The project is supported by

Wilhelmina Children's Hospital

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EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Neuro-MIG

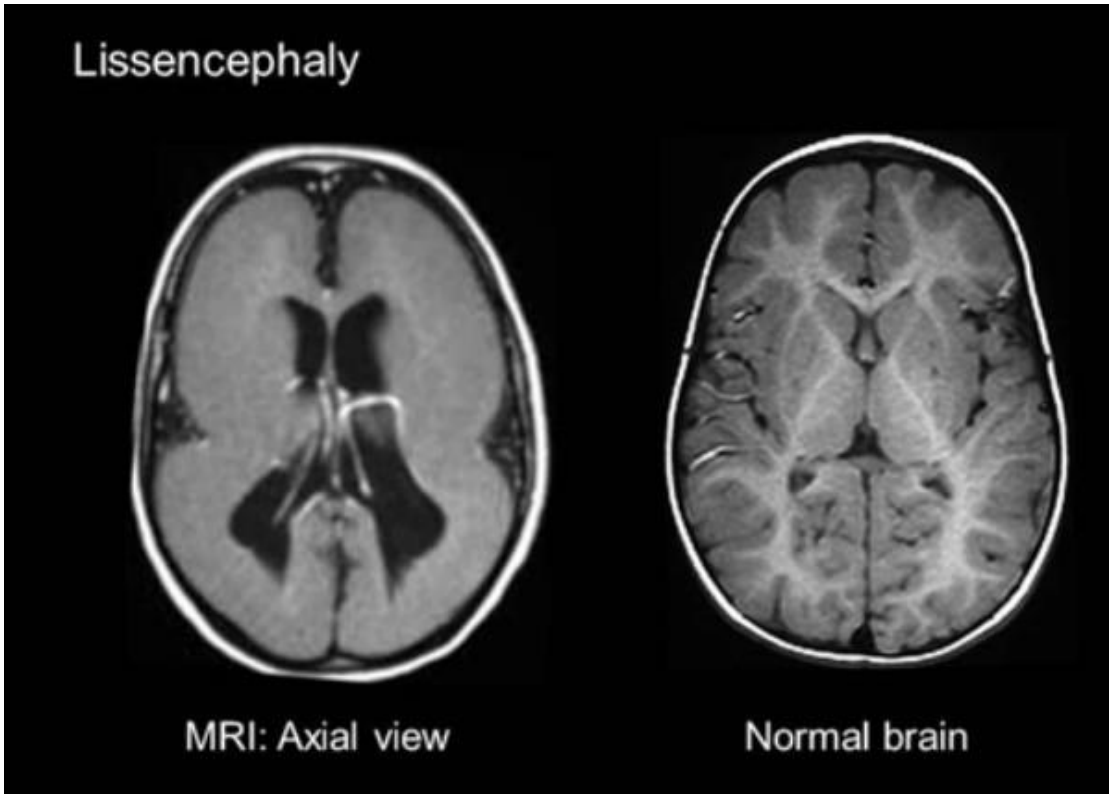
Diagnostic approach to malformations of cortical development

Renske Oegema, MD, PhD
clinical geneticist UMC Utrecht WKZ, the Netherlands

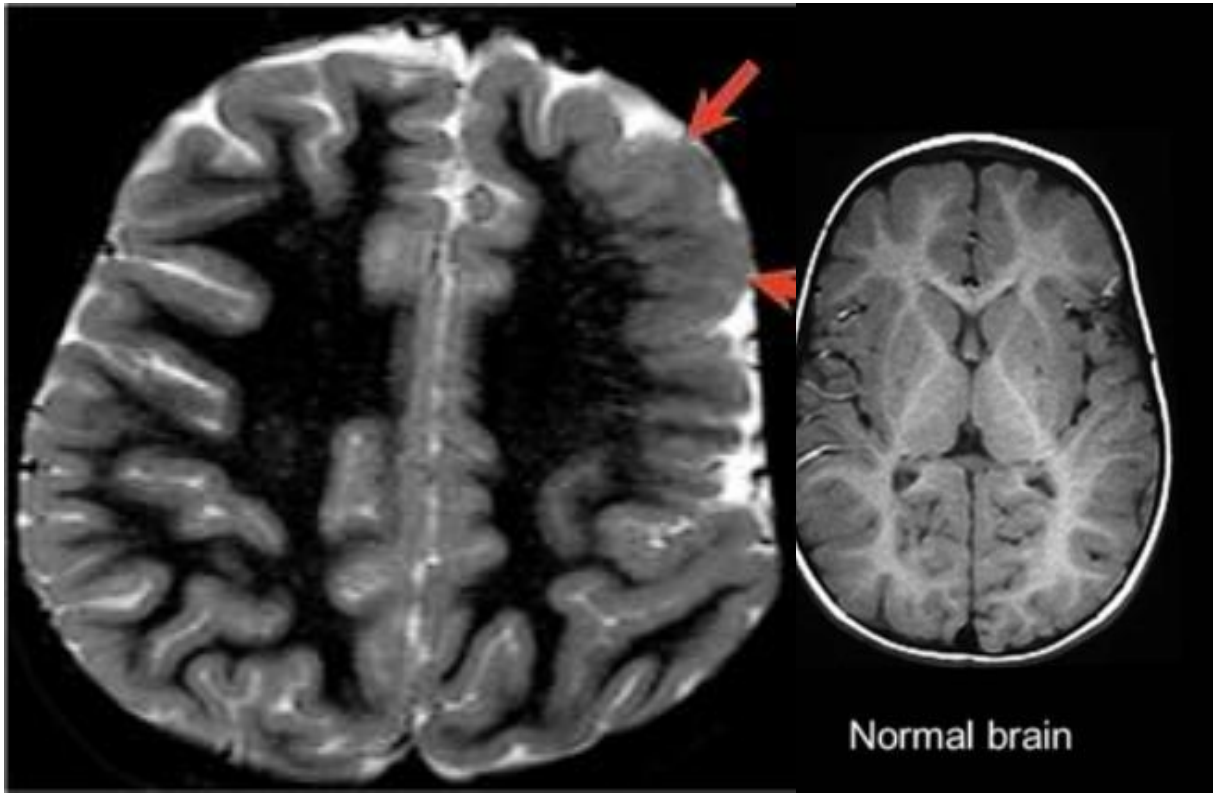
EPNS satellite 2019

Overview

- Introduction to MCD
- Diagnostic approach
- Specific recommendations and syndromes



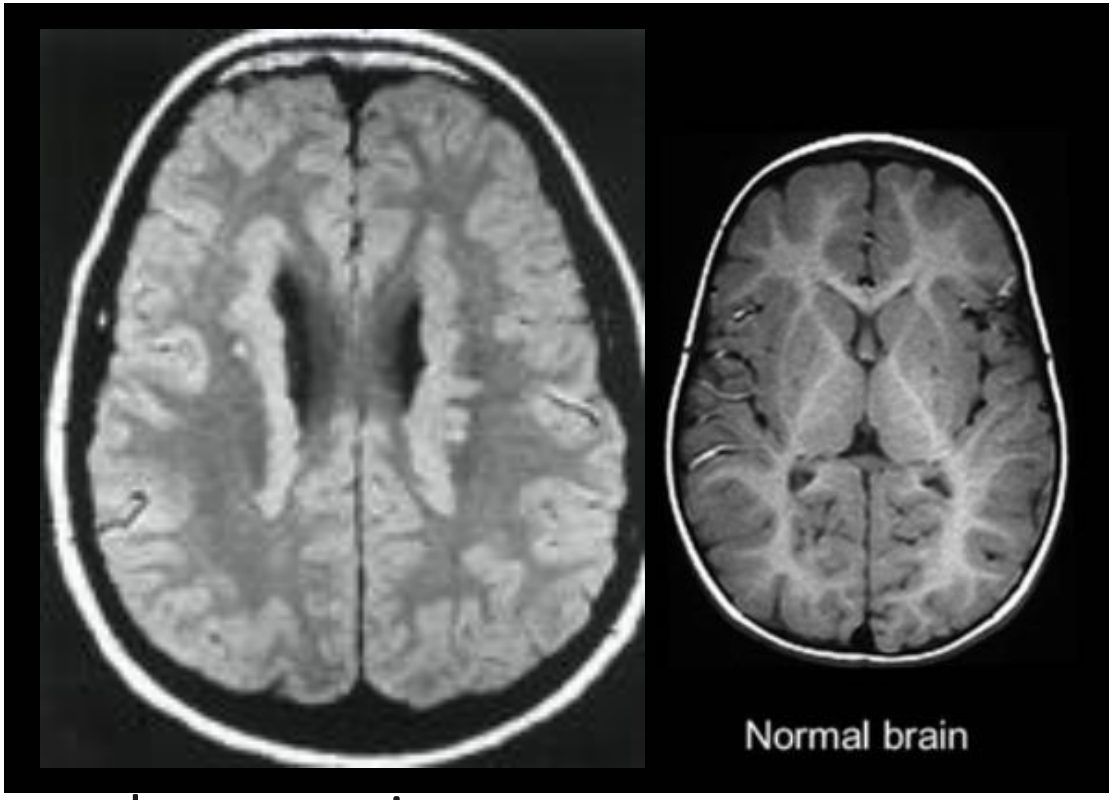
Malformations of Cortical Development



polymicrogyria

- = MCD
- Most individually rare
- As a group burden on healthcare and society

Malformations of Cortical Development



heterotopia

- = MCD
- Most individually rare
- As a group burden on healthcare and society

doi:10.1093/brain/aws019 Brain 2012: Page 1 of 22 | 1

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

A developmental and genetic classification for malformations of cortical development: update 2012

A. James Barkovich,[1] Renzo Guerrini,[2,3] Ruben I. Kuzniecky,[4] Graeme D. Jackson[5,6] and William B. Dobyns[7,8]

1. Abnormal neuro-glial proliferation or apoptosis

a. Microcephalies

b. Megalencephalies

2. Abnormal neuronal migration

a. Lissencephalies / Band heterotopia

b. Cobblestone complex

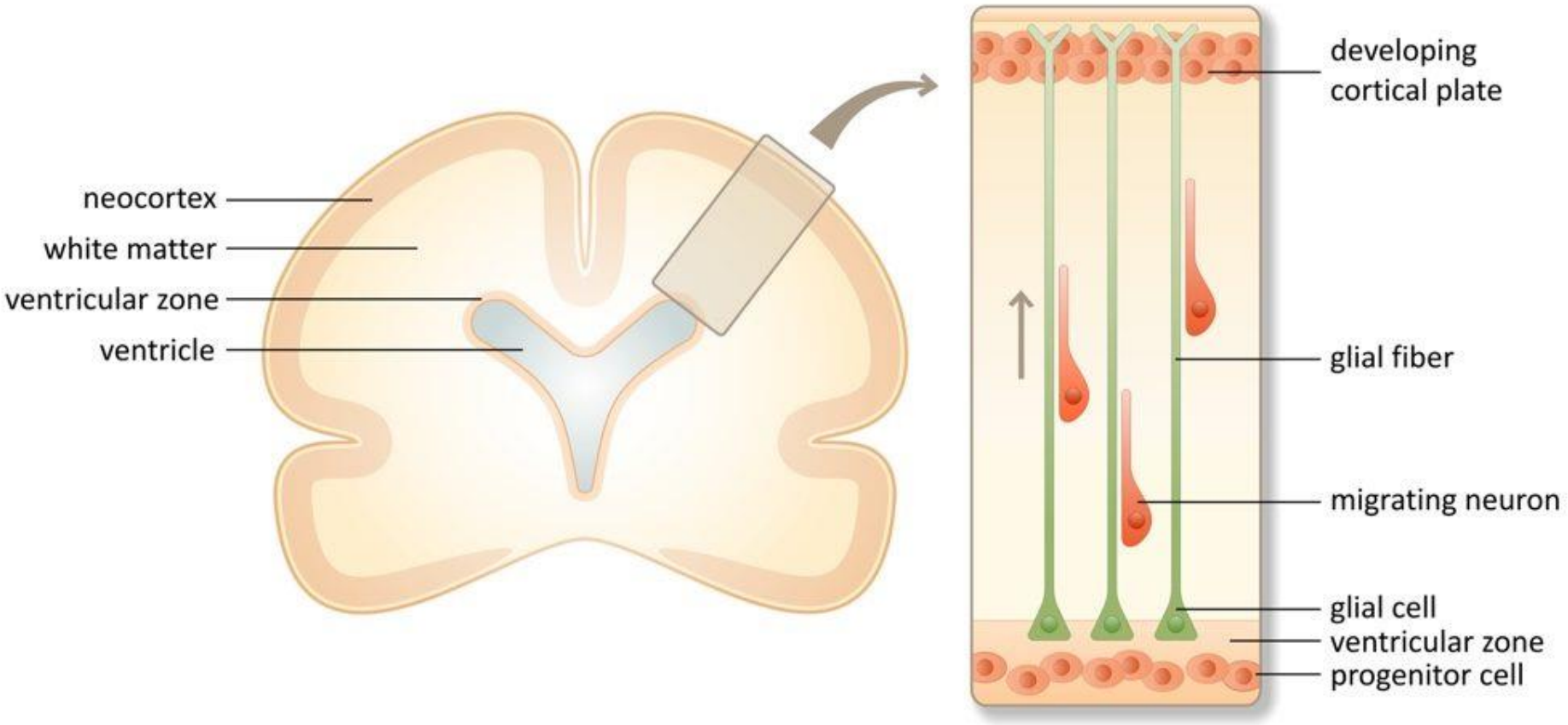
c. Nodular heterotopia

3. Abnormal cortical organization

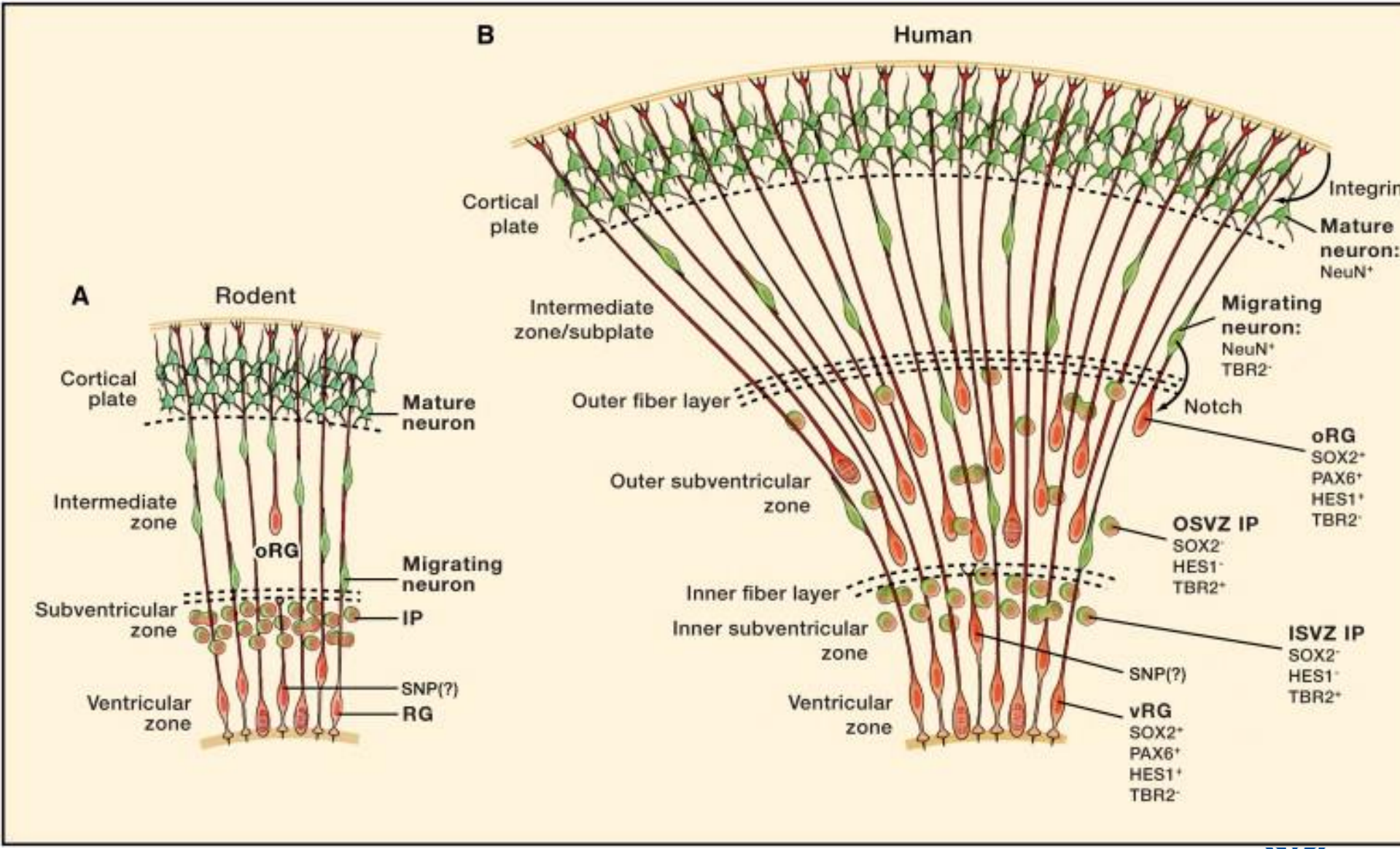
a. Polymicrogyria

4. Not otherwise specified

Defect of neuronal proliferation migration proliferation



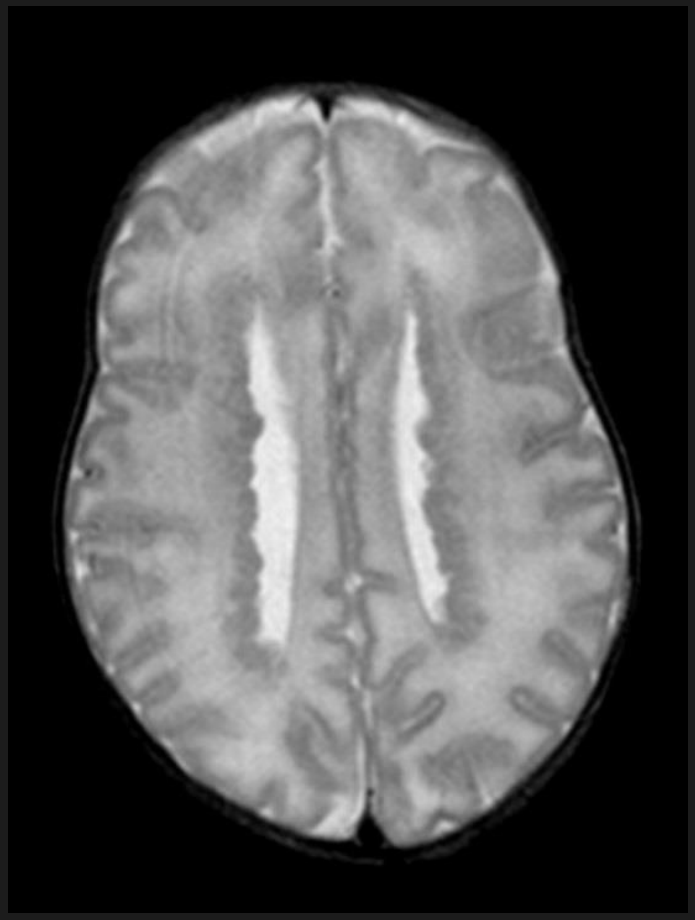
www.virology.ws



Lui et al Cell 2011

Diagnosis?

G. Mancini



Periventricular nodular heterotopia

Female

Normal cognition

No seizures

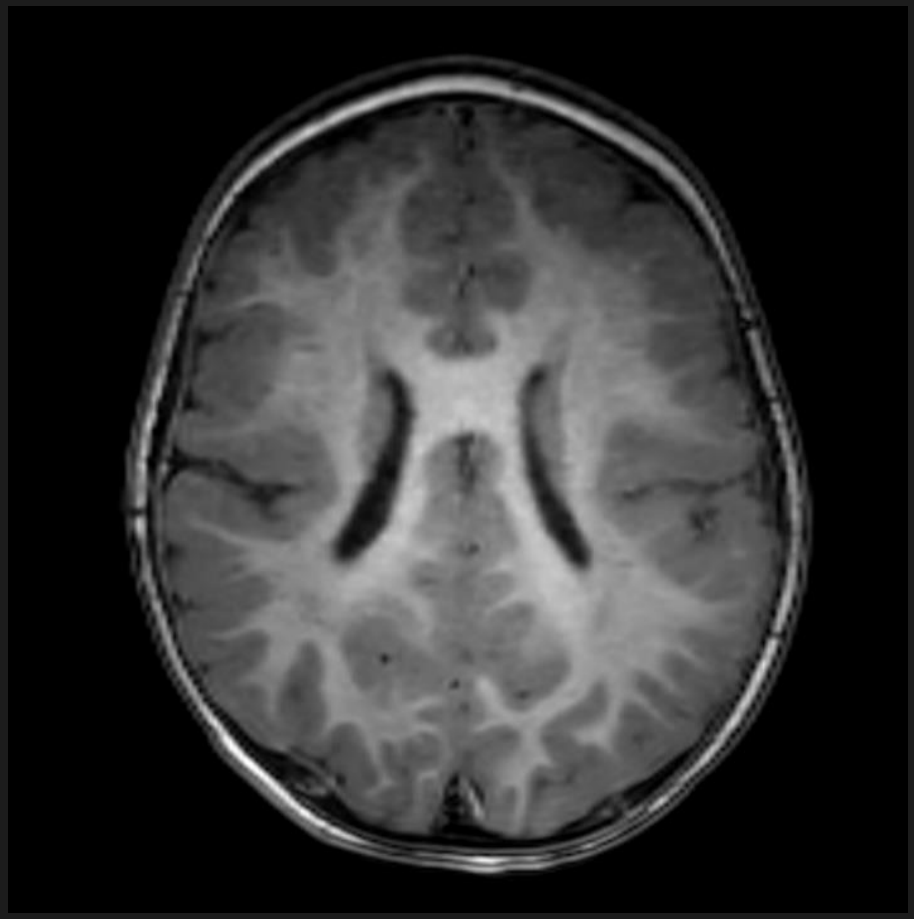
Congenital heart disease of outflow tract

X-linked PVNH: *FLNA* mutation

Diagnosis?

- 22m- old boy
- Motor delay
- Spastic paraplegia

- Polymicrogyria



Polymicrogyria - etiology

Chromosomal

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

Non-genetic

- Vascular, twinning
- Infectious

Monogenic

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

[Guerrini and Dobyns, Lancet Neurol 2014]

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 & Dobyns 2014

Why diagnose?

To

- Inform the patient
- Target patient management
- Predict outcome
- Counsel risk to family members
- Offer reproductive choices

How to diagnose?

- MCD expertise
  - Neuroradiologist
  - (pediatric) Neurologist
  - Clinical geneticist
  - Molecular geneticist + lab
  - Opthalmologist
  - Scientist
  - Etc.

However:

- Not available in every center
- Knowledge is fragmented
- No standardized approach

Neuro-MIG

European Network

COST Action 2017-2021

- To bring together clinicians and researchers in the field of brain malformations,
- to create an interdisciplinary network advancing the understanding of cortical malformations pathophysiology,
- and to translate this knowledge to improve the diagnostic and clinical management of the patients.

- **www.neuro-mig.org**

Working groups 1-5

WG1: Integration, harmonisation and standardisation of clinical phenotyping and medical management

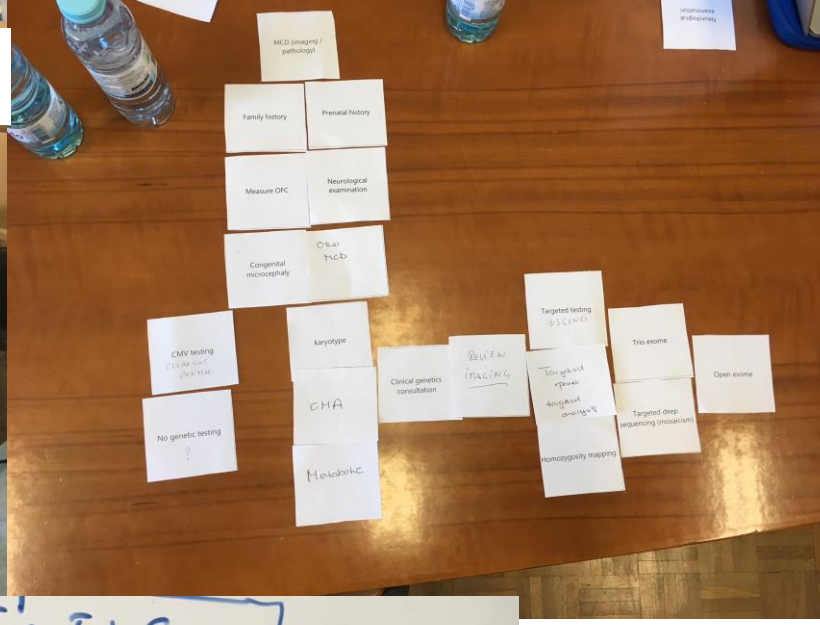
WG3: Molecular genetics and functional genomics

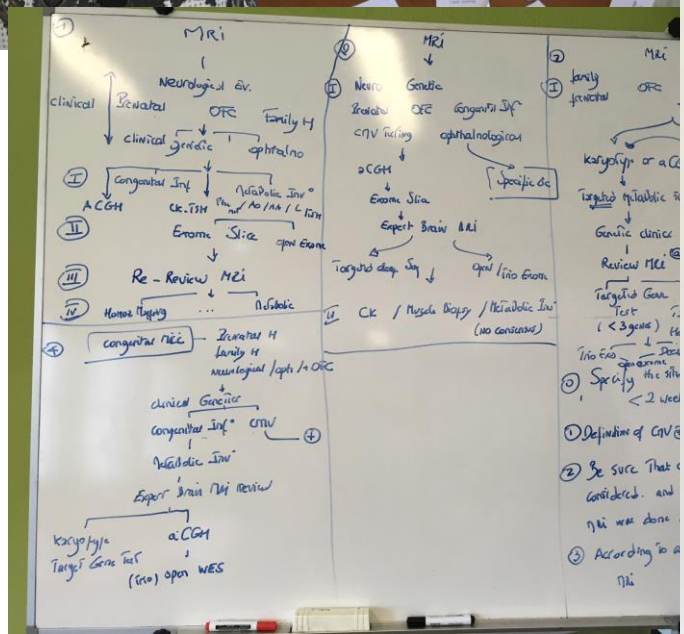
Paper:

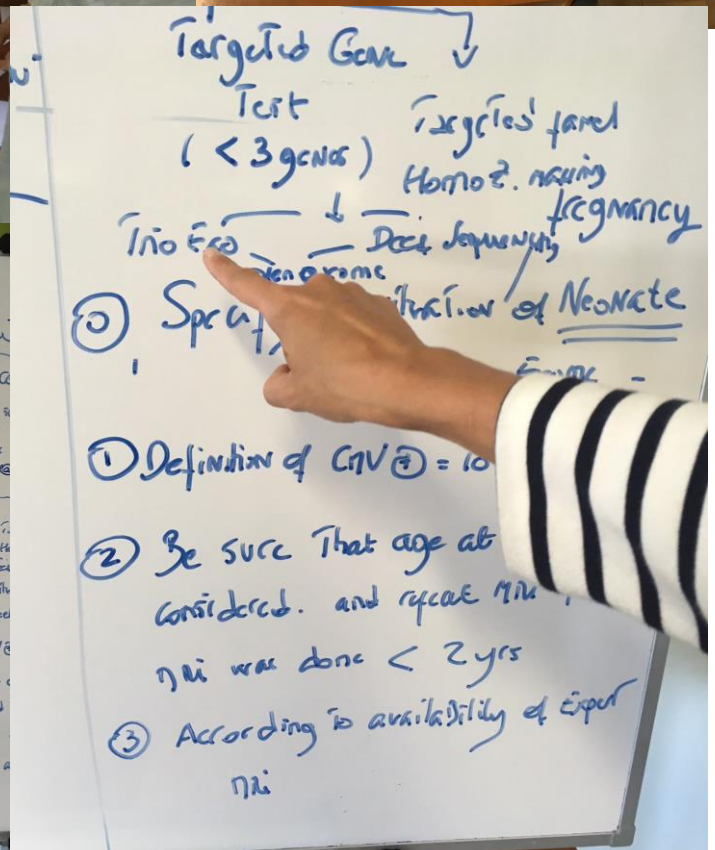
Malformations of cortical development, international consensus recommendations on diagnostic workup

Renske Oegema, Nataliya Di Donato *et al. (submitted)*

Neuro-MIG meeting Lisbon sept 2018

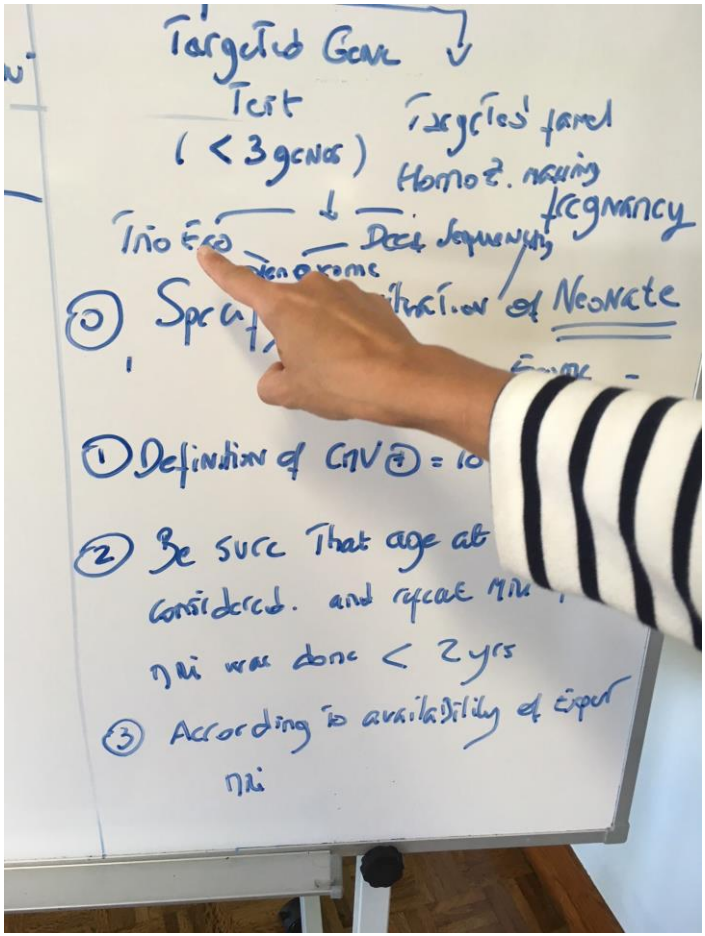




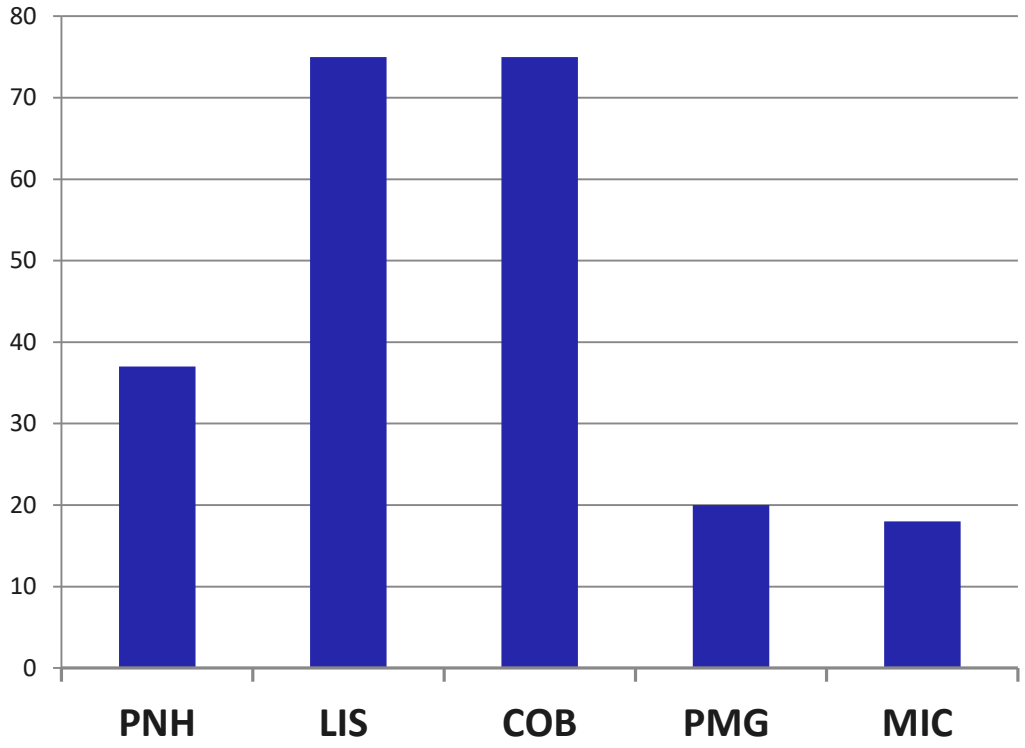


Methods

- Literature review, expert input
  - Diagnostic yield
  - MCD gene lists
- Group discussions
- Feedback from all COST members



Diagnostic yield



Microarrays:

LIS: 9% (del 17p13.3)

PNH: 36%

PMG: 6-9%

MIC: 7%

Targeted gene testing:

SBH: 79% (LIS1/ DCX)

PNH: 9-100% (FLNA)

MIC: 10-40% (ASPM)

Regensburg MCD cohort:

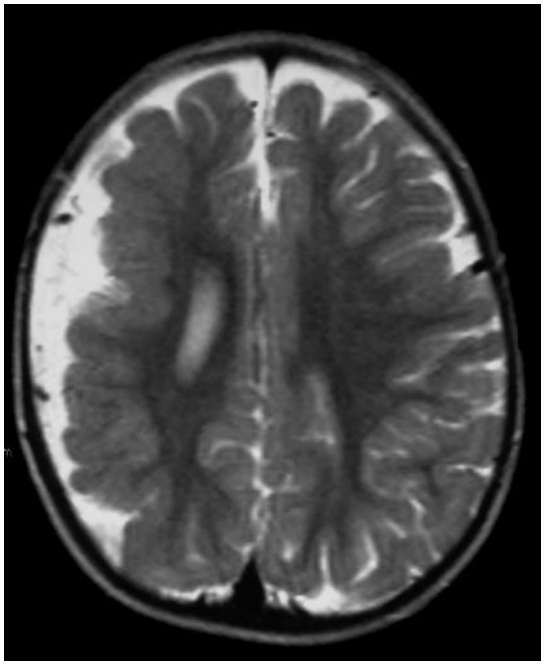
Yield w/o MRI: 18%

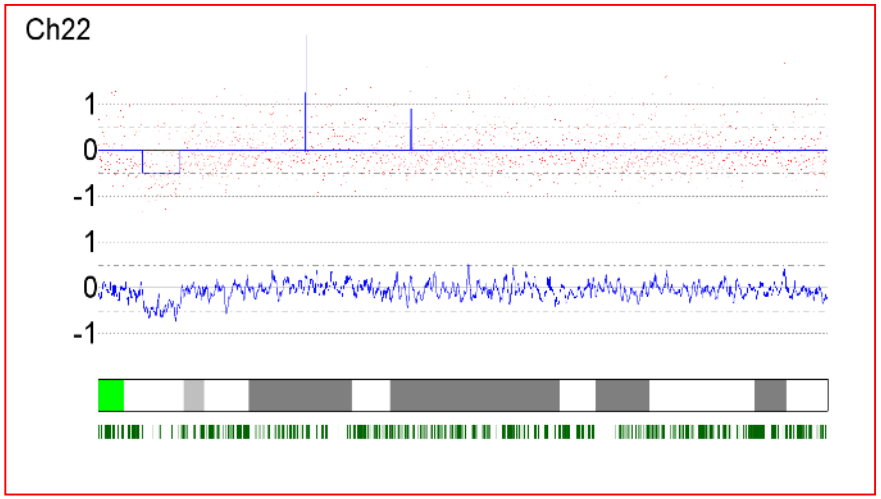
Yield w/ MRI: 37%

Average 1.5 gene tested

22q11.2 microdeletion

Grazia Mancini



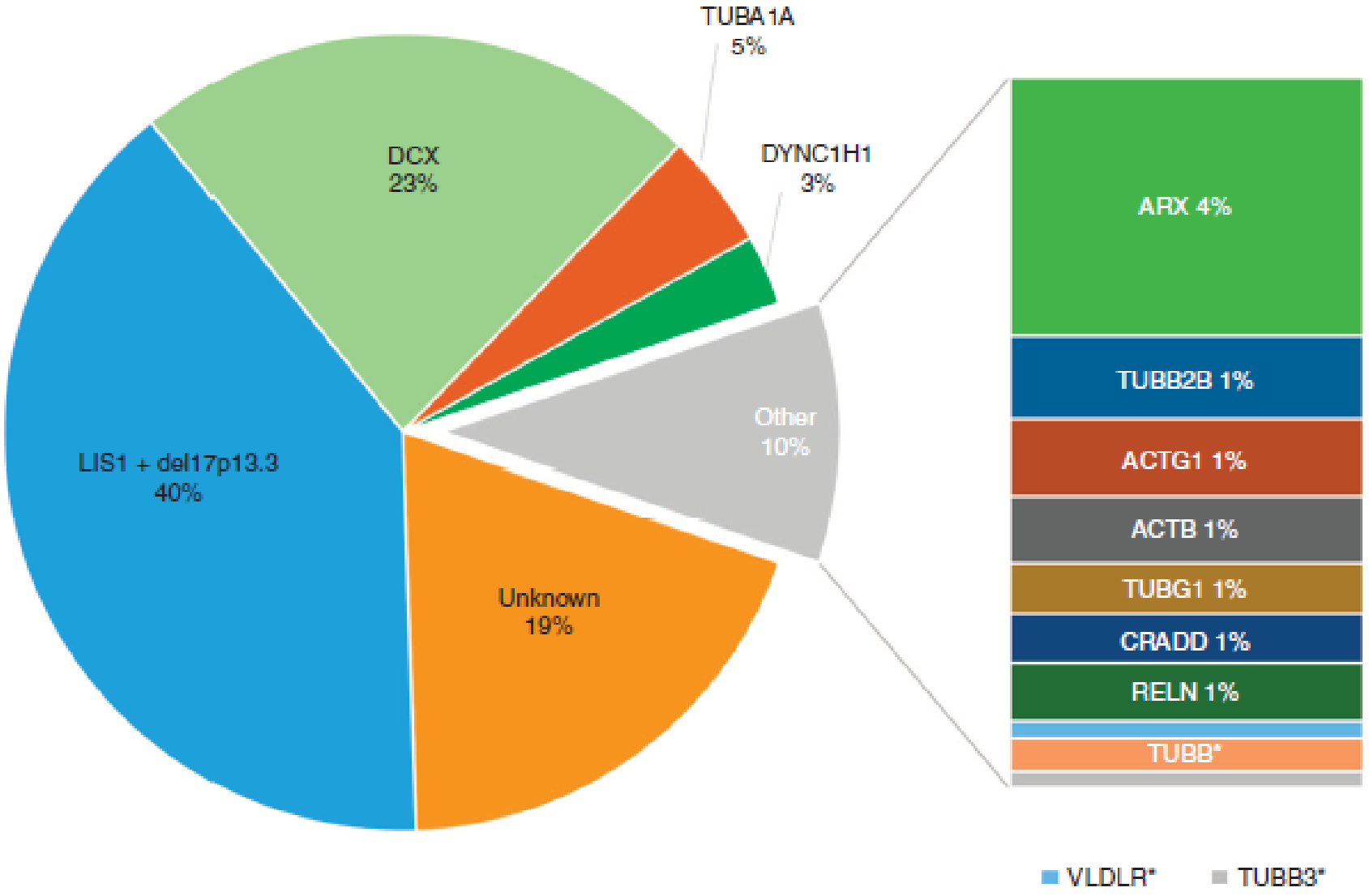


Hemiparesis, mild cognitive delay

Unilateral polymicrogyria

Analysis of 17 genes detects mutations in 81% of 811 patients with lissencephaly

Nataliya Di Donato, MD[1], Andrew E. Timms, PhD[2], Kimberly A. Aldinger, PhD[3], Ghayda M. Mirzaa, MD[3,4], James T. Bennett, MD, PhD[2,4], Sarah Collins[3], Carissa Olds[3]



NGS

- No large gene panel studies published
- Yield 15-20% in diagnostic labs
  - Clinical info often lacking, not all MCD?

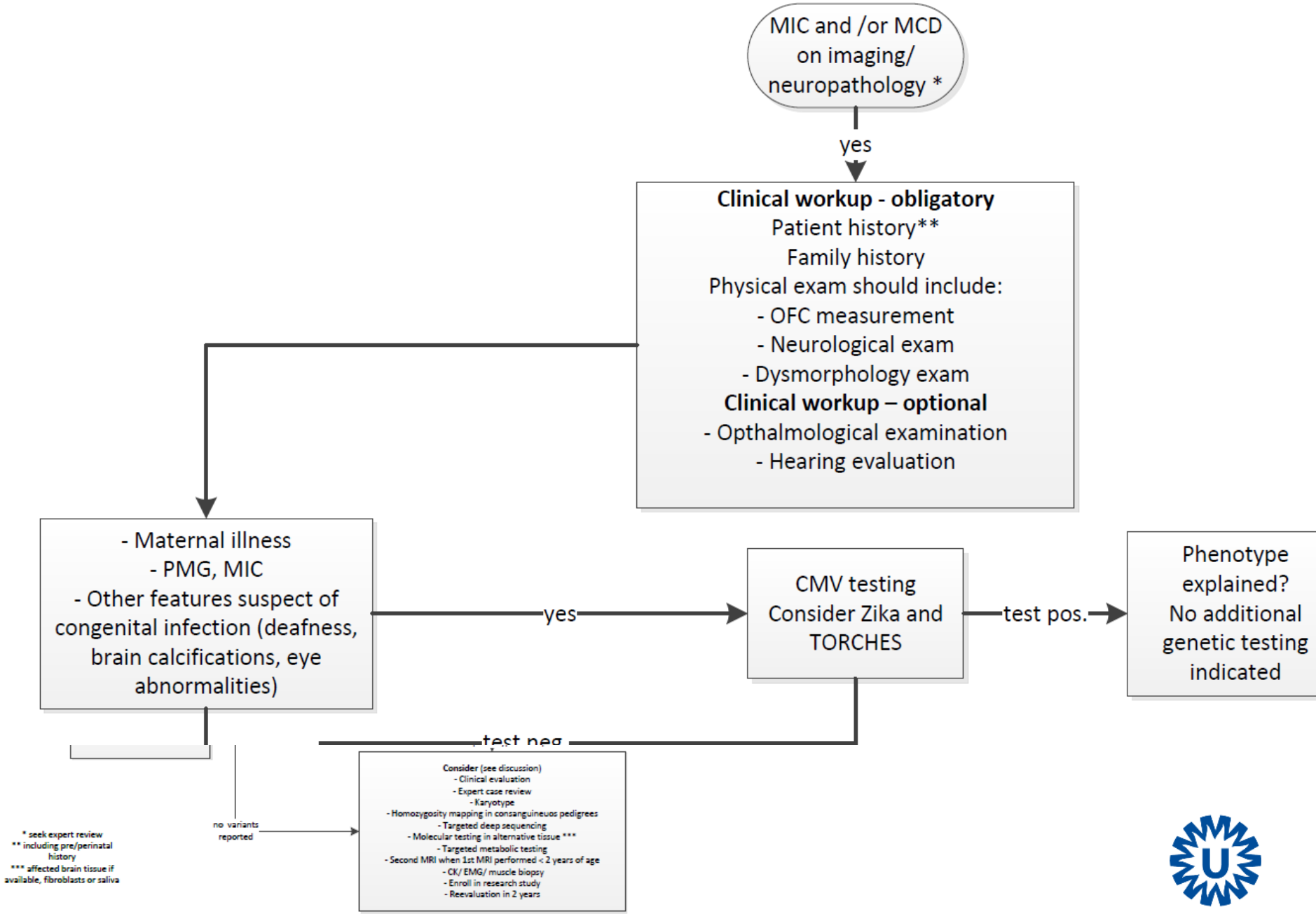
Array + WES

1 study 54 MCD patients [Wiszniewski 2018]:

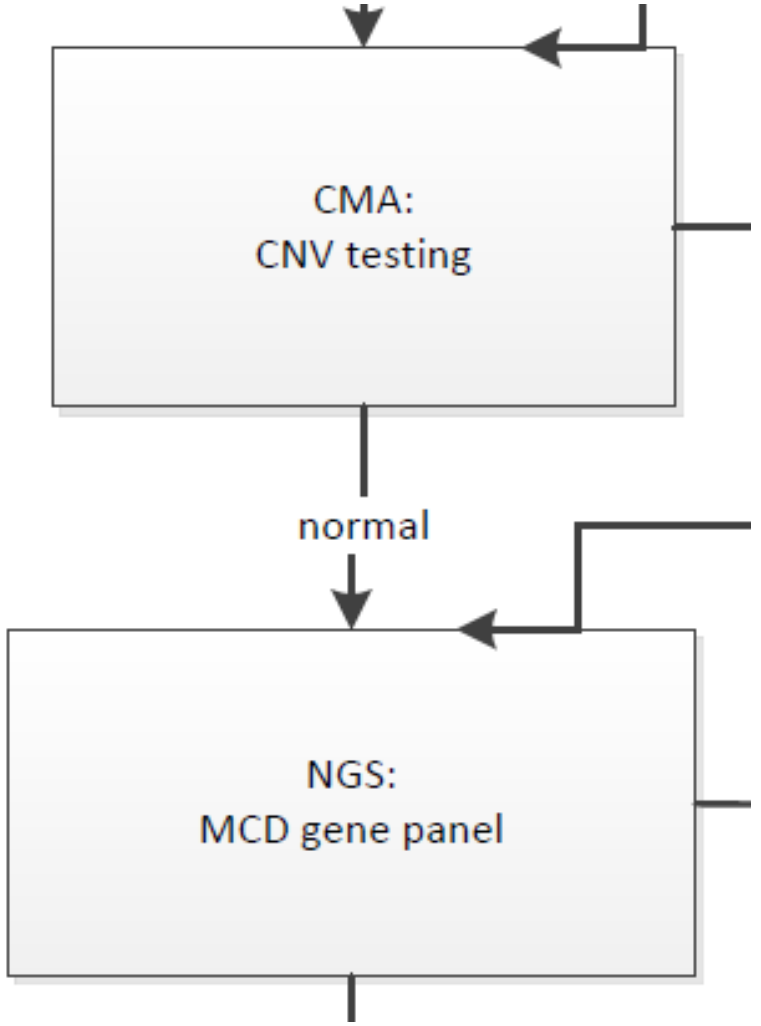
definitive (9/16) or presumptive (7/16) molecular diagnosis in **16/54 (30%)**

Optimal diagnostic strategy

- Broad approach
  - 1 gene > several phenotypes, eg TUBA1A, WDR62
  - Low quality imaging
  - Molecular diagnosis should not rely on resources/ physician's expertise
- MCD gene list
- Diagnostic work flow


MIC and /or MCD on imaging/ neuropathology *
yes
Clinical workup - obligatory
Patient history**
Family history
Physical exam should include:
- OFC measurement
- Neurological exam
- Dysmorphology exam
Clinical workup – optional
- Opthalmological examination
- Hearing evaluation
- Maternal illness
- PMG, MIC
- Other features suspect of congenital infection (deafness, brain calcifications, eye abnormalities)
yes
CMV testing
Consider Zika and TORCHES
test pos.
Phenotype explained?
No additional genetic testing indicated
test neg
no variants reported
Consider (see discussion)
- Clinical evaluation
- Expert case review
- Karyotype
- Homozygosity mapping in consanguineuos pedigrees
- Targeted deep sequencing
- Molecular testing in alternative tissue ***
- Targeted metabolic testing
- Second MRI when 1st MRI performed < 2 years of age
- CK/ EMG/ muscle biopsy
- Enroll in research study
- Reevaluation in 2 years
* seek expert review
** including pre/perinatal history
*** affected brain tissue if available, fibroblasts or saliva

- List of > 200 MCD genes

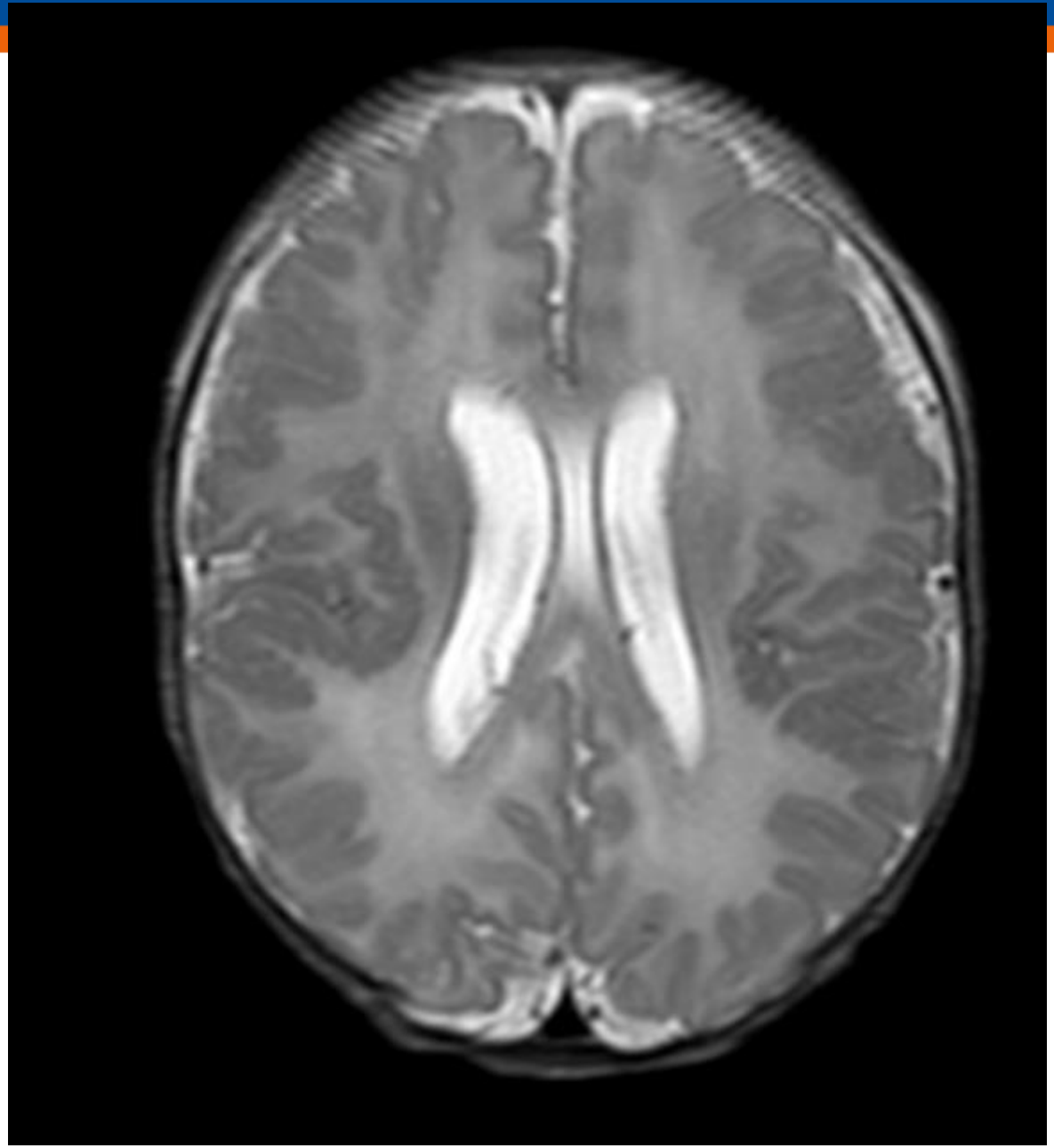


phenotype not explained

Consider (see discussion)

- Clinical evaluation
- Expert case review
- Karyotype
- Homozygosity mapping in consanguineuos pedigrees
- Targeted deep sequencing
- Molecular testing in alternative tissue ***
- Targeted metabolic testing
- Second MRI when 1st MRI performed < 2 years of age
- CK/ EMG/ muscle biopsy
- Enroll in research study
- Reevaluation in 2 years

- Diagnostic yield
  - Literature review, personal communication
- Optimal diagnostic strategy
- Special recommendations and syndromes associated with brain malformations



Macrocephaly

Capillary malformations

MRI:

Megalencephaly

PMG

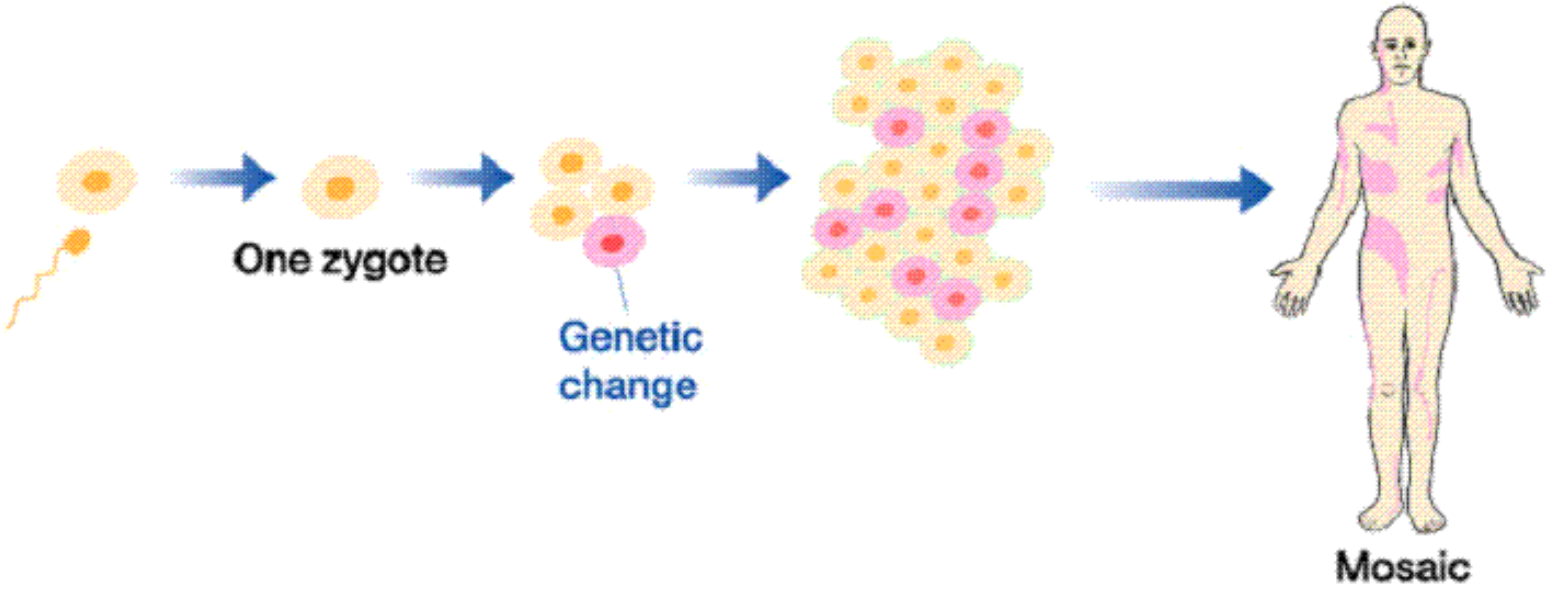
MCAP syndrome (*PIK3CA* 32% Pro104Leu)

De novo germline and postzygotic mutations in *AKT3*, *PIK3R2* and *PIK3CA* cause a spectrum of related megalencephaly syndromes

nature genetics

Jean-Baptiste Rivière[1], Ghayda M Mirzaa[2], Brian J O'Roak[3], Margaret Beddaoui[4], Diana Alcantara[5], Robert L Conway[6], Judith St-Onge[1], Jeremy A Schwartzentruber[7], Karen W Gripp[8], Sarah M Nikkel[9], Thea Worthylake[4], Christopher T Sullivan[1], Thomas R Ward[1], Hailly E Butler[1], Nancy A Kramer[10], Beate Albrecht[11], Christine M Armour[12], Linlea Armstrong[13], Oana Caluseriu[14], Cheryl Cytrynbaum[15], Beth A Drolet[16,17], A Micheil Innes[14], Julie L Lauzon[14], Angela E Lin[18], Grazia M S Mancini[19], Wendy S Meschino[20], James D Reggin[21], Anand K Saggar[22], Tally Lerman-Sagie[23], Gökhan Uyanik[24], Rosanna Weksberg[15], Birgit Zirn[25], Chandree L Beaulieu[4], Finding of Rare Disease Genes (FORGE) Canada Consortium[26], Jacek Majewski[27], Dennis E Bulman[28], Mark O'Driscoll[5], Jay Shendure[3], John M Graham Jr[10], Kym M Boycott[4,9] & William B Dobyns[1,29,30]

published online 24 June 2012;



Characterisation of mutations of the phosphoinositide-3-kinase regulatory subunit, *PIK3R2*, in perisylvian polymicrogyria: a next-generation sequencing study

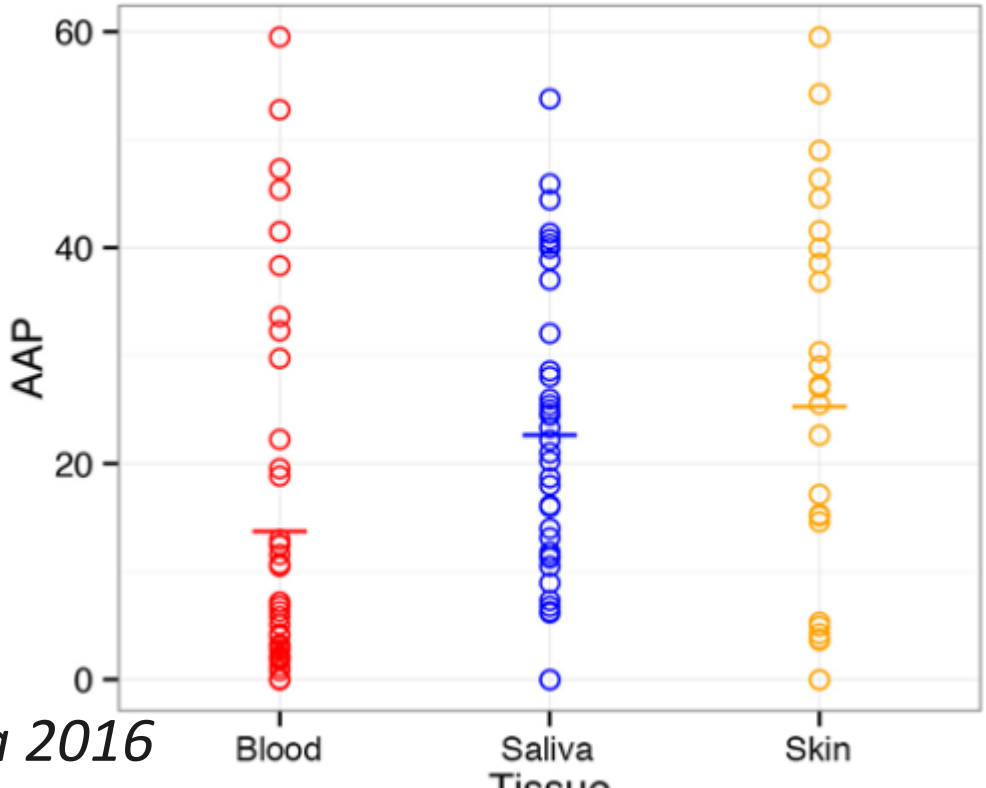
Ghayda M Mirzaa, Valerio Conti, Andrew E Timms, Christopher D Smyser, Sarah Ahmed, Melissa Carter, Sarah Barnett, Robert B Hufnagel, Amy Goldstein, Yoko Narumi-Kishimoto, Carissa Olds, Sarah Collins, Kathreen Johnston, Jean-François Deleuze, Patrick Nitschké, Kathryn Friend, Catharine Harris, Allison Goetsch, Beth Martin, Evan August Boyle, Elena Parrini, Davide Mei, Lorenzo Tattini, Anne Slavotinek, Ed Blair, Christopher Barnett, Jay Shendure, Jamel Chelly, William B Dobyns, Renzo Guerrini

- +- Macrocephaly
- +- MPPH syndrome
- Mutations in 19/126 patiënten with PMG (15%)
  - De novo germline and mosaic mutations

Detecting mosaicism

- Examine carefully
- Extract DNA from affected tissue
- Or saliva/ skin fibroblasts
- **Targeted deep sequencing** (500-5000x)
- Validate variant eg with ddPCR

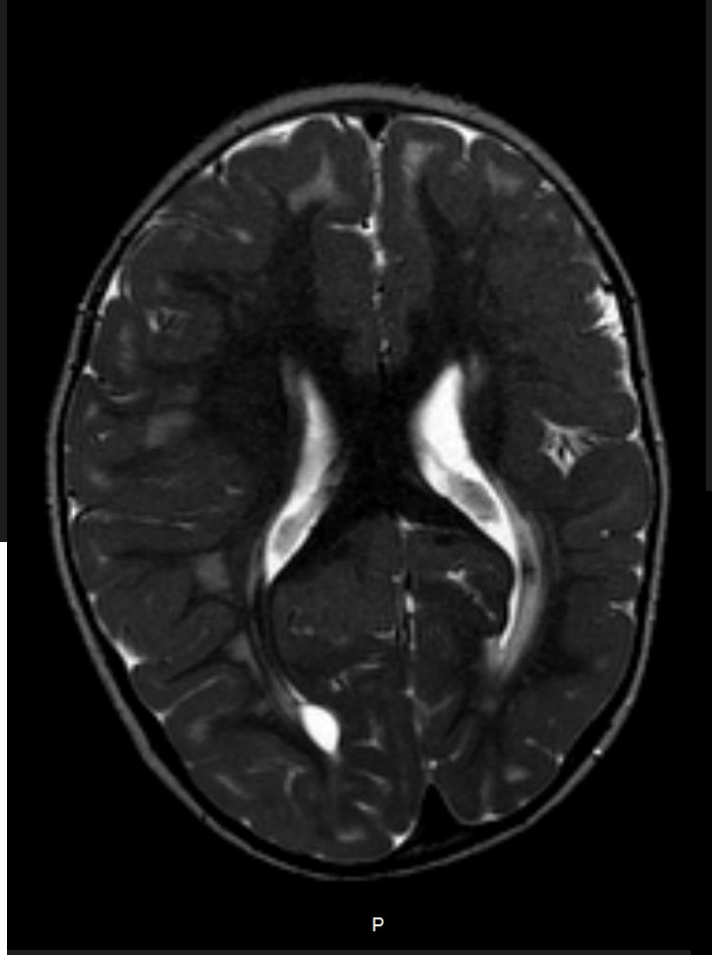
- Consider especially in MEG and FCD (and PMG)

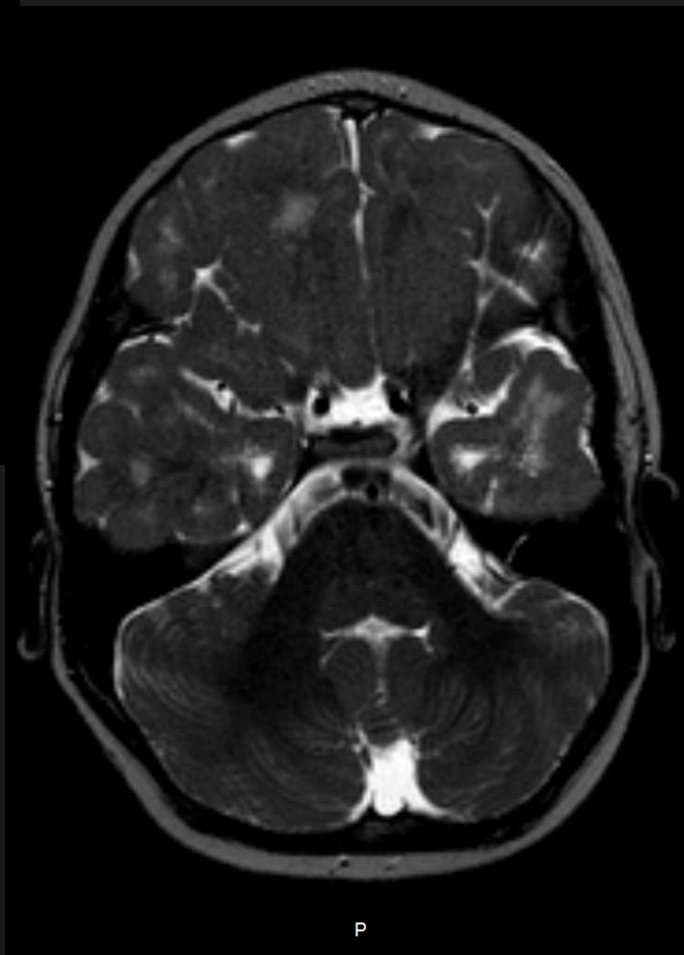


Mirzaa 2016

- 2y girl
- Focal seizures
- Hemiplegia
- OFC -2.5 SD
- Scar macula

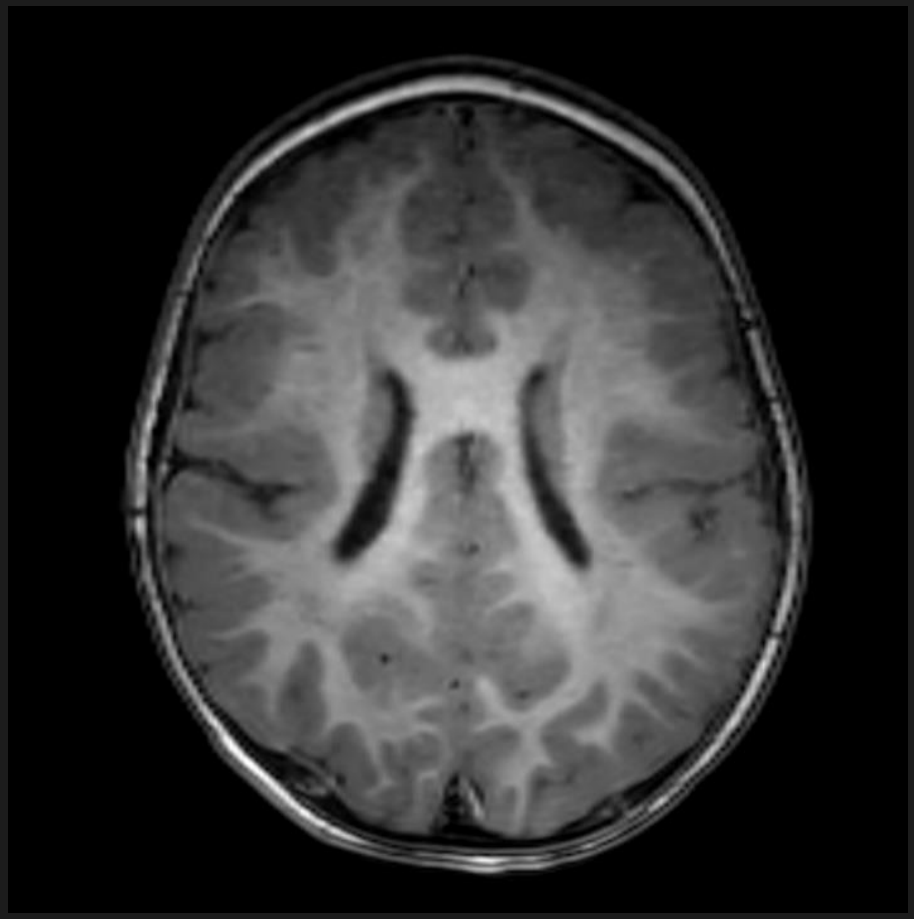
- **CMV +**





- 22m-old boy
- Motor delay
- Spastic paraplegia

- **CMV +**



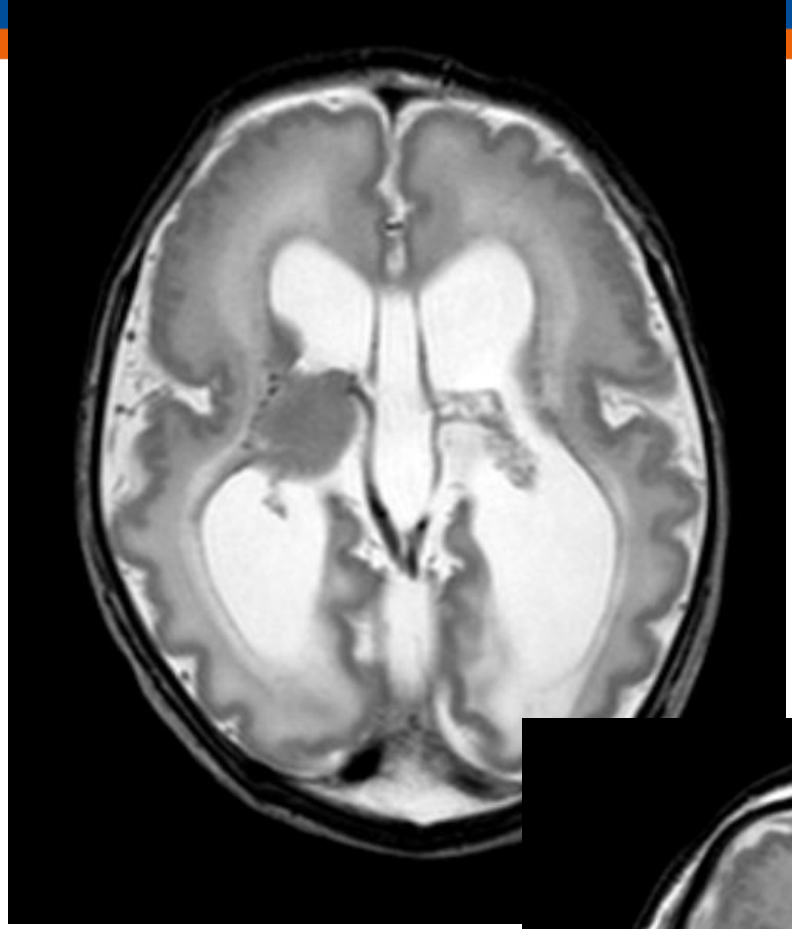
Prenatal anomalies:

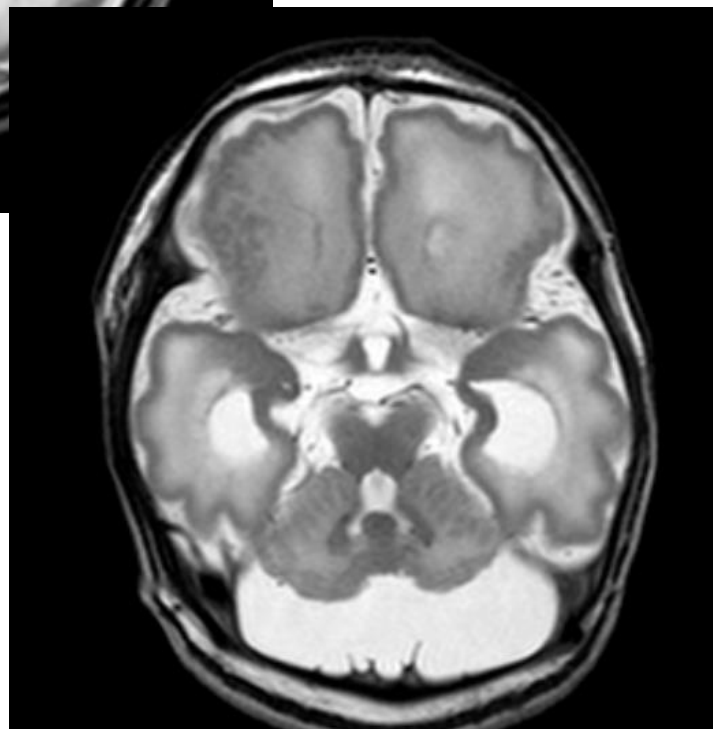
- IUGR, microcephaly
- ventriculomegaly
- lung agenesis?
- clenched fists

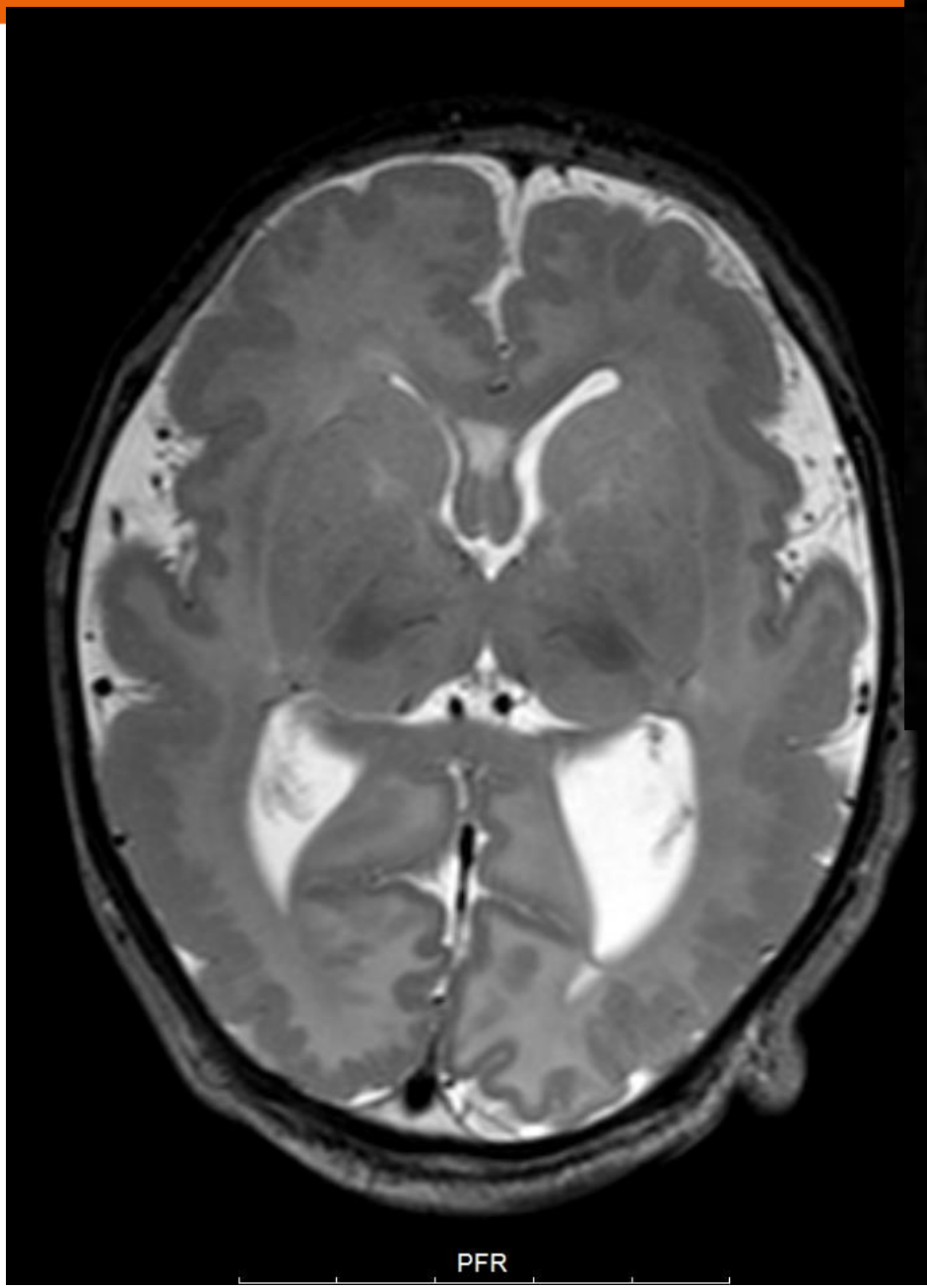
Postpartum

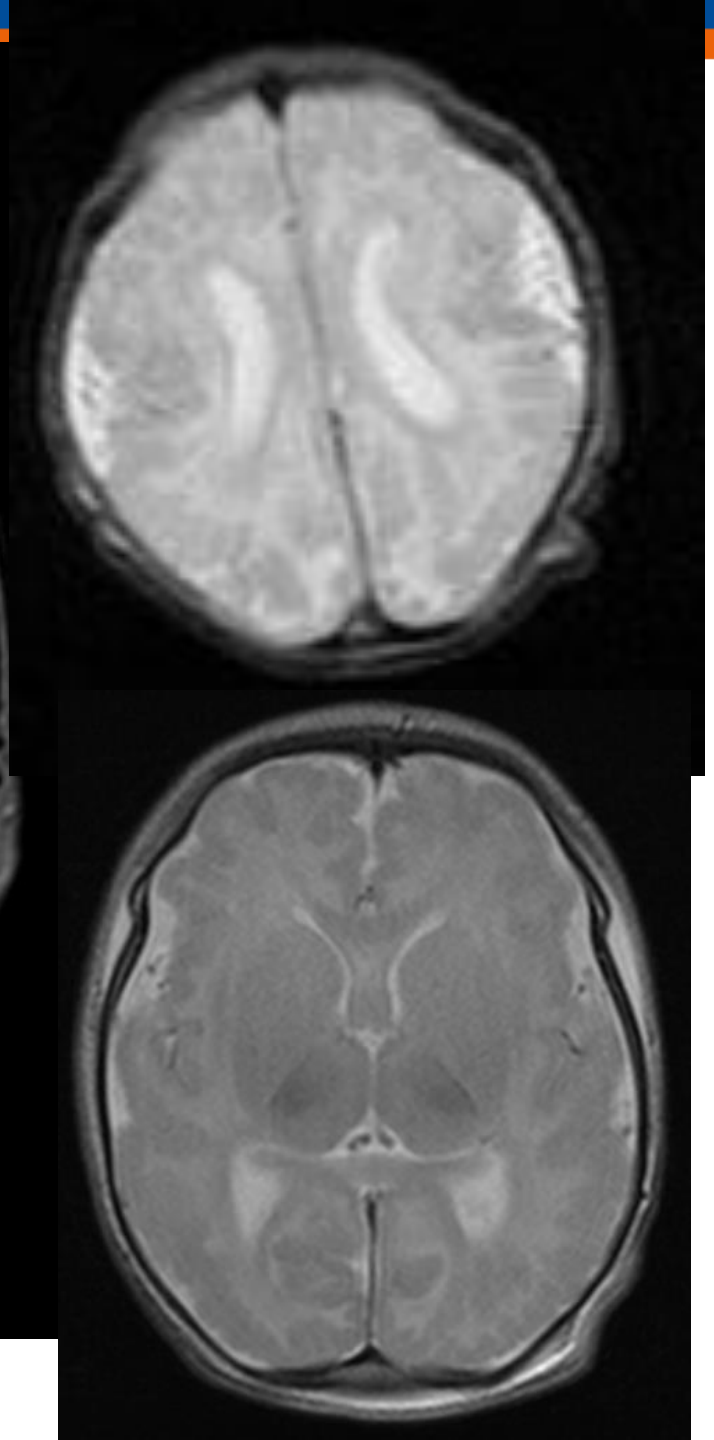
- seizures
- PMG
- oxygen dependant
- arthrogryposis
- thrombocytopenia

CMV +





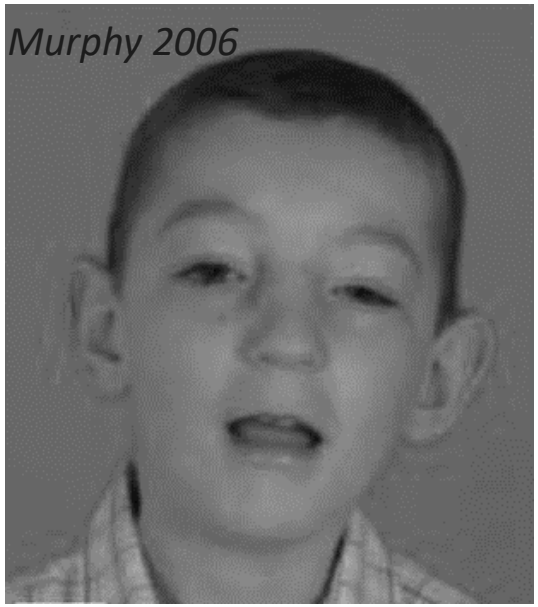




Mancini

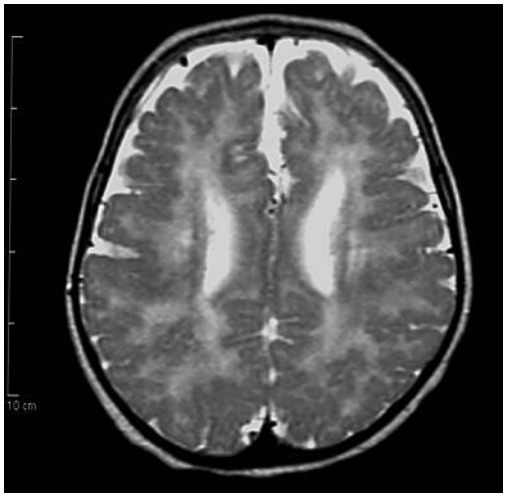
Fry

Goldberg-Shprintzen syndrome



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

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



Brooks. AJHG 2005

Take home messages MCD

- Broad spectrum of presentation and etiology
- Associated with both common and rare syndromes
- Think chromosomal, monogenic and non-genetic
- Pattern recognition vs general workflow > diagnosis

- Collaborate, share, publish!

Thank you!

The project is supported by

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EUROPEAN COOPERATION
IN SCIENCE & TECHNOLOGY

Neuro-MIG

UMC Utrecht - WKZ