from the ventricular surface to the pial surface[174]
Focal cortical dysplasia (FCD)	HP:0032046	Cortical dyslamination, with or without abnormal cell types (dysmorphic neurons and balloon cells). Other features can include gyral and/or sulcal irregularities; increased cortical thickness; blurring of the cortex–white matter junction; and white matter abnormalities, such as increased signal on T2-weighted images or a radially oriented 'transmantle sign' of T2 hyperintensity extending from the abnormal cortex to the lateral ventricle[171]
Dysgyria	HP:0032398	A cortex of variable thickness and a smooth grey–white boundary but with an abnormal gyral pattern characterized by irregularities of sulcal depth and or orientation[30,31]. This term is only used to characterize cortical malformations that do not meet the classic features of any of the abovementioned subtypes

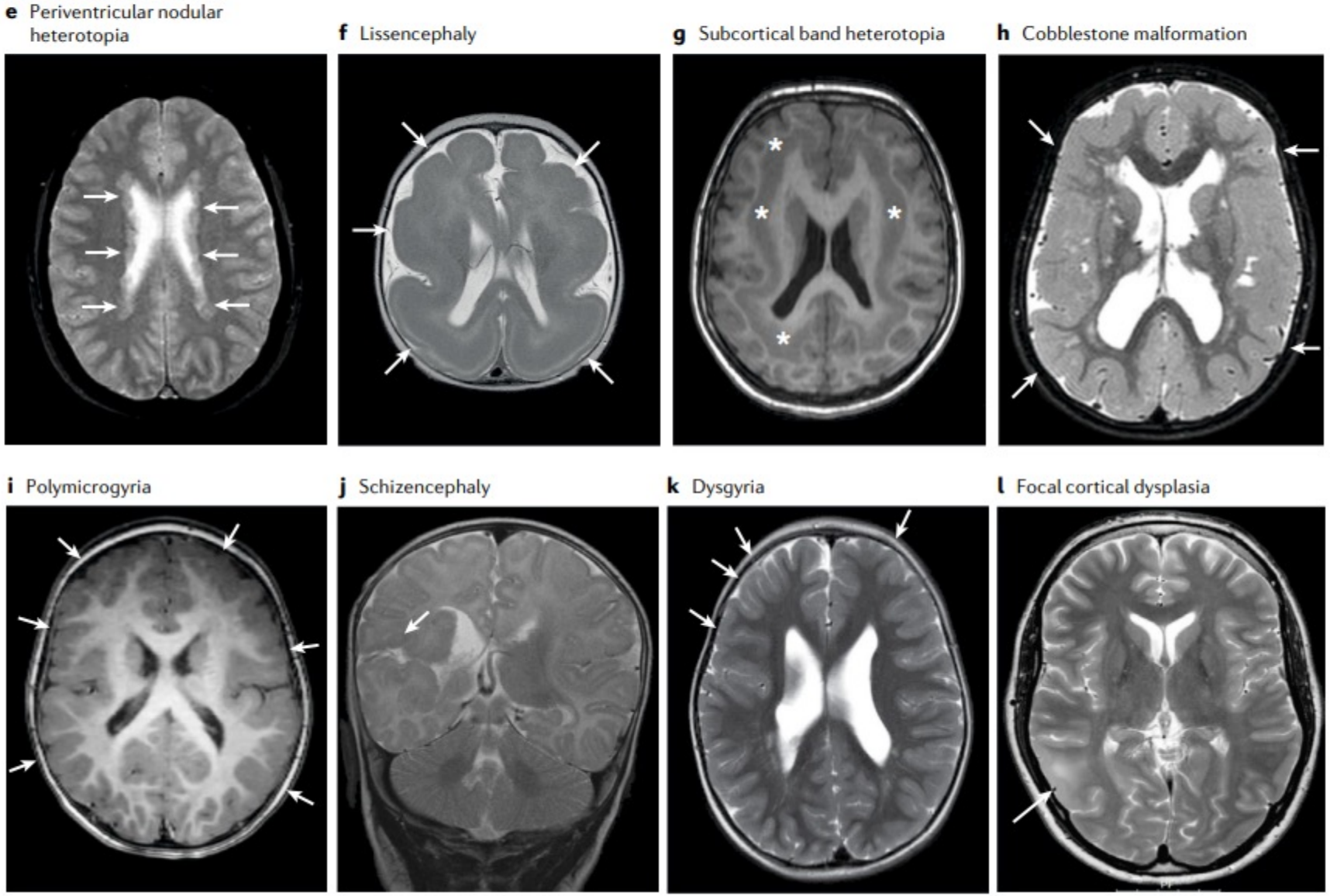
Neuro-MIG

Oegema et al Nat Rev Neurol. 2020 Nov;16(11):618-635.

IMAGING OF MCD



Oegema et al Nat Rev Neurol. 2020 Nov;16(11):618-635.



Oegema et al Nat Rev Neurol. 2020 Nov;16(11):618-635.

IMAGING GUIDELINES FOR MCD

doi:10.1093/brain/awaa174 BRAIN 2020: 143; 2874–2894 | 2874

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Definitions and classification of malformations of cortical development: practical guidelines

Mariasavina Severino,[1] Ana Filipa Geraldo,[1,2] Norbert Utz,[3] Domenico Tortora,[1] Ivana Pogledic,[4] Wlodzimierz Klonowski,[5] Fabio Triulzi,[6] Filippo Arrigoni,[7] Kshitij Mankad,[8] Richard J. Leventer,[9] Grazia M.S. Mancini,[10] James A. Barkovich,[11,12,*] Maarten H. Lequin,[13,*] and Andrea Rossi[1,*] on behalf of the European Network on Brain Malformations (Neuro-MIG)

CLUES TO DIAGNOSIS

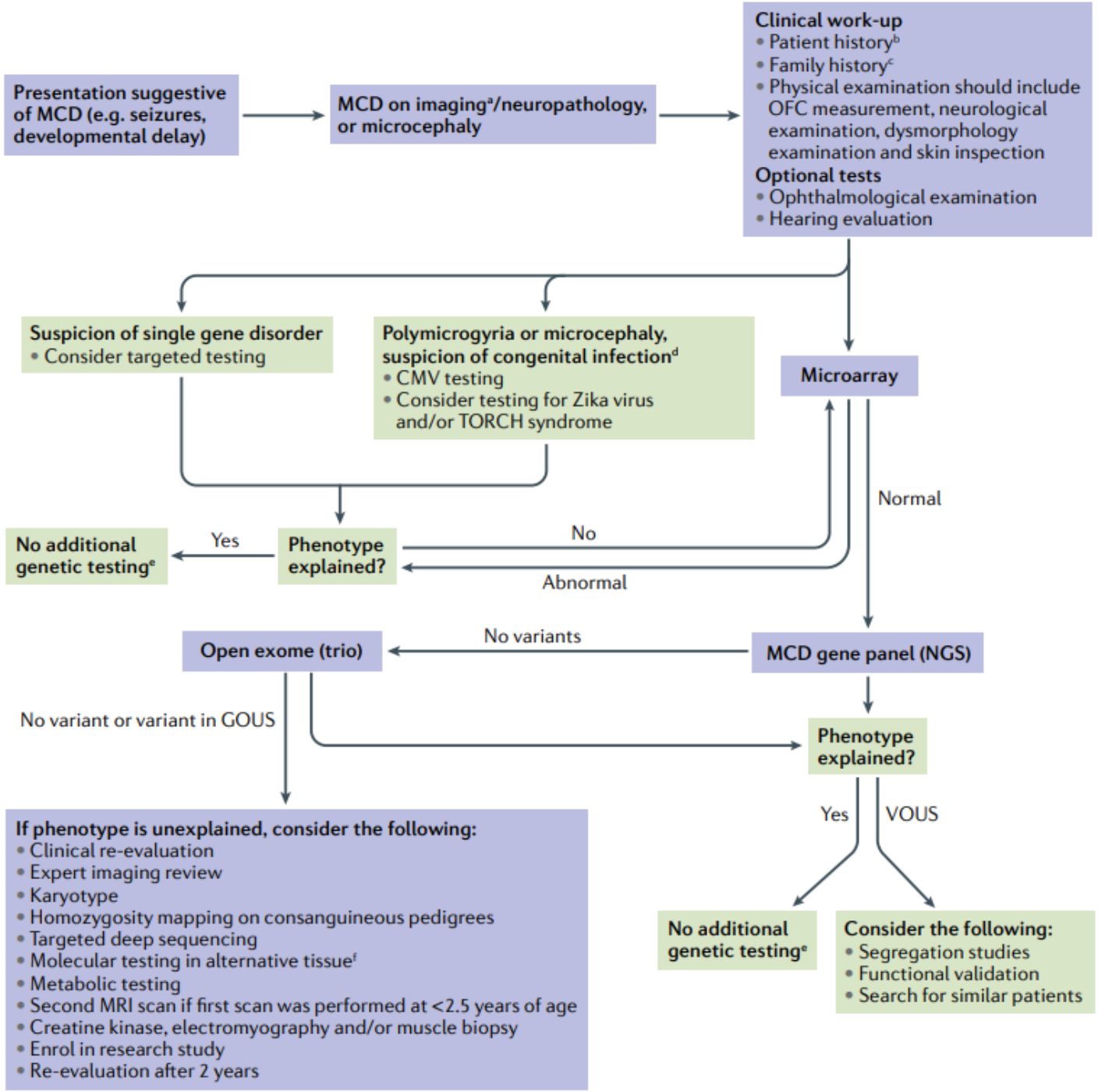
COST ACTION CA16118 NEURO-MIG

OPEN

Check for updates

International consensus recommendations on the diagnostic work-up for malformations of cortical development

Renske Oegema[1]✉, Tahsin Stefan Barakat[2], Martina Wilke[2], Katrien Stouffs[3], Dina Amrom[4,5], Eleonora Aronica[6,7], Nadia Bahi-Buisson[8], Valerio Conti[9], Andrew E. Fry[10,11], Tobias Geis[12], David Gomez Andres[13], Elena Parrini[9], Ivana Pogledic[14], Edith Said[14,15], Doriette Soler[16,17], Luis M. Valor[18], Maha S. Zaki[19], Ghayda Mirzaa[20,21], William B. Dobyns[20,21], Orly Reiner[21], Renzo Guerrini[9], Daniela T. Pilz[22], Ute Hehr[23], Richard J. Leventer[24], Anna C. Jansen[25], Grazia M. S. Mancini[2,26] and Nataliya Di Donato[27]✉



Oegema et al 2020

1. PATIENT HISTORY

TWINNING

MCBA twin pregnancy

C-section at 32 4/7 WG because of twin anemia polycythemia sequence (TAPS) and fetal distress fetus 1

BW 2060g, H 40.5cm, HC 31cm

Good start, partial exchange transfusion for polycythemia

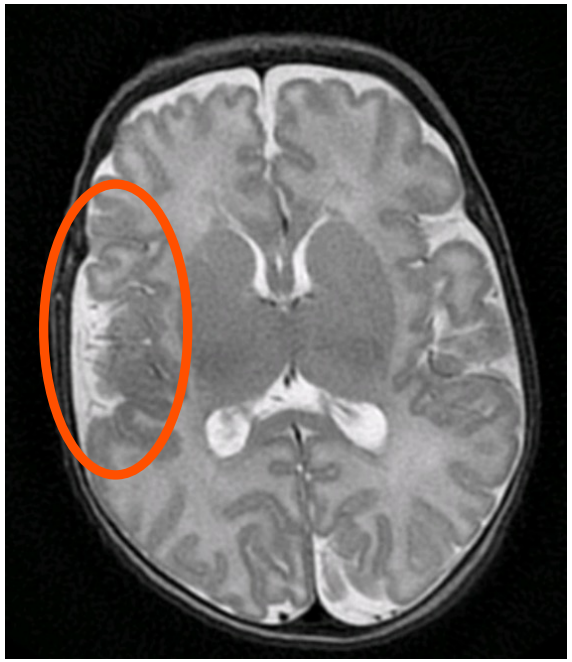
cCMV screening negative

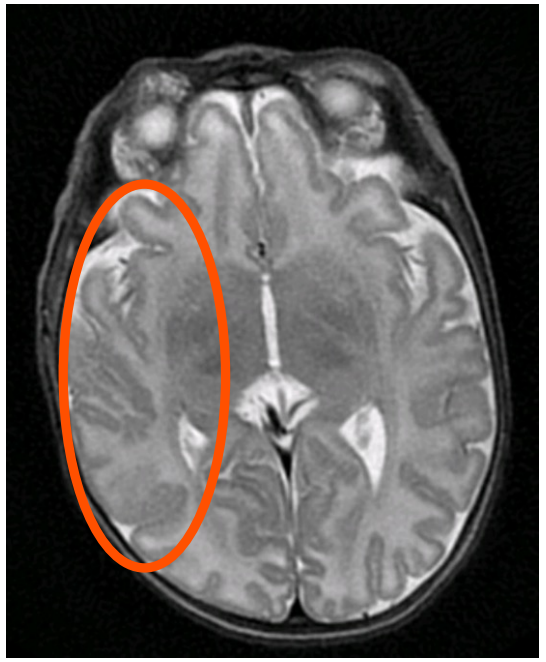
Normal hearing

PRENATAL RISK FACTORS

TWINNING

Brain MRI at age 6 weeks (2 weeks c.a.)

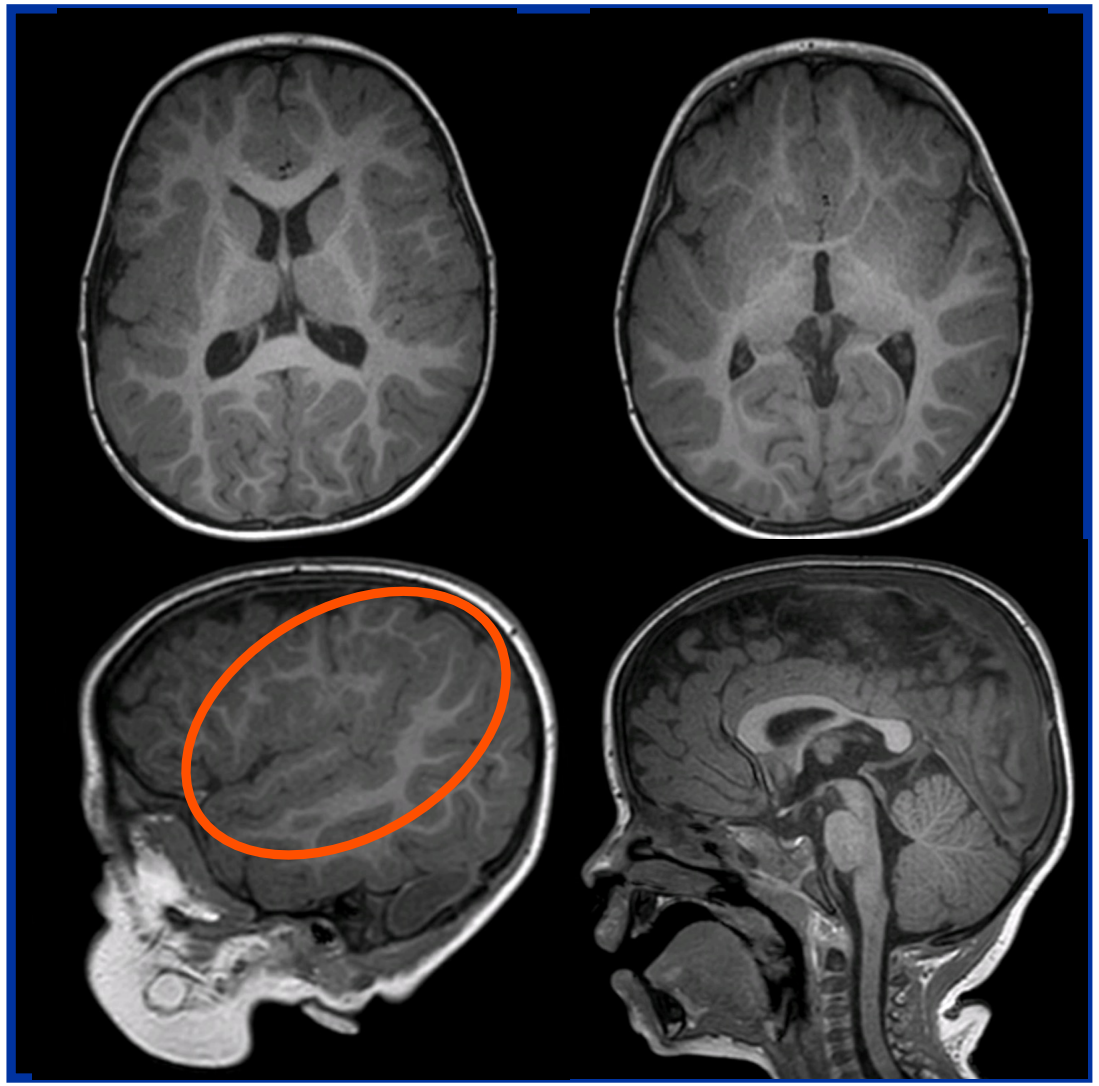




PRENATAL RISK FACTORS

TWINNING

Brain MRI at age 2.5years



PRENATAL RISK FACTORS

TWINNING

Developmental assessment at calendar age 29 months, corrected age 21 months

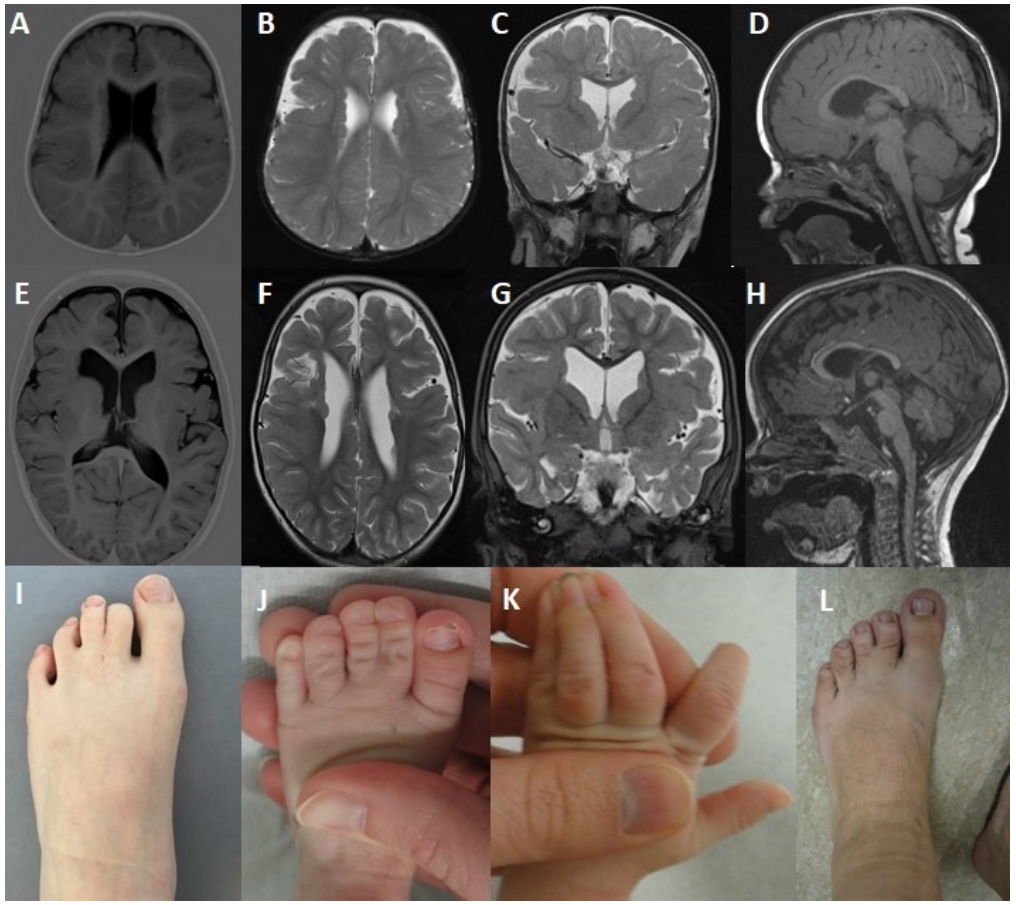
- BSID-III
  - cognition 24 months

- BSID-III
  - fine motor skills 28 months
  - gross motor skills 40 months

- Communicative Development Inventory (N-CDI)
  - receptive language 20-21 months
  - expressive language 20 – 21 months

2. SUSPICION OF A SINGLE GENE DISORDER

TEAMWORK



Recurrent NEDD4L Variant in Periventricular Nodular Heterotopia, Polymicrogyria and Syndactyly

Katrien Stouffs[1,2], Patrick Verloo[3], Stefanie Brock[2,4], Luc Régal[5], Diane Beysen[6], Berten Ceulemans[6], Anna C. Jansen[2,5†] and Marije E.C. Meuwissen[7,8†]*

frontiers in Genetics

CASE REPORT
published: 05 February 2020
doi: 10.3389/fgene.2020.00026

WHAT DID WE LEARN?

A **novel c.623G>A, p.(Arg208Gln) variant** in *NEDD4L,* which encodes an E3 ubiquitin ligase

This variant affects the **WW domain** whereas all previously reported variants affected the HECT domain

Familial occurrence of a variant in *NEDD4L*

The same variant occurred *de novo* in an unrelated individual with similar phenotype, suggesting a **potential mutational hotspot**

The combination of **PNH and PMG** should prompt for careful evaluation for syndactyly, clefts and/or hypospadias since these findings are suggestive of NEDD4L-involvement

When lab reports come back negative, think again!

Clin Genet 2013

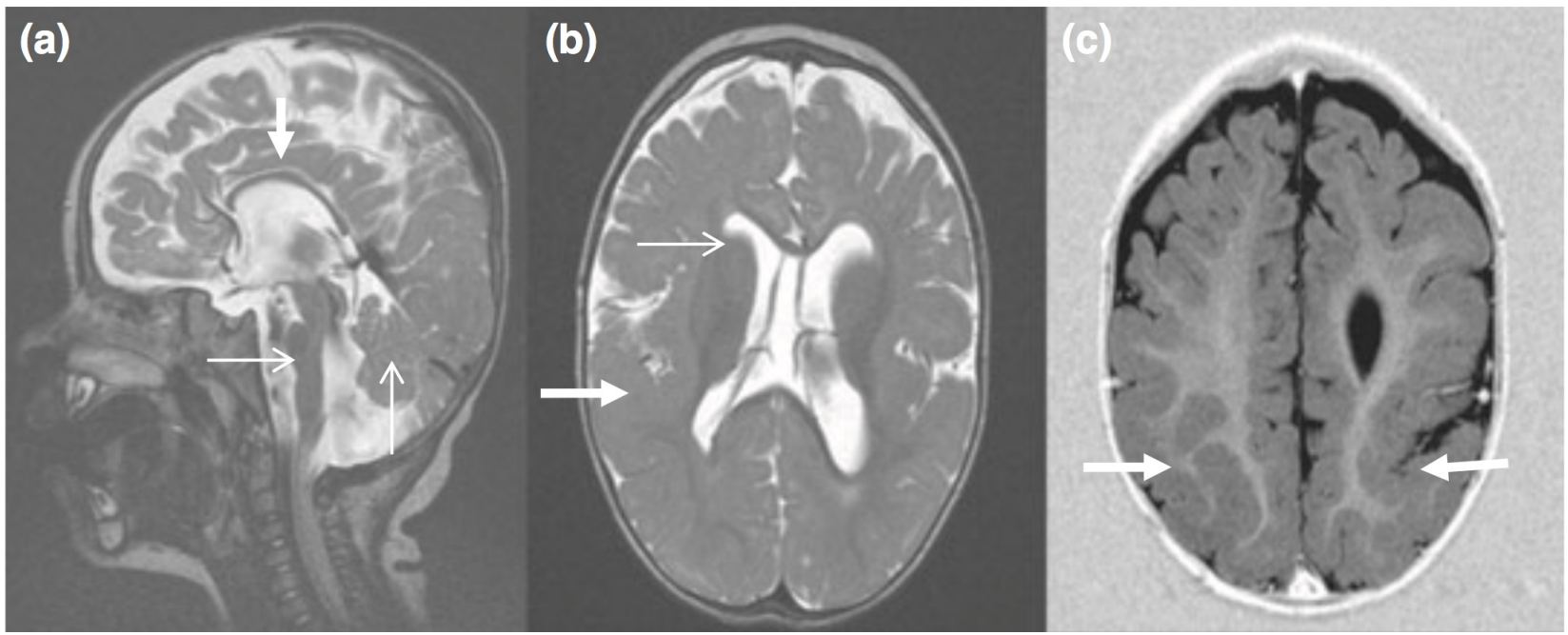
Published by Blackwell Publishing Ltd

CLINICAL GENETICS
doi: 10.1111/cge.12141

Short Report

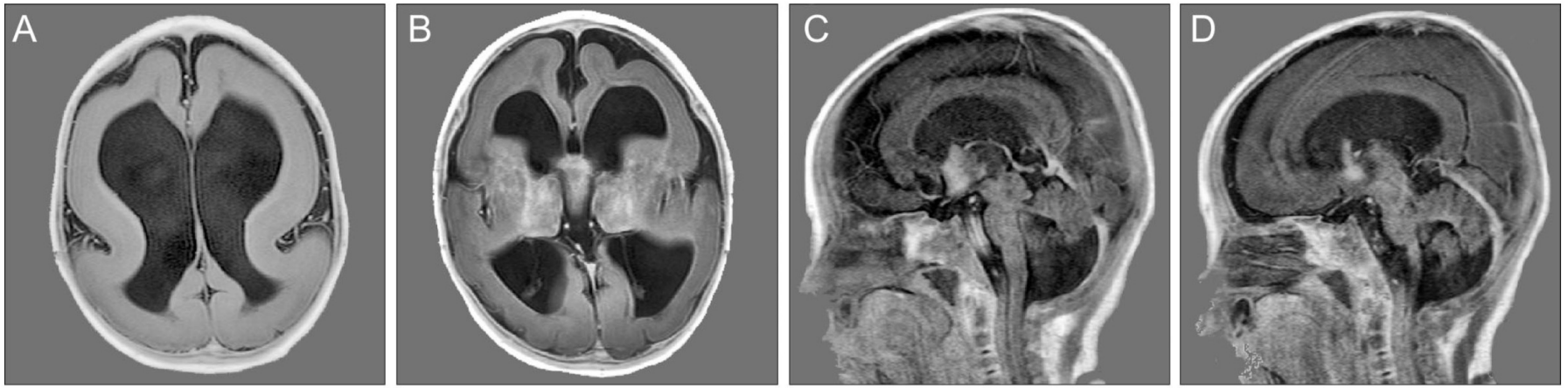
Polymicrogyria with dysmorphic basal ganglia? Think tubulin!

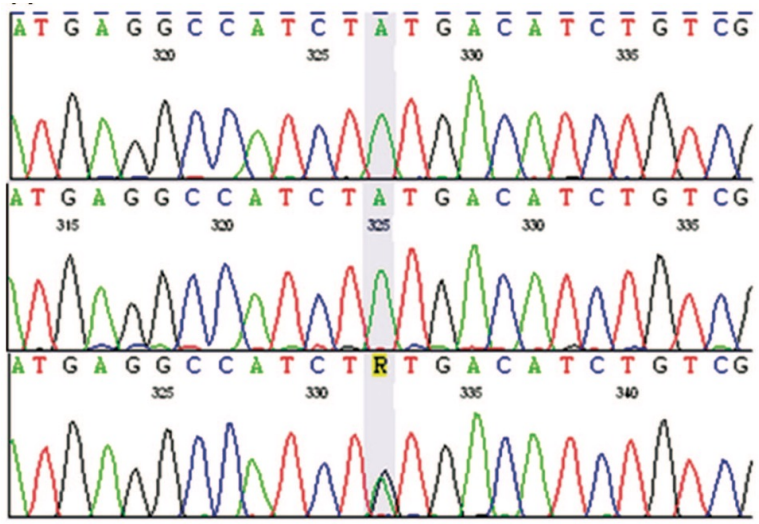
D Amrom[a,b,†], I Tanyalçin[c,†], H Verhelst[d], N Deconinck[e], GJ Brouhard[f], J-C Décarie[g], T Vanderhasselt[h], S Das[i], FF Hamdan[a], W Lissens[c,j], JL Michaud[a] and AC Jansen[k,l]



VARIANTS IN *TUBA1A*

TUBA1A mutations: From isolated lissencephaly to familial polymicrogyria.
Jansen AC, et al. Neurology. 2011 Mar 15;76(11):988-92

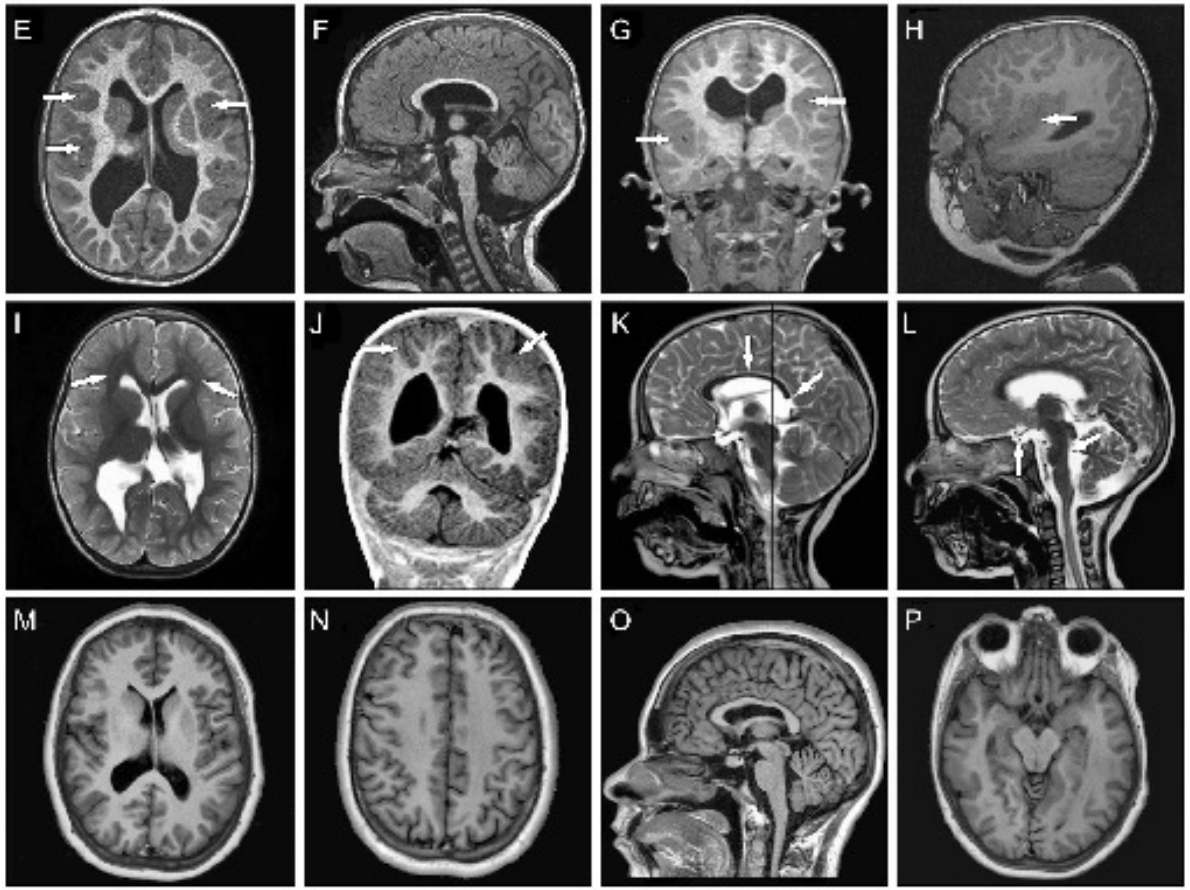


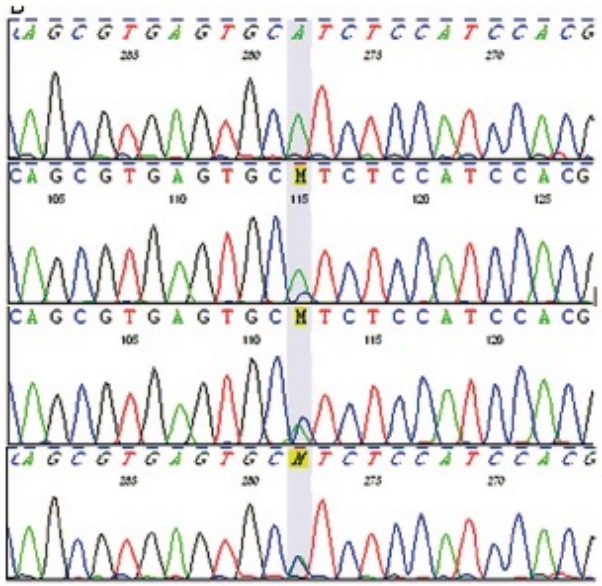


c.629A G (p.Tyr210Cys)

VARIANTS IN *TUBA1A*

TUBA1A mutations: From isolated lissencephaly to familial polymicrogyria.
Jansen AC, et al. Neurology. 2011 Mar 15;76(11):988-92





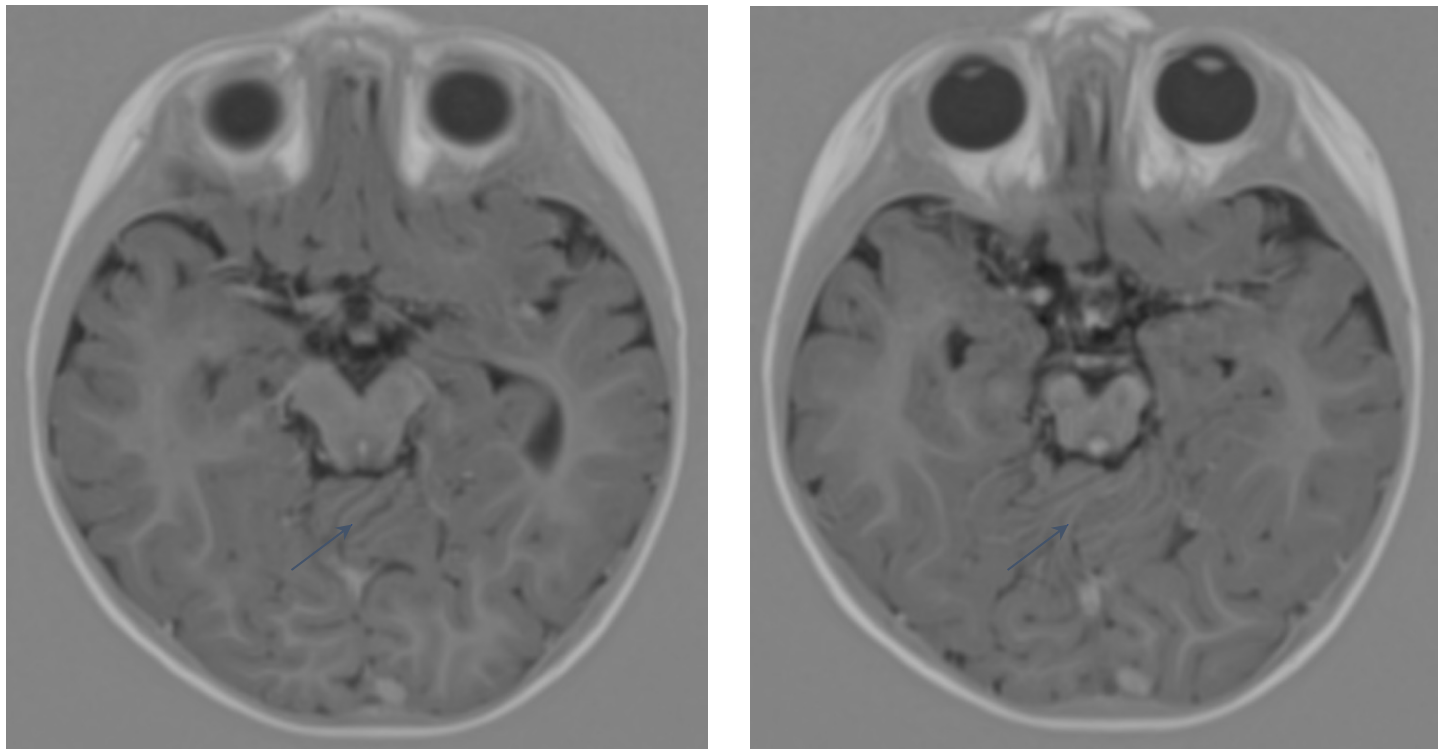
c.13A>C (p.Ile5Leu)

ORIGINAL ARTICLE

Recognizable cerebellar dysplasia associated with mutations in multiple tubulin genes

Renske Oegema[1,*,†], Thomas D. Cushion[2,†], Ian G. Phelps[4], Seo-Kyung Chung[2,3], Jennifer C. Dempsey[4], Sarah Collins[7], Jonathan G.L. Mullins[2], Tracy Dudding[8,9], Harinder Gill[10], Andrew J. Green[10,11], William B. Dobyns[4,5,7], Gisele E. Ishak[6], Mark I. Rees[2,3,†] and Dan Doherty[4,7,*,†]

Human Molecular Genetics, 2015, 1–13



TUBB3 c.292G>A, p.Gly98Ser *(de novo)*

TUBULINS

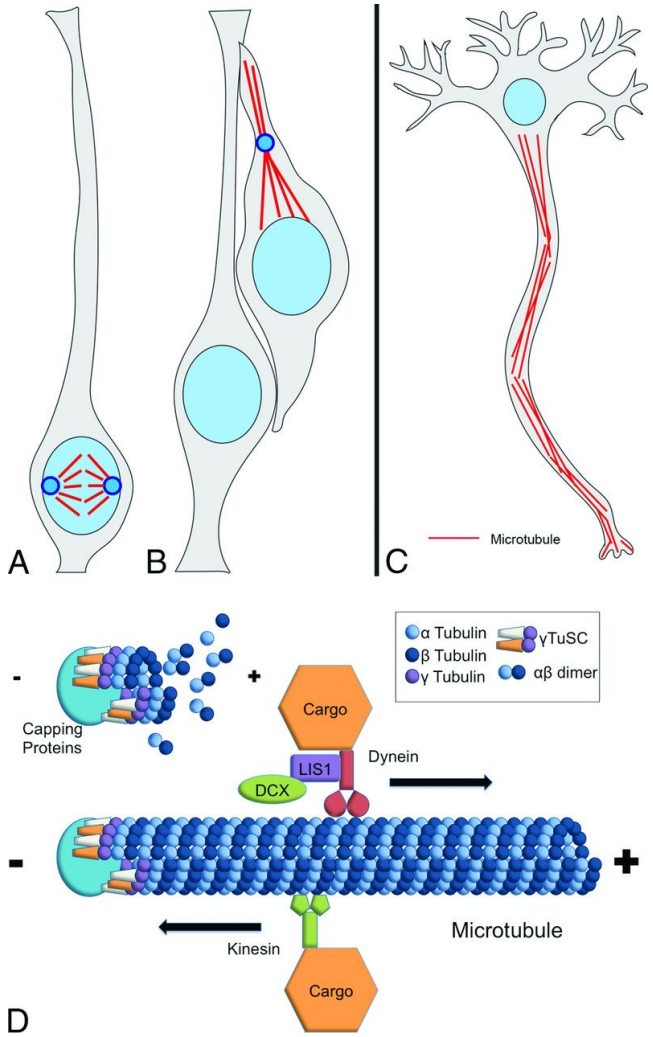
Mutations in genes belonging to the tubulin superfamily result in a wide spectrum of cortical malformations

TUBA1A, TUBB2A, TUBB2B, TUBB3, TUBB5, TUBA8 and *TUBG1*

MRI characteristics

- ‘tubulin related dysgyria’
- thin corpus callosum, (partial) agenesis of the corpus callosum
- dysplastic basal ganglia
- hypoplasia of brainstem and cerebellum
- dysgenesis of the cerebellar vermis

Multiple roles of microtubules in development.



C.A. Mutch et al. AJNR Am J Neuroradiol 2016;37:528-535

3. SUSPICION OF TORCH?

PMG – MICROCEPHALY – CALCIFICATIONS – WHITE MATTER ABNL

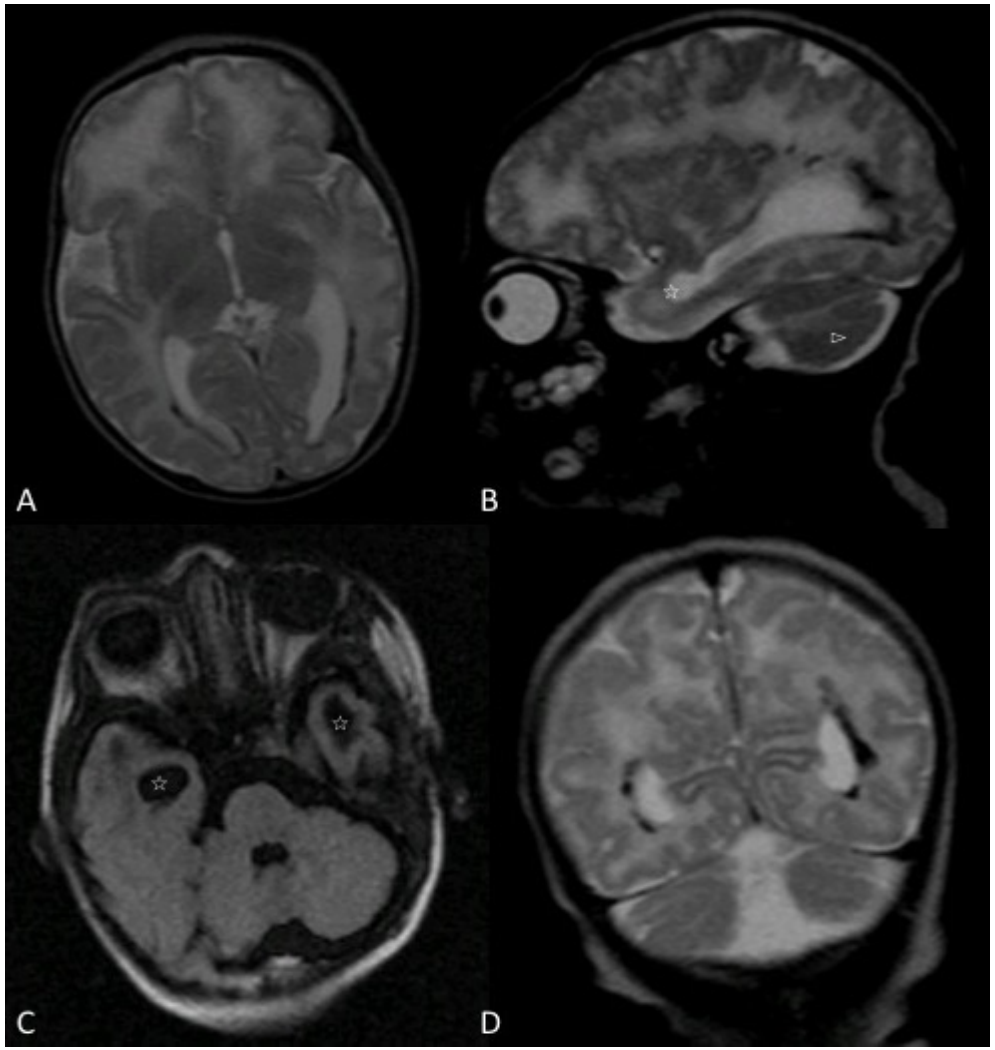
F - Born at 41 weeks gestation after an uneventful pregnancy and delivery with a birth weight of 2.660kg, height of 45,5cm and head circumference of 33cm

Presented at age 2 months with poor visual contact and axial hypotonia

Transcranial ultrasound showed calcifications in the basal ganglia and white matter

CMV detection on Guthrie card used for metabolic screening on day 3 of life confirmed the presence of a congenital CMV infection

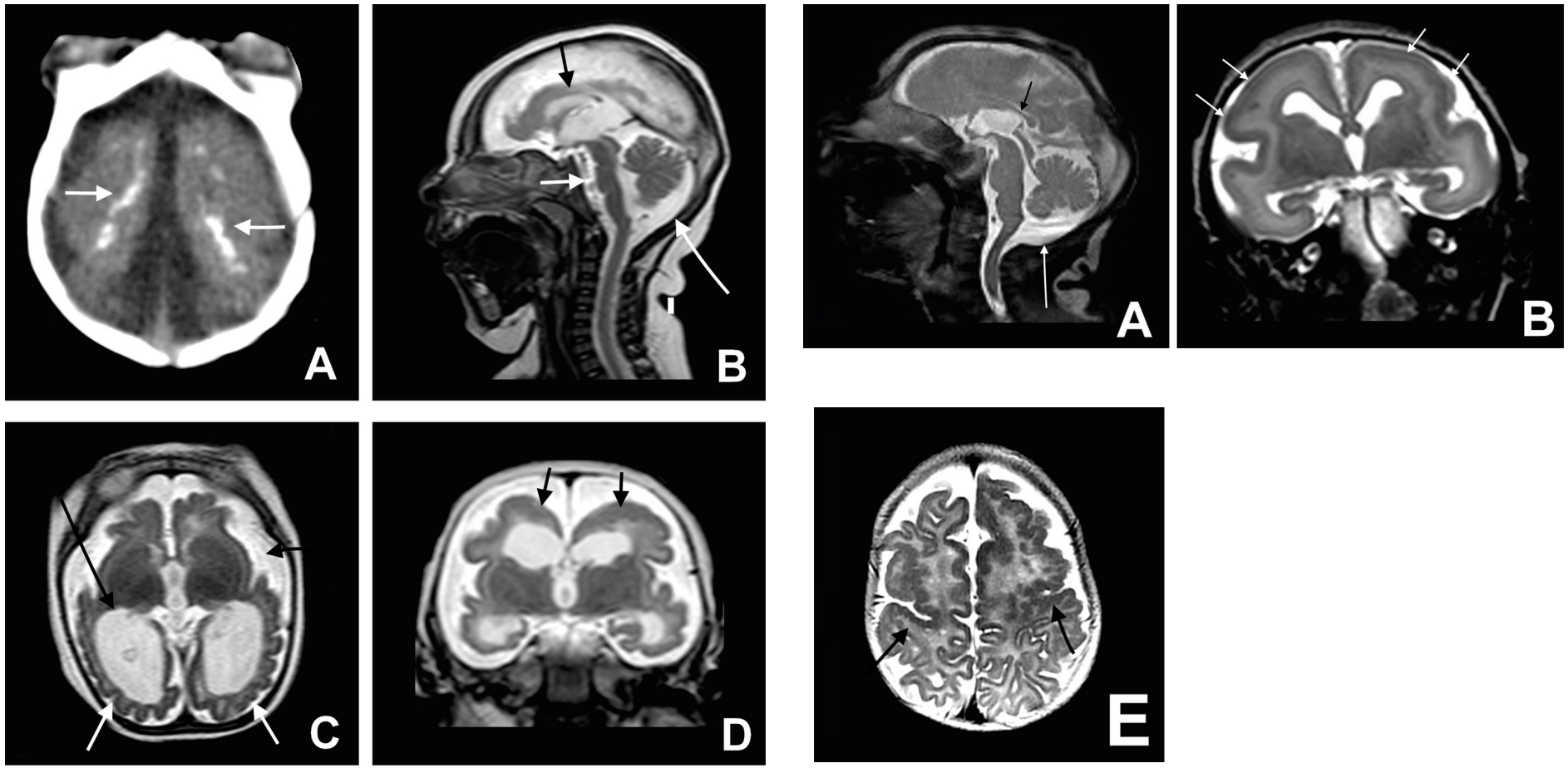
Fundoscopy was compatible with retinitis



Clinical features and neuroimaging (CT and MRI) findings in presumed Zika virus related congenital infection and microcephaly: retrospective case series study

Maria de Fatima Vasco Aragao,[1] Vanessa van der Linden,[2] Alessandra Mertens Brainer-Lima,[3] Regina Ramos Coeli,[4] Maria Angela Rocha,[4] Paula Sobral da Silva,[4] Maria Durce Costa Gomes de Carvalho,[4] Ana van der Linden,[5] Arthur Cesario de Holanda,[6] Marcelo Moraes Valenca[7]

the bmj | *BMJ* 2016;353:i1901 | doi: 10.1136/bmj.i1901



3. SUSPICION OF TORCH?

THINGS ARE NOT ALWAYS WHAT THEY SEEM

F - second child of healthy non-consanguineous parents after an uneventful pregnancy and delivery

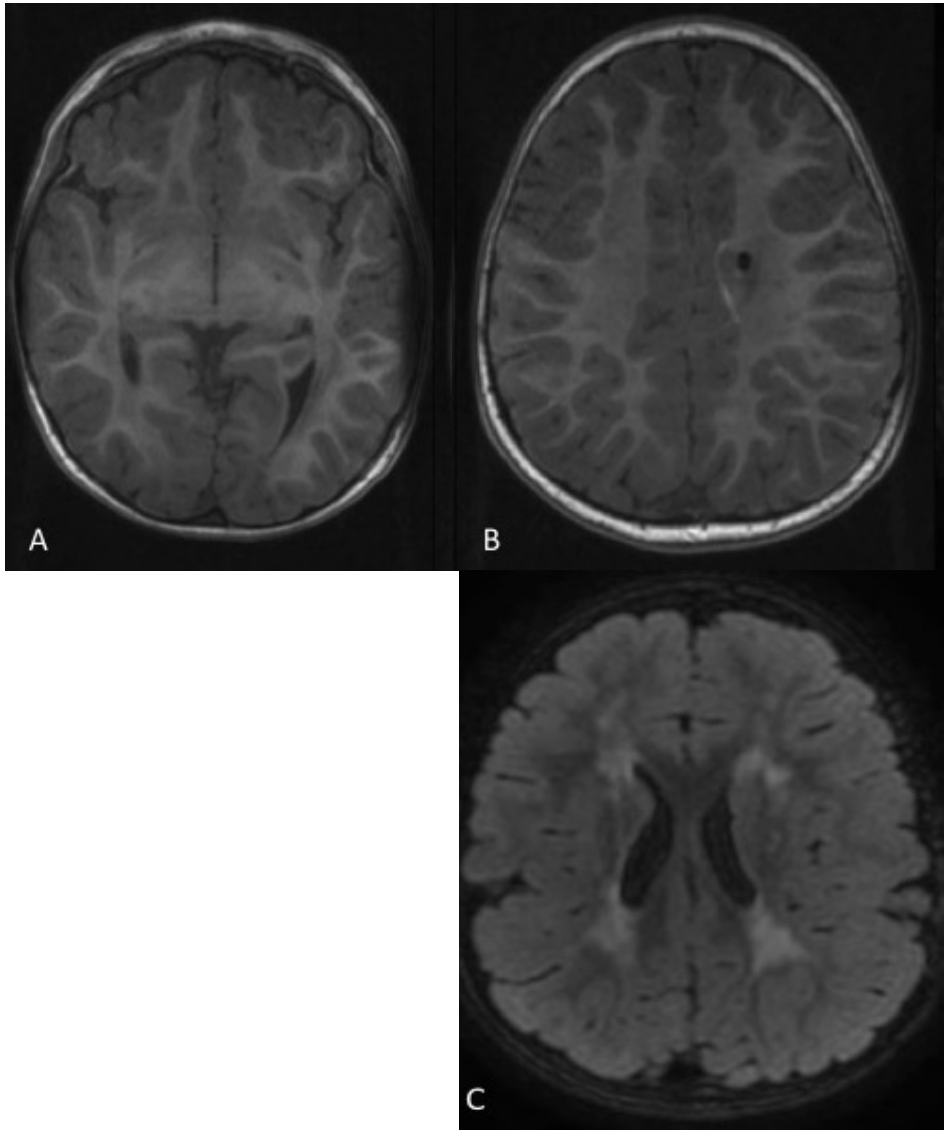
Presented with hypotonia, bilateral cataracts and head circumference of 32 cm (-1.5SD)

Transcranial ultrasound showed calcifications

Extensive TORCH-screening remained **negative**

@18 months focal seizures refractory to multiple AED

@30 months developmental age of 24 months



de novo c.3548G>T missense variant in *COL4A1*

The expanding phenotype of *COL4A1* and *COL4A2* mutations: clinical data on 13 newly identified families and a review of the literature

Marije E.C. Meuwissen, MD, PhD[1,2], Dicky J.J. Halley, PhD[1], Liesbeth S. Smit, MD[3], Maarten H. Lequin, MD, PhD[4], Jan M. Cobben, MD, PhD[5], René de Coo, MD, PhD[3], Jeske van Harssel, MD[6], Suzanne Sallevelt, MD[7], Gwendolyn Woldringh, MD, PhD[8], Marjo S. van der Knaap, MD, PhD[9], Linda S. de Vries, MD, PhD[10] and Grazia M.S. Mancini, MD, PhD[1]

Brain MRI findings

- Periventricular leukoencephalopathy/small-vessel disease
- Porencephaly
- Cerebral calcification
- Microbleeds
- Intracerebral hemorrhage
- Cerebellar atrophy
- Intracranial aneurysm
- Lacunar infarct
- Schizencephaly
- Intraventricular hemorrhage (without porencephaly)
- Dysplastic brain stem
- Hydrocephalus
- Hydranencephaly
- Mild ventriculomegaly
- Abnormal basal ganglia
- Gyral abnormalities
- Multicystic encephalomalacia
- Lissencephaly
- Traumatic subarachnoidal hemorrhage
- Tortuosity of infra- and supratentorial vessels
- Dandy Walker malformation
- Focal cortical dysplasia

Ophthalmological findings

- Cataract
- Retinal arterial tortuosity
- Strabismus
- Iris hypoplasia
- Posterior embryotoxon
- Corneal opacities
- Retinal hemorrhage
- Anterior segment
- Optic atrophy
- Microcornea
- Microphthalmia
- Glaucoma
- High myopia
- Reduced cone and rod responses
- Nystagmus
- Optic coloboma
- Retinal detachment
- Hypermetropia

Renal findings

- Renal cysts
- Hematuria
- Renal agenesis
- Hyperechogenicity of renal pyramids
- Dilated pyelum

Muscular abnormalities

- Elevated creatine kinase
- Muscle cramps
- Myopathy
- Muscular atrophy

Cardiac abnormalities

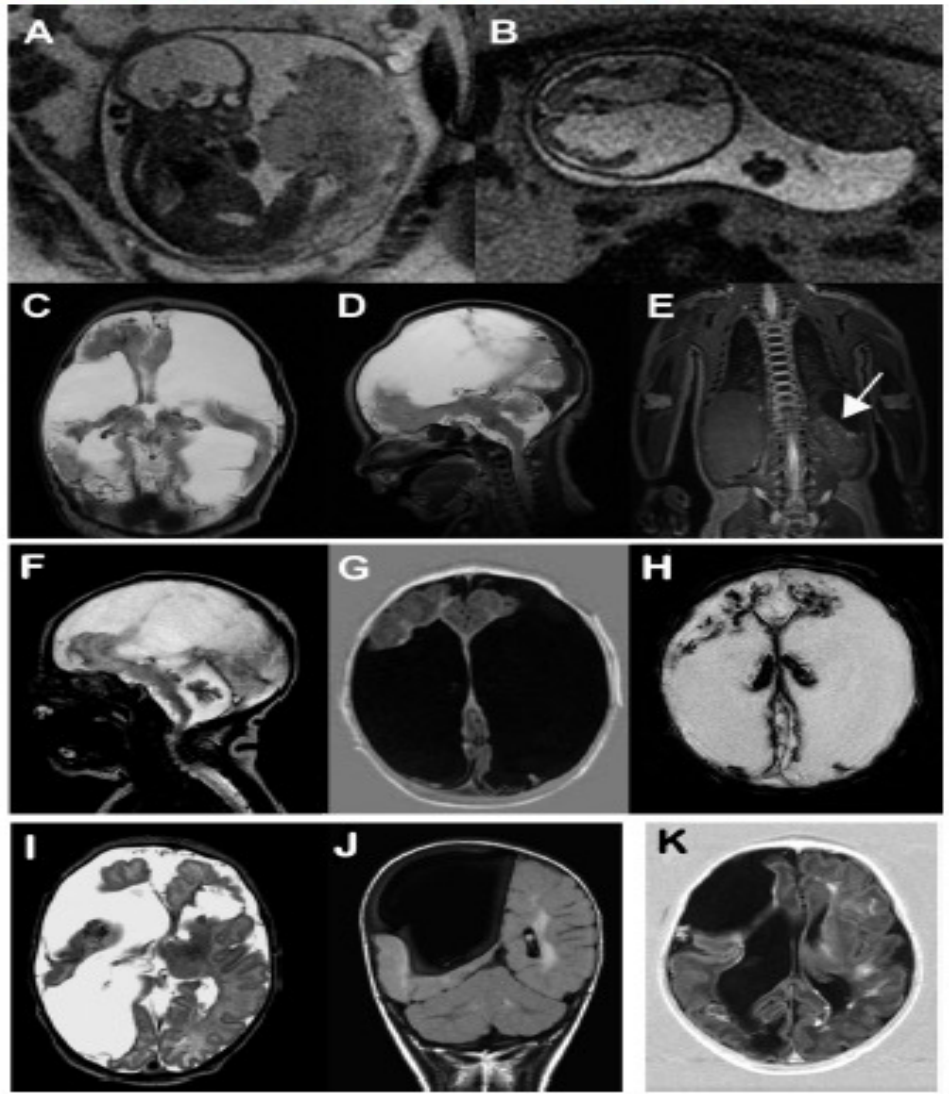
- Raynaud
- Cardiac (supraventricular) arrhythmia
- Mitral valve prolapsed
- Ventricular deptal defect

Other findings

- Hemolytic anemia
- Thymus, liver, and adrenal hemorrhage
- Sensorineural deafness

M.E.C. Meuwissen, MD*
L.S. de Vries, MD, PhD*
H.A. Verbeek, BSc
M.H. Lequin, MD, PhD
P.P. Govaert, MD, PhD
R. Schot, BSc
F.M. Cowan, MD, PhD
R. Hennekam, MD, PhD
P. Rizzu, PhD
F.W. Verheijen, PhD
M.W. Wessels, MD, PhD*
G.M.S. Mancini, MD, PhD*

SPORADIC COL4A1 MUTATIONS WITH EXTENSIVE PRENATAL PORENCEPHALY RESEMBLING HYDRANENCEPHALY



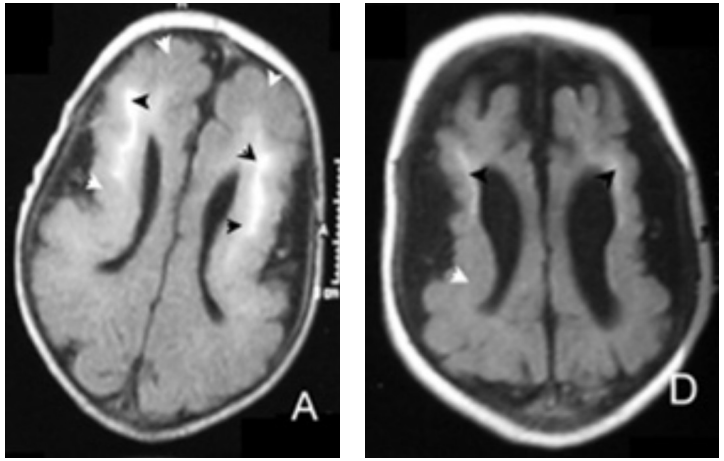
PSEUDO-TORCH SYNDROMES

MCD - WHITE MATTER CHANGES - CALCIFICATIONS

REPORT

Recessive Mutations in the Gene Encoding the Tight Junction Protein Occludin Cause Band-like Calcification with Simplified Gyration and Polymicrogyria

Mary C. O'Driscoll,[1] Sarah B. Daly,[1] Jill E. Urquhart,[1] Graeme C.M. Black,[1] Daniela T. Pilz,[2] Knut Brockmann,[3] Meriel McEntagart,[4] Ghada Abdel-Salam,[5] Maha Zaki,[5] Nicole I. Wolf,[6,7] Roger L. Ladda,[8] Susan Sell,[8] Stefano D'Arrigo,[9] Waney Squier,[10] William B. Dobyns,[11] John H. Livingston,[12] and Yanick J. Crow[1,*]



Variants in *USP18, JAM3*
Variants in *ADAR, IFIH1, TREX1, RNASEH2A, RNASEH2B, RNASEH2C and SAMHD1* (AGS)

4. MICRODELETION OR DUPLICATION?

SNP-array

Clinical Report

Prenatal Diagnosis of Monosomy 1p36:

A Focus on Brain Abnormalities and a Review of the Literature

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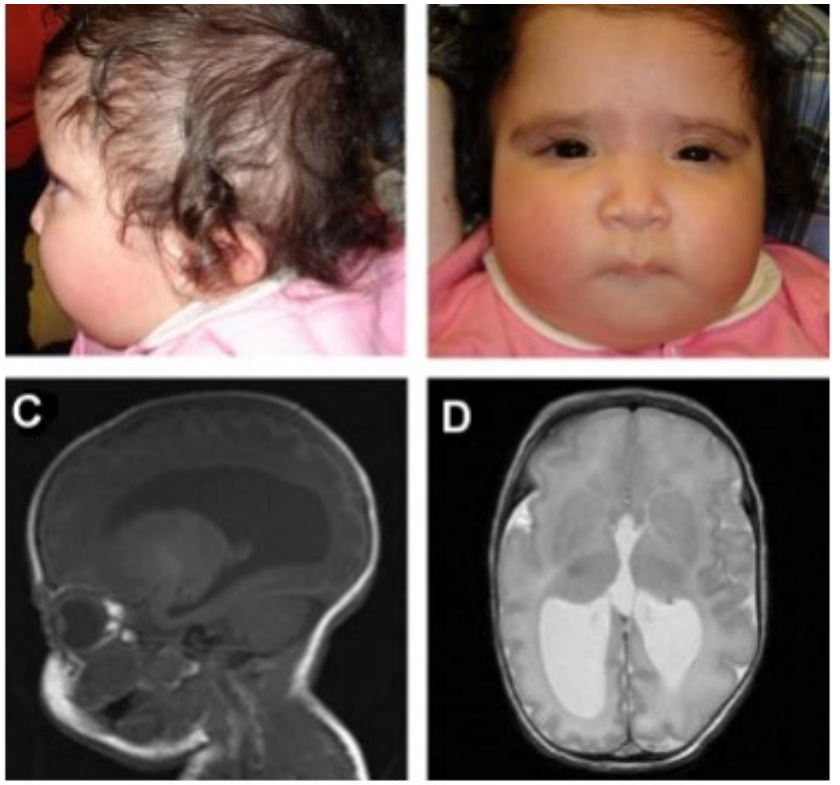
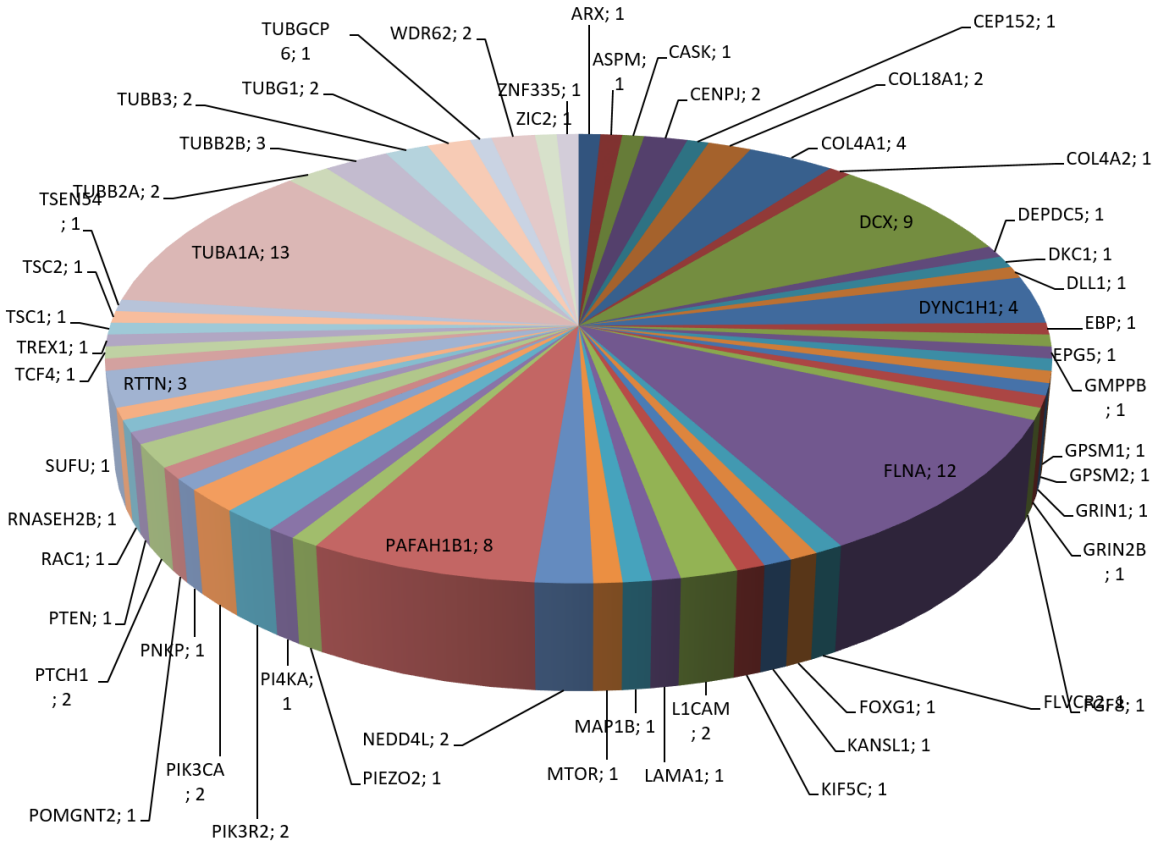


FIG. 1. **A**,**B**: Patient 1 at 6 months of age displaying a high forehead, a flat facial profile, a small nose with a broad base, low-set posteriorly rotated ears, narrow palpebral fissures, deep-set eyes and micrognathia. **C**: Sagittal T1-weighted MRI image of the brain of patient 1 at 5½ months. **D**: Transverse T2-weighted MRI image of the brain of patient 1 at 5½ months showing moderate to severe non-obstructive hydrocephalus and bilateral colpocephaly.

5. MCD PANEL

UZ Brussel - Prof Katrien Stouffs

- 620 MCD samples tested
- Diagnostic yield ~ 19,5% (120/620)
  - Higher in subgroups (lissencephaly)



6. NEXT STEPS

SKIN BIOPSY OR SALIVA SAMPLE

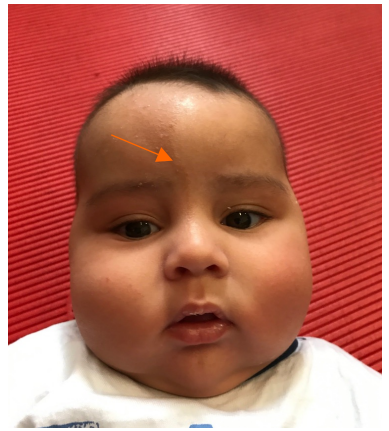
Presented with clonic movements of the left arm and foot on day 3 of life, increasing in frequency. Admitted on day 7.
EEG burst suppression pattern
NE severe axial hypotonia, HC +2SD
Phenobarbital, carbamazepine, valproic acid, vigabatrin and ACTH, epilepsy surgery

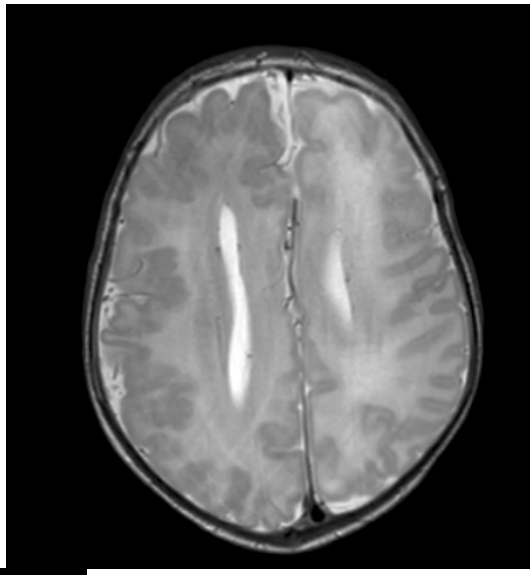
Evolution

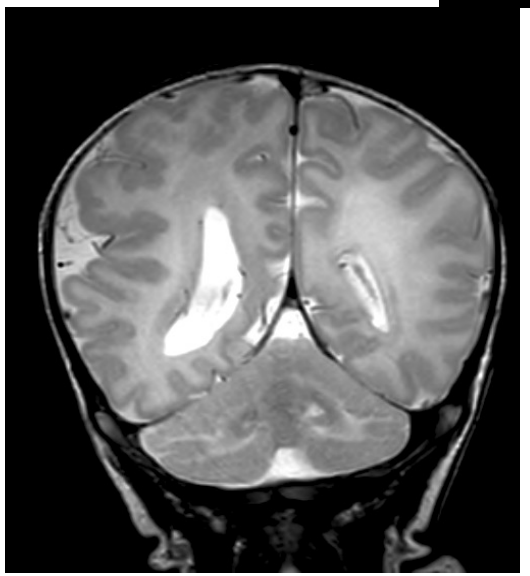
- Refractory focal epilepsy – controlled after surgery
- Severe developmental delay
- Left hemiparesis

Genetic work-up

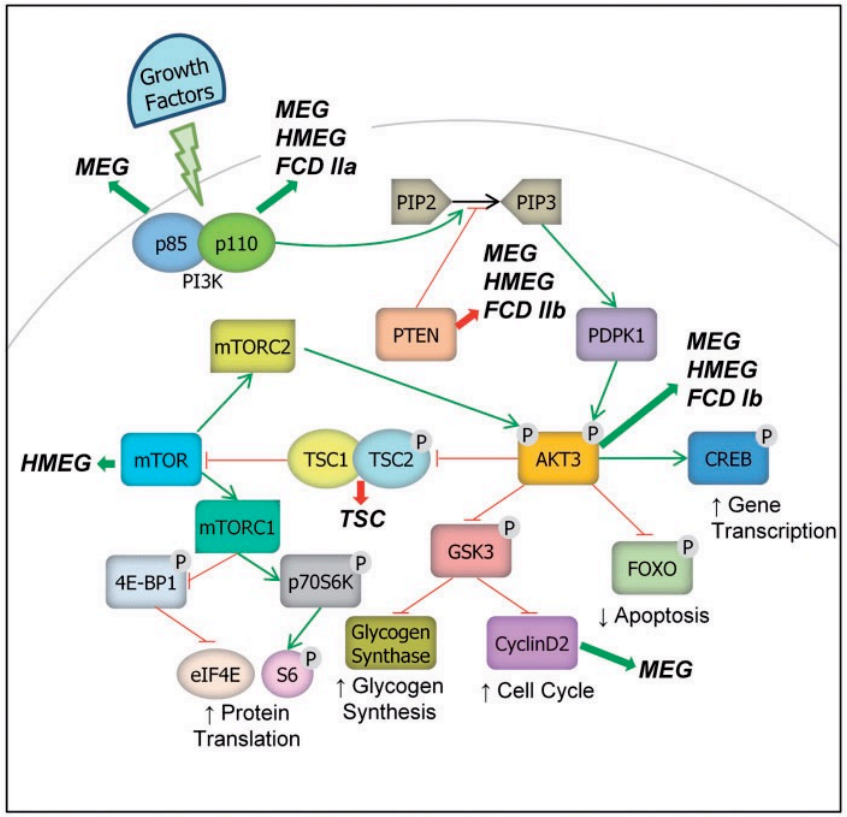
- MCD panel with special attention for mTOR pathway genes: negative
- MCD panel fibroblasts from hyperpigmented lesion (arrow): c.1624G>A, p.(Glu542Lys) substitution in *PIK3CA* in 30% of cells (somatic mosaicism)





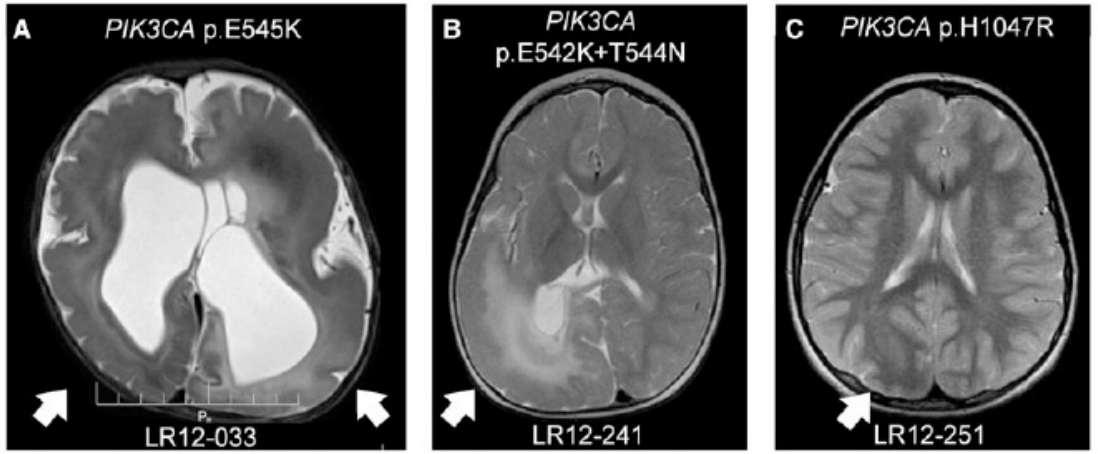


PIK3CA IN MEGALENCEPHALY AND FCD

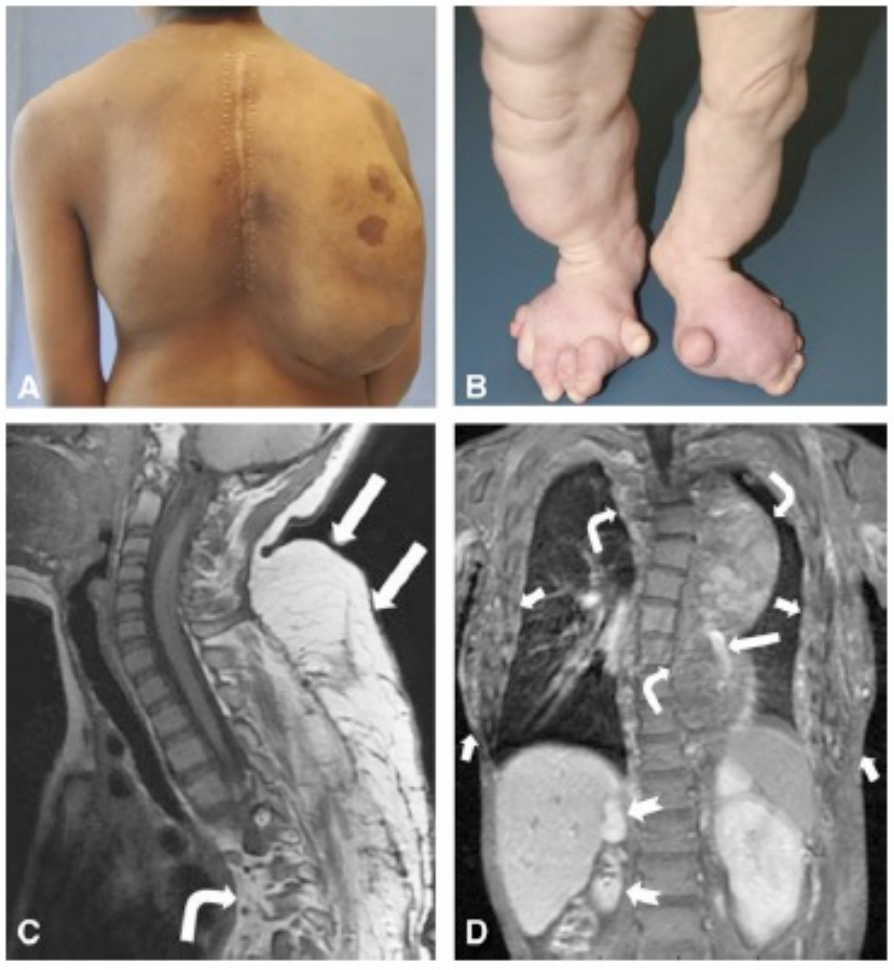


PI3K/AKT pathway mutations cause a spectrum of brain malformations from megalencephaly to focal cortical dysplasia

Laura A. Jansen,[1,2] Ghayda M. Mirzaa,[2,3] Gisele E. Ishak,[4] Brian J. O'Roak,[5,6] Joseph B. Hiatt,[5] William H. Roden,[2] Sonya A. Gunter,[1] Susan L. Christian,[2] Sarah Collins,[2] Carissa Adams,[2] Jean-Baptiste Rivière,[2,7] Judith St-Onge,[2,7] Jeffrey G. Ojemann,[8] Jay Shendure,[5] Robert F. Hevner[2,8] and William B. Dobyns[2,3]



PIK3CA IN CLOVES SYNDROME



REPORT

Somatic Mosaic Activating Mutations in *PIK3CA* Cause CLOVES Syndrome

Kyle C. Kurek,[1] Valerie L. Luks,[2] Ugur M. Ayturk,[2,9] Ahmad I. Alomari,[3,6] Steven J. Fishman,[4,6] Samantha A. Spencer,[2,6] John B. Mulliken,[5,6] Margot E. Bowen,[2,9] Guilherme L. Yamamoto,[7] Harry P.W. Kozakewich,[1,6] and Matthew L. Warman[2,6,8,9,*]

6. NEXT STEPS

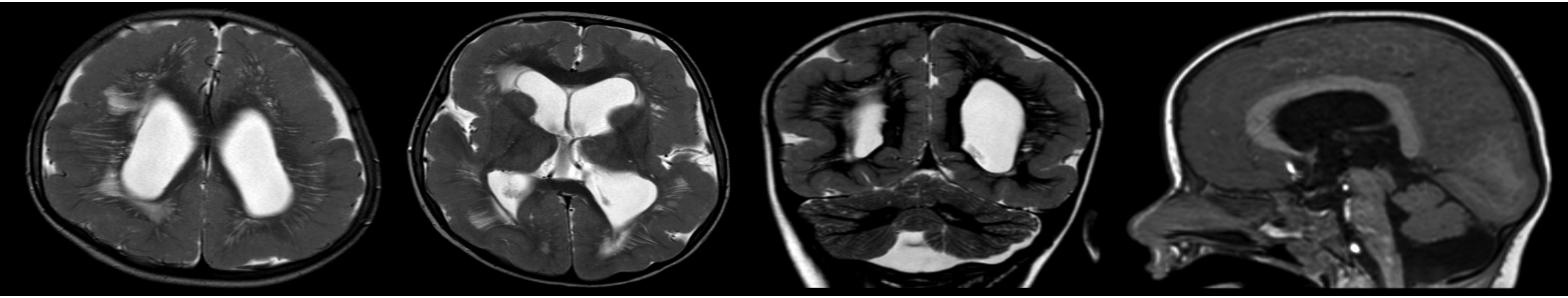
SEARCH FOR ADDITIONAL PATIENTS

7-year-old girl

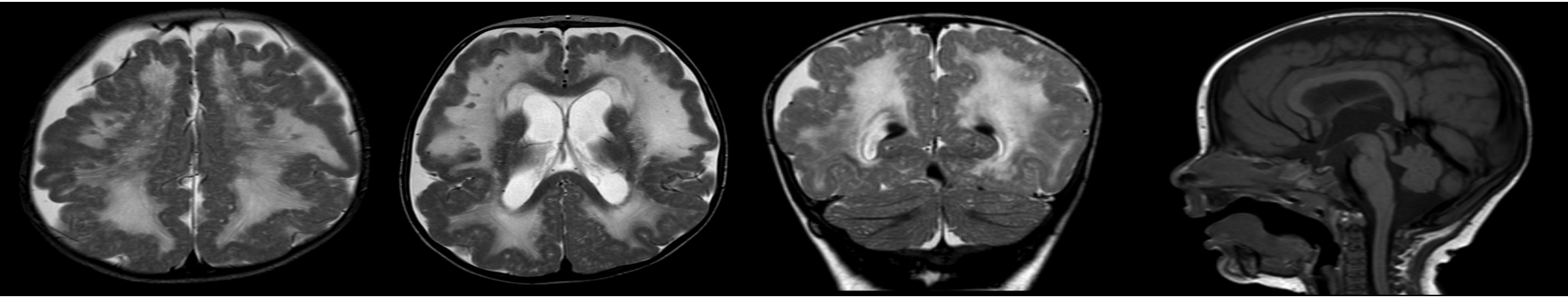
- Global developmental delay, walks without support, uses a few words
- HC >90th centile
- Spasms ° 5 years

3-year-old boy

- Global developmental delay, sits with support, no words
- HC >97th centile
- Spasms ° 26 months



MRI at age 34 months

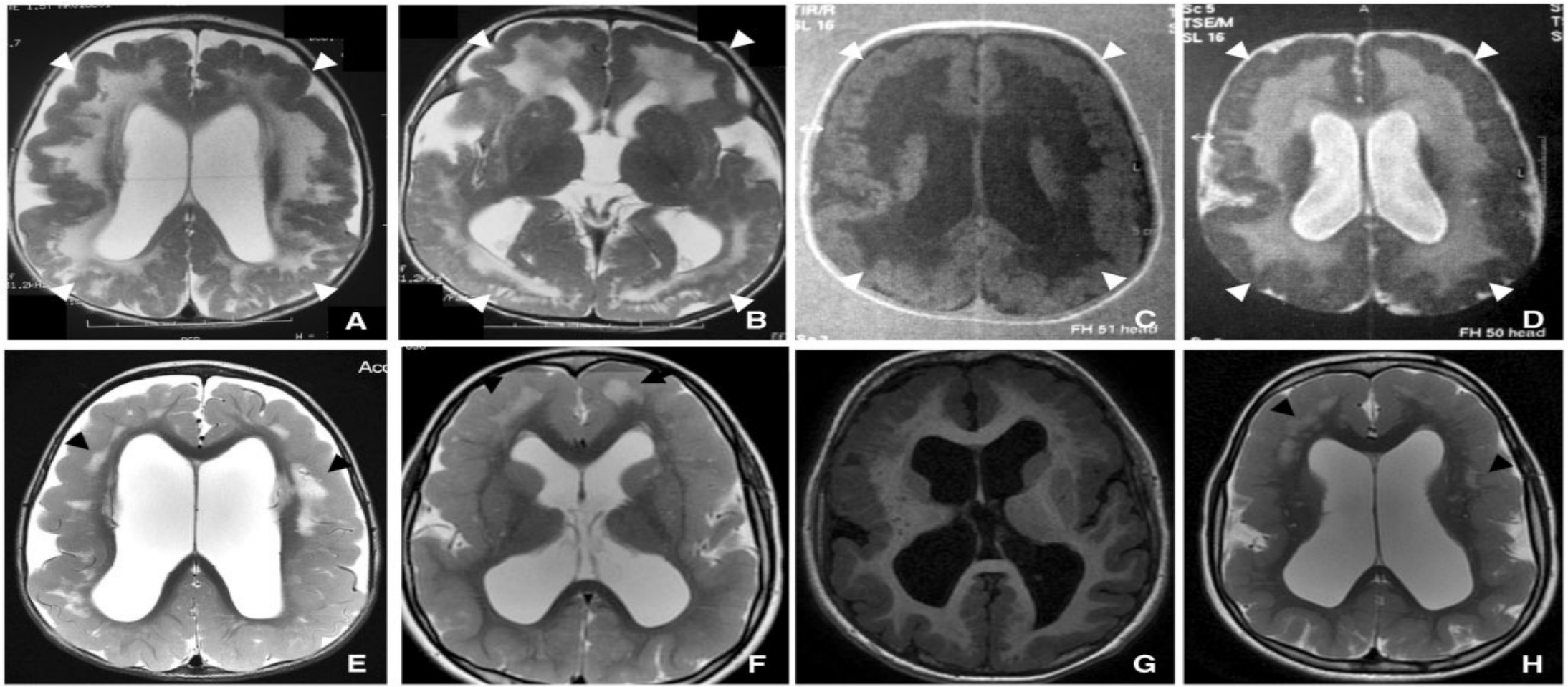


MRI at age 6 months

GPR56-related bilateral frontoparietal polymicrogyria: further evidence for an overlap with the cobblestone complex

Nadia Bahi-Buisson,[1,2,3,4,*] Karine Poirier,[2,3,*] Nathalie Boddaert,[5,6] Catherine Fallet-Bianco,[7,8] Nicola Specchio,[9] Enrico Bertini,[10] Okay Caglayan,[11] Karine Lascelles,[12] Caroline Elie,[13] Jérôme Rambaud,[1,2,3] Michel Baulac,[14] Isabelle An,[14] Patricia Dias,[15] Vincent des Portes,[16] Marie Laure Moutard,[17] Christine Soufflet,[18] Monique El Maleh,[19] Cherif Beldjord,[20] Laurent Villard[21,22] and Jamel Chelly[2,3]

Brain 2010: 133; 3194–3209 | 3194



G protein-coupled receptor 56 and collagen III, a receptor-ligand pair, regulates cortical development and lamination

Rong Luo[1], Sung-Jin Jeong[1], Zhaohui Jin[1], Natalie Strokes, Shihong Li, and Xianhua Piao[2]

PNAS | August 2, 2011 | vol. 108 | no. 31 | 12925–12930

OPEN ACCESS Freely available online

PLoS one

Disease-Associated Mutations Prevent GPR56-Collagen III Interaction

Rong Luo, Zhaohui Jin, Yiyu Deng, Natalie Strokes, Xianhua Piao*

OPEN ACCESS Freely available online

PLoS one

Loss of *Col3a1*, the Gene for Ehlers-Danlos Syndrome Type IV, Results in Neocortical Dyslamination

Sung-Jin Jeong, Shihong Li, Rong Luo, Natalie Strokes, Xianhua Piao*

EJHG Open

European Journal of Human Genetics (2014), 1–7

www.nature.com/ejhg

ARTICLE

Vascular Ehlers–Danlos Syndrome in siblings with biallelic *COL3A1* sequence variants and marked clinical variability in the extended family

Agnete Jørgensen*[,1], Toril Fagerheim[1], Svend Rand-Hendriksen[2], Per I Lunde[3], Torgrim O Vorren[4], Melanie G Pepin[5], Dru F Leistritz[5] and Peter H Byers[5,6]

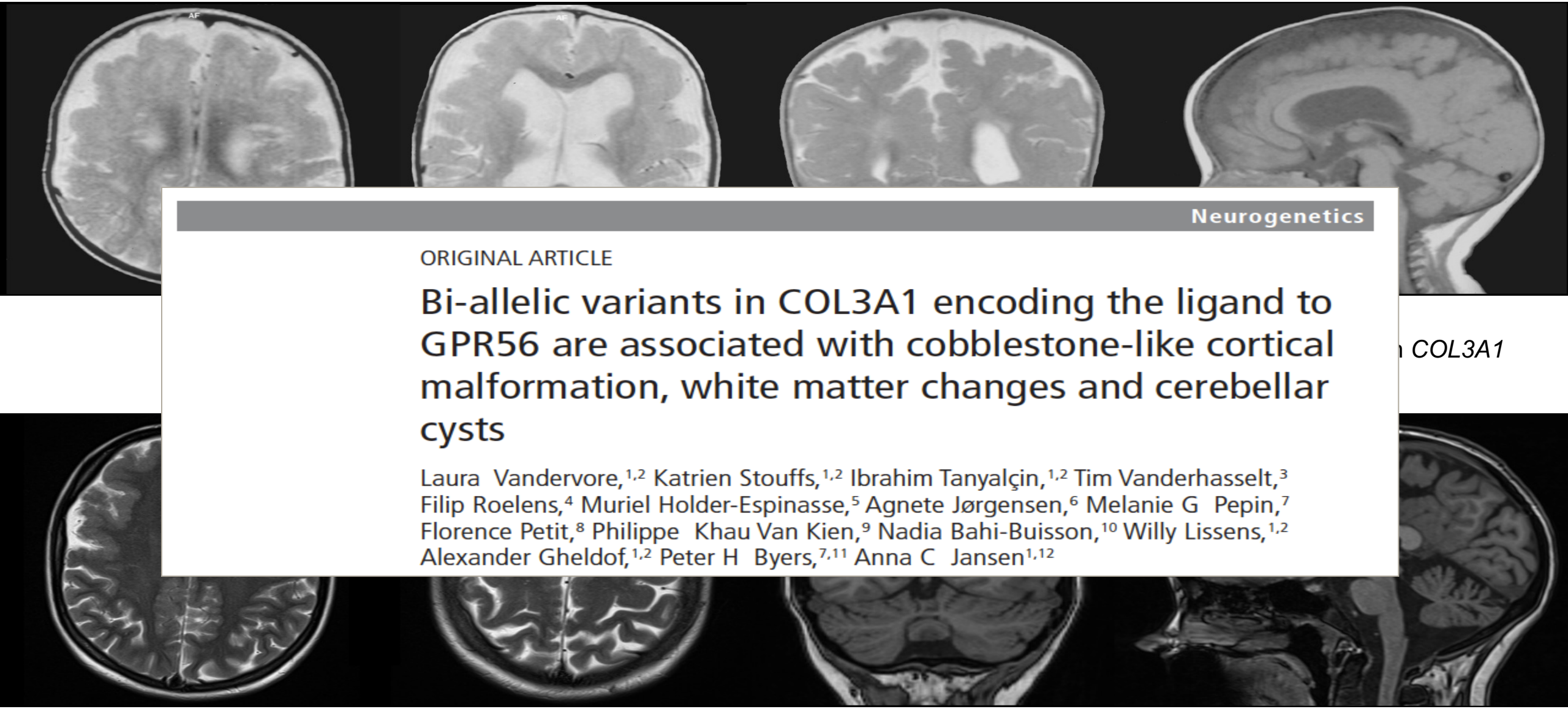
European Journal of Human Genetics (2009) 17, 1411–1416

www.nature.com/ejhg

ARTICLE

Homozygosity for a null allele of *COL3A1* results in recessive Ehlers–Danlos syndrome

Aurélie Plancke[1], Muriel Holder-Espinasse[2], Valérie Rigau[3], Sylvie Manouvrier[2], Mireille Claustres[1,4,5] and Philippe Khau Van Kien*[,1]



Neurogenetics

ORIGINAL ARTICLE

Bi-allelic variants in COL3A1 encoding the ligand to GPR56 are associated with cobblestone-like cortical malformation, white matter changes and cerebellar cysts

Laura Vandervore,[1,2] Katrien Stouffs,[1,2] Ibrahim Tanyalçin,[1,2] Tim Vanderhasselt,[3] Filip Roelens,[4] Muriel Holder-Espinasse,[5] Agnete Jørgensen,[6] Melanie G Pepin,[7] Florence Petit,[8] Philippe Khau Van Kien,[9] Nadia Bahi-Buisson,[10] Willy Lissens,[1,2] Alexander Gheldof,[1,2] Peter H Byers,[7,11] Anna C Jansen[1,12]

COL3A1

Compound heterozygous c.1786C>T (p.Arg596*; exon 26) and c.3851G>A (p.Gly1284Glu; exon 50) mutation in *COL3A1*

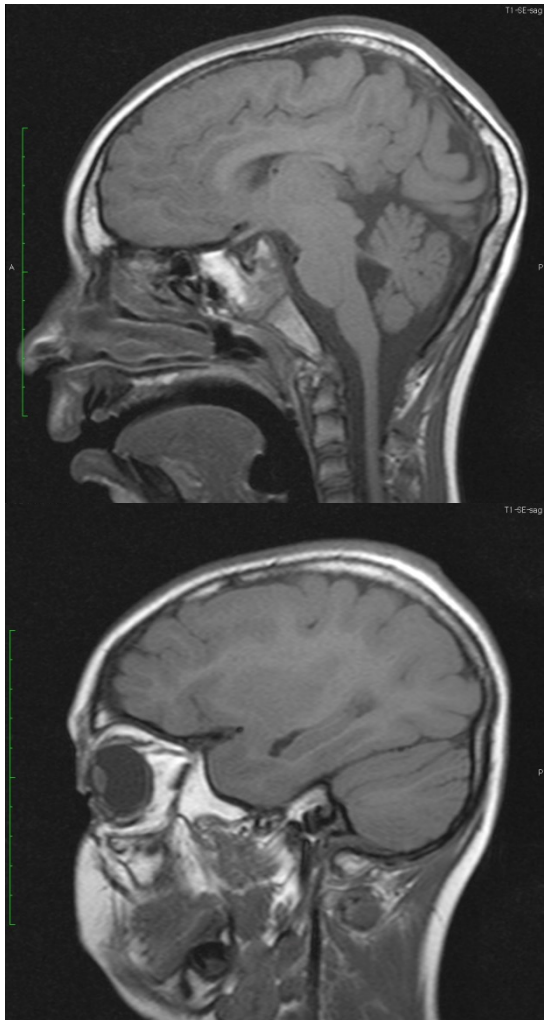
5. NEXT STEPS

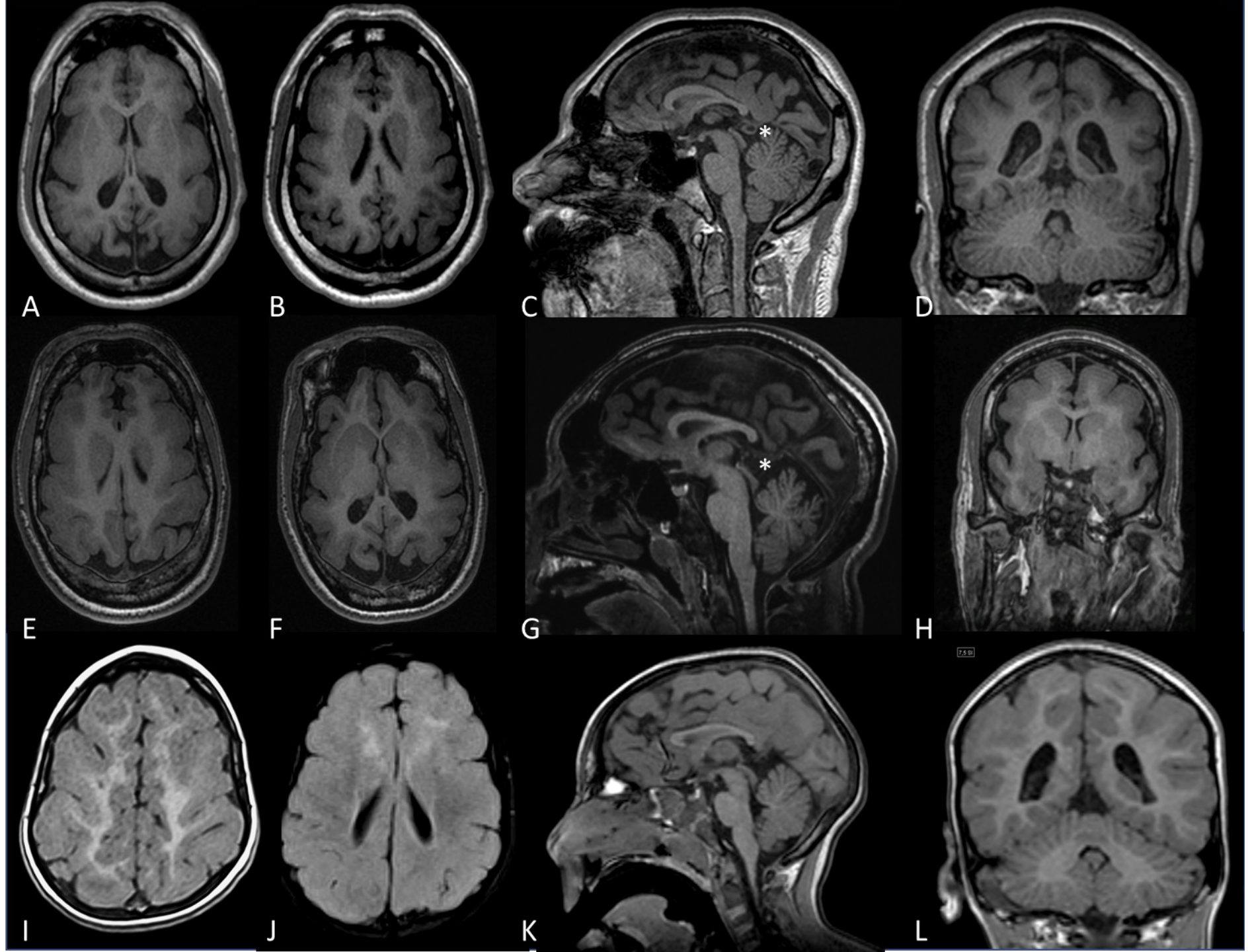
FUNCTIONAL STUDIES

- Two sisters (46,XX)
- Non-consanguinous parents
- Primary microcephaly (-4.5 SD)
- Short stature (-2 SD)
- Severe intellectual disability
- Mild facial dysmorphism

Compound heterozygous (c.2594A>G/c.4186del)

variant in *RTTN*

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Contents lists available at ScienceDirect

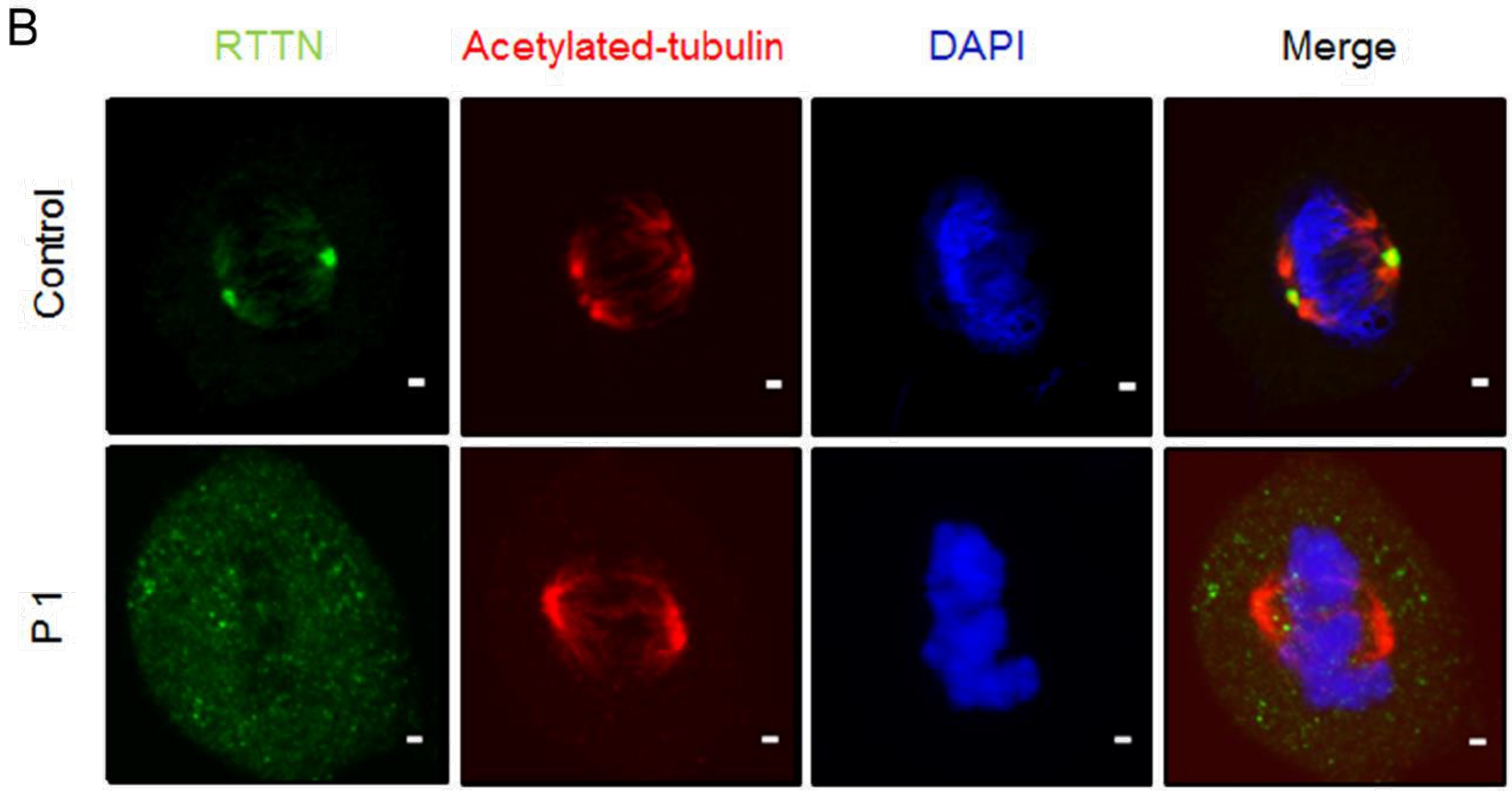
European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Biallelic mutations in *RTTN* are associated with microcephaly, short stature and a wide range of brain malformations

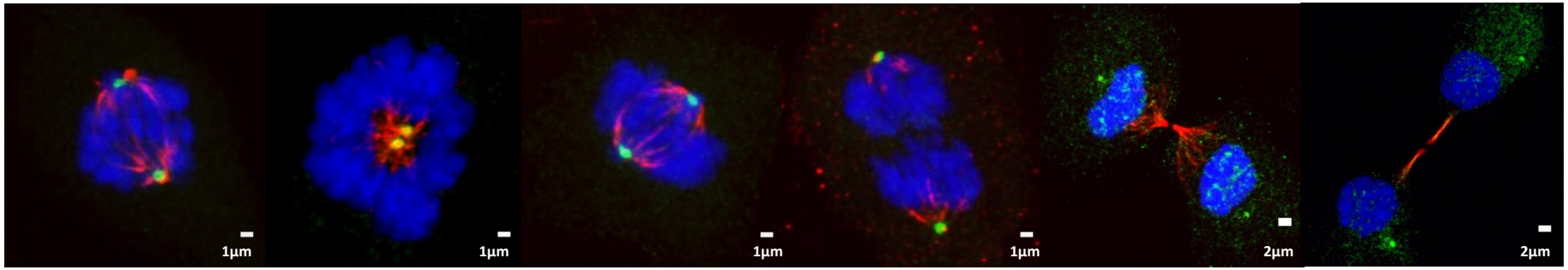
Katrien Stouffs[a,b,*], Stéphanie Moortgat[c,1], Tim Vanderhasselt[d], Laura Vandervore[a,b], Alice Dica[e], Mikaël Mathot[f], Kathelijn Keymolen[a], Sara Seneca[a,b], Alexander Gheldof[a], Linda De Meirleir[g,h], Anna C. Jansen[g,h]

RTTN – expression in centrosomes



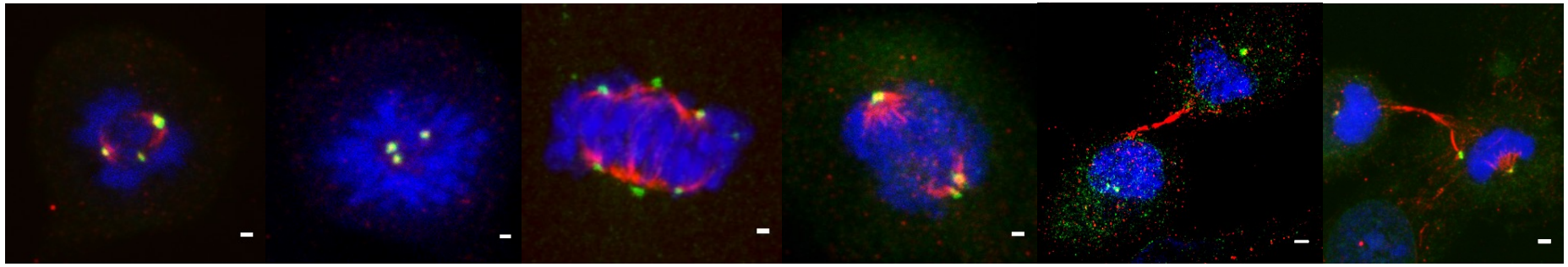
RTTN – abnormal centrosome amplification in patient fibroblasts

Wildtype



Prophase Prometaphase Metaphase Anaphase Telophase Cytokinesis

RTTN patients



Prophase Prometaphase Metaphase Anaphase Telophase Cytokinesis

Localisation of mutated RTTN

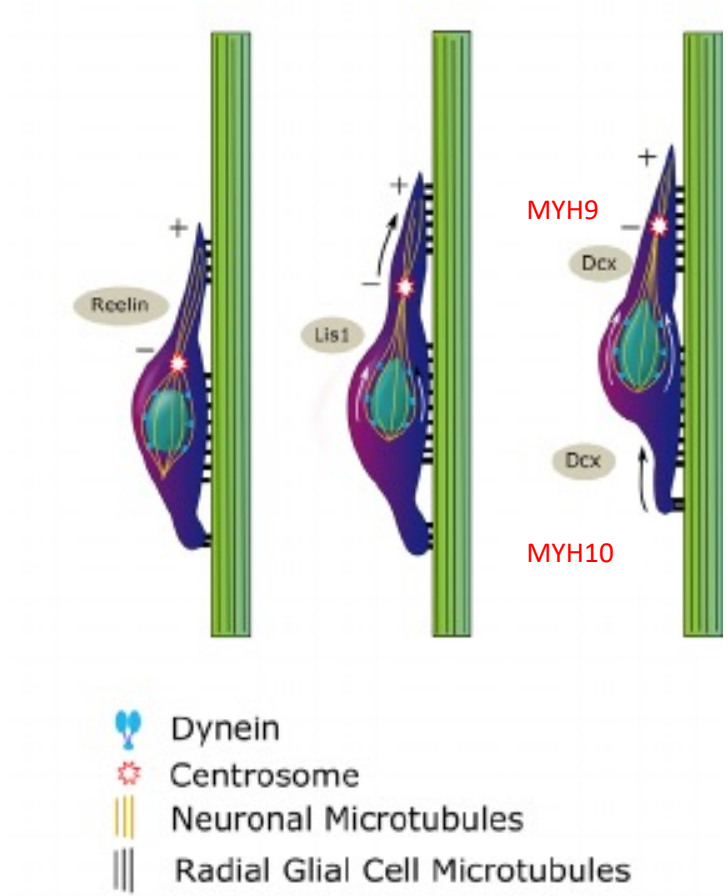
y-tubulin : centrosome
AC-tubulin: spindle
DAPI: nucleus

Vandervore et al, Brain 2019

RTTN – pivotal role in neuronal migration

RTTN interacts with MYH10 =>

involved in nucleokinesis



doi:10.1093/brain/awz045 BRAIN 2019: 142; 867–884 | 867

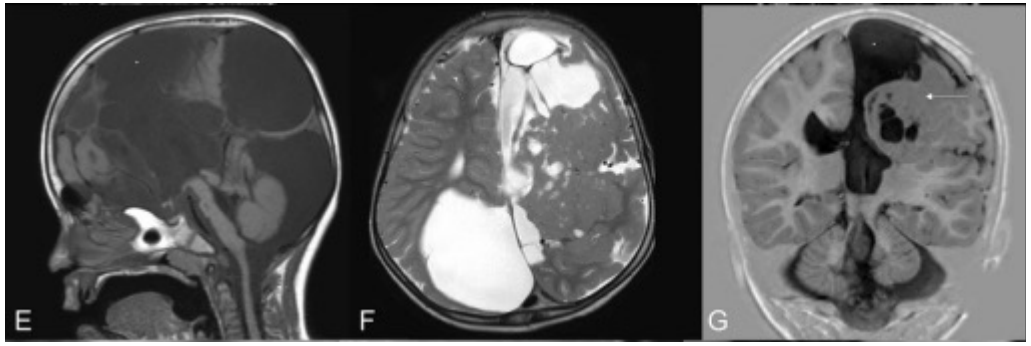
BRAIN
A JOURNAL OF NEUROLOGY

Heterogeneous clinical phenotypes and cerebral malformations reflected by rotatin cellular dynamics

Laura V. Vandervore,[1,2,3] Rachel Schot,[1] Esmee Kasteleijn,[1] Renske Oegema,[1,‡] Katrien Stouffs,[2,3] Alexander Gheldof,[2,3] Martyna M. Grochowska,[1] Marianne L.T. van der Sterre,[1] Leontine M.A. van Unen,[1] Martina Wilke,[1] Peter Elfferich,[1] Peter J. van der Spek,[4] Daphne Heijsman,[1,4] Anna Grandone,[5] Jeroen A.A. Demmers,[6] Dick H.W. Dekkers,[6] Johan A. Slotman,[7] Gert-Jan Kremers,[7] Gerben J. Schaaf,[1,8] Roy G. Masius,[1] Anton J. van Essen,[9,*] Patrick Rump,[9] Arie van Haeringen,[10] Els Peeters,[11] Umut Altunoglu,[12] Tugba Kalayci,[12] Raymond A. Poot,[13] William B. Dobyns,[14,15] Nadia Bahi-Buisson,[16] Frans W. Verheijen,[1] Anna C. Jansen[2,3,17] and Grazia M.S. Mancini[1]

6. NEXT STEPS

FUNCTIONAL STUDIES



18-year-old male

Fetal US at 21WG: interhemispheric cysts, agenesis of the corpus callosum, vermis hypoplasia

Five siblings in good health. Paternal cousin with epilepsy.

Postnatal brain MRI: interhemispheric cysts type 2C, extensive subcortical heterotopia, polymicrogyric cortex, complete ACC, malrotation of the hippocampus, hypoplasia of the brainstem and cerebellum

Age 7 months: cysto-peritoneal derivation

Age 20 months: a single prolonged febrile convulsion

Age 12 years: operated for strabismus

Age 18 years: macrocephalic, has retrognathia and a cleft in the left earlobe, can express himself, counts to 50 and reads simple phrases. There are no behavioral challenges. He has a dystonic quadriplegia, which is more pronounced on the left, but he can walk independently.

5. NEXT STEPS

FUNCTIONAL STUDIES

ARTICLE

Impaired catabolism of free oligosaccharides due to *MAN2C1* variants causes a neurodevelopmental disorder

Nuno Maia,[1,2,23] Sven Potelle,[3,4,23] Hamide Yildirim,[5,23] Sandrine Duvet,[6] Shyam K. Akula,[7,8,9,10,11] Celine Schulz,[6] Elsa Wiame,[3,4] Alexander Gheldof,[12,13] Katherine O'Kane,[7,8,9,10,11] Abbe Lai,[7,8,9,10,11] Karen Sermon,[13] Maïa Proisy,[14] Philippe Loget,[15] Tania Attié-Bitach,[16,17] Chloé Quelin,[18] Ana Maria Fortuna,[1,2] Ana Rita Soares,[1] Arjan P.M. de Brouwer,[19] Emile Van Schaftingen,[3,4] Marie-Cécile Nassogne,[20,21] Christopher A. Walsh,[7,8,9,10,11] Katrien Stouffs,[12,13] Paula Jorge,[1,2,24] Anna C. Jansen,[5,22,24,*] and François Foulquier[6,24,*]

Free oligosaccharides (fOSs) are soluble oligosaccharide species generated during N-glycosylation of proteins.

The catabolism of fOSs has been linked to the activity of a specific cytosolic mannosidase, MAN2C1, which cleaves α1,2-, α1,3-, and α1,6-mannose residues.

Clinical, biochemical, and molecular features of six individuals from 4 different families, including two fetuses, with bi-allelic pathogenic variants in *MAN2C1* were collected.

Complementation experiments with isogenic MAN2C1-KO HAP1 cells confirm the pathogenicity of three of the identified *MAN2C1* variants.

MAN2C1 variants lead to accumulation and delay in the processing of fOSs in proband-derived cells

Maia et al Am J Hum Genet. 2022 Feb 3;109(2):345-360

THANK YOU