Polymicrogyria

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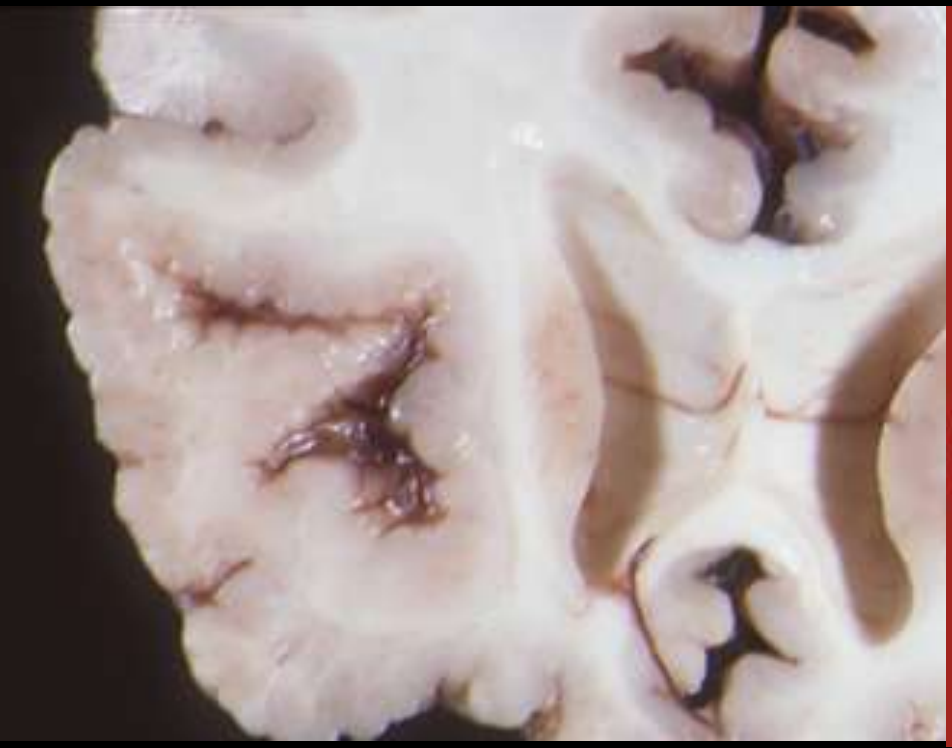
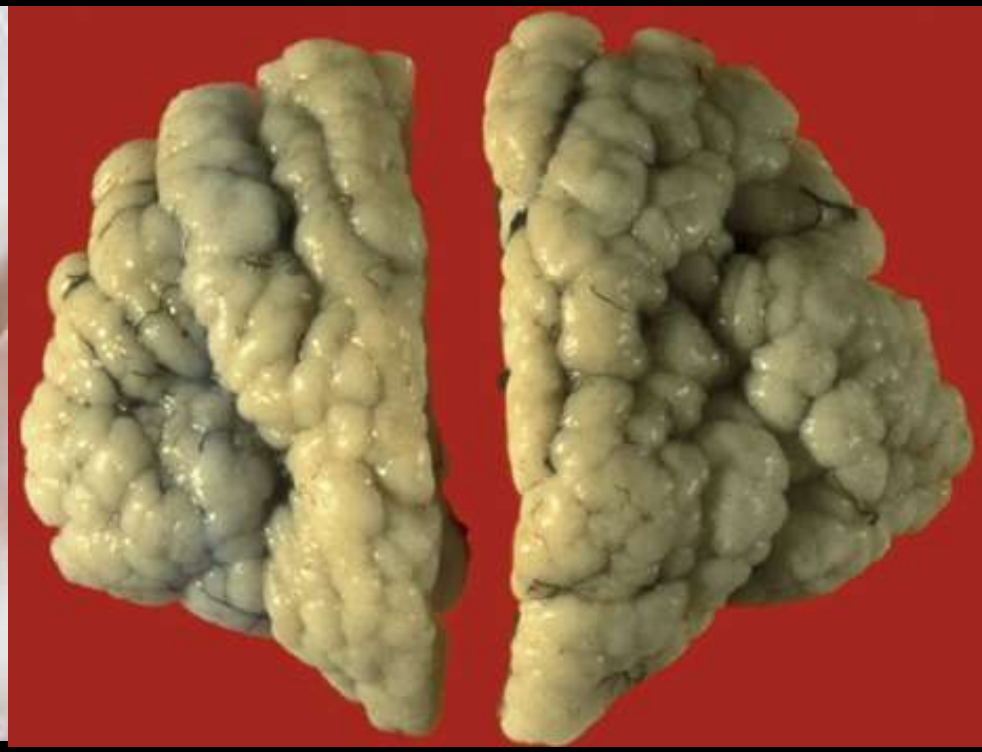
Polymicrogyria (PMG)

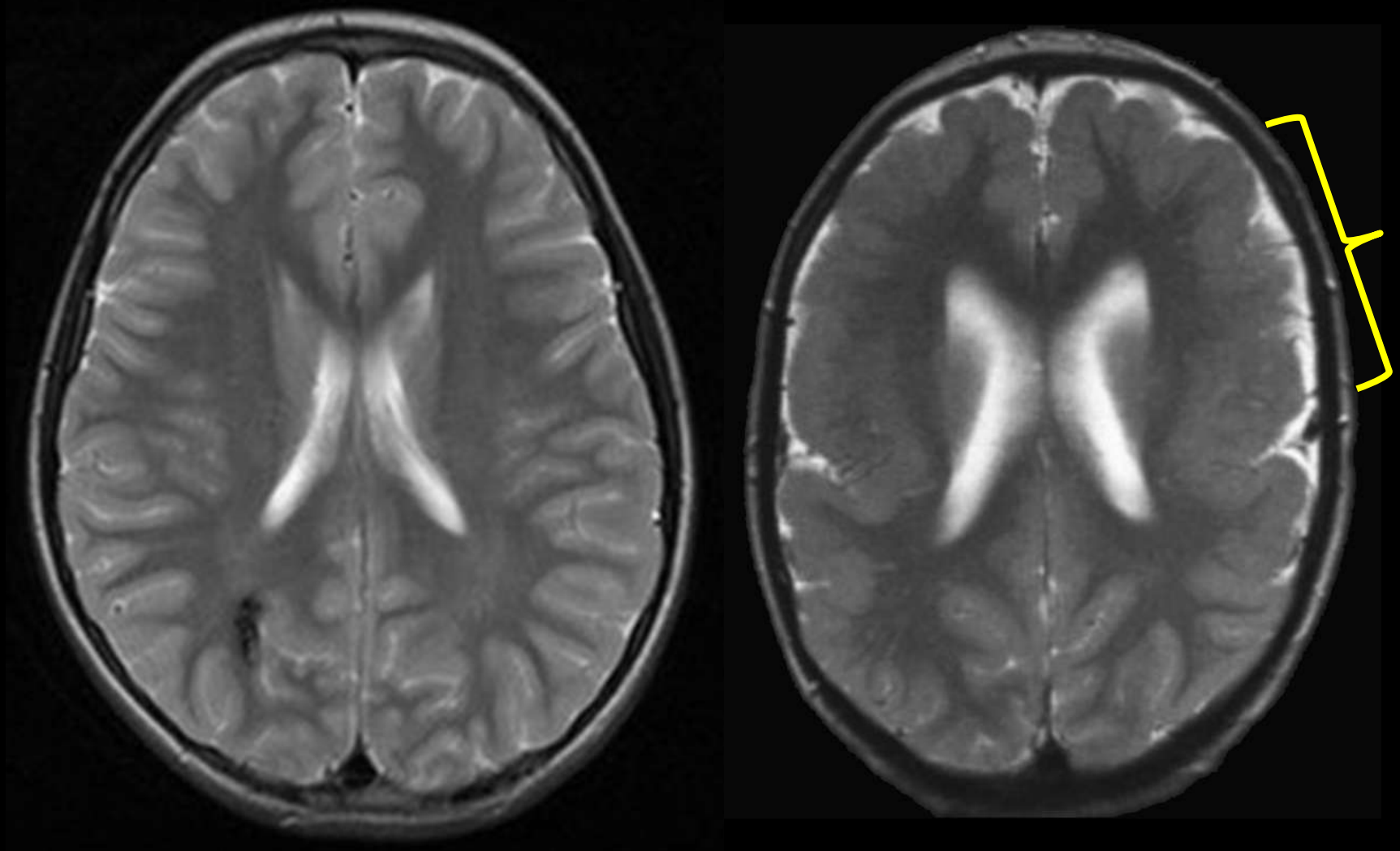
‘Many–small–folds’





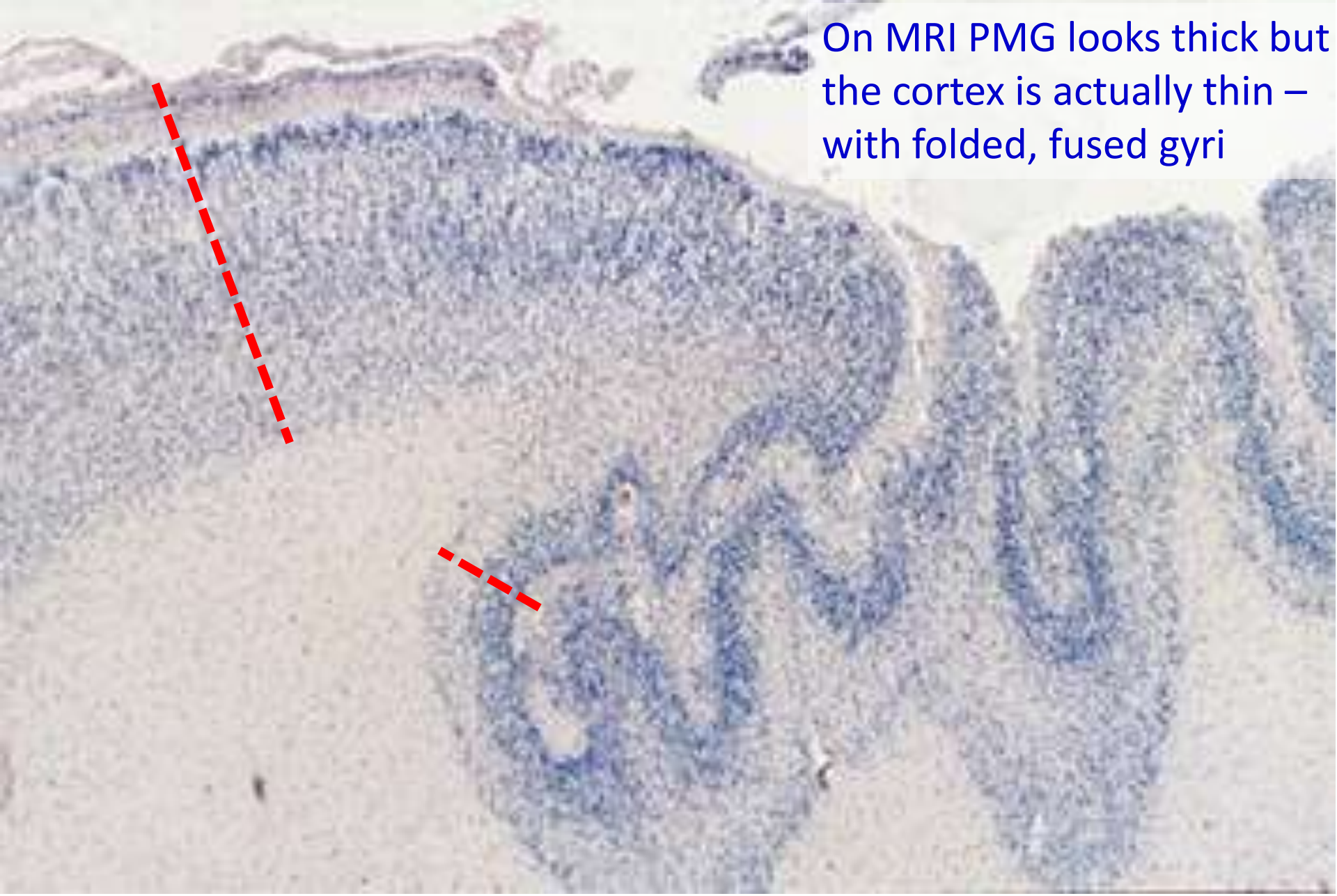
- PMG is heterogeneous – in aetiology and phenotype
- A disorder of post-migrational cortical organisation.

PMG often appears thick on MRI with blurring of the grey-white matter boundary



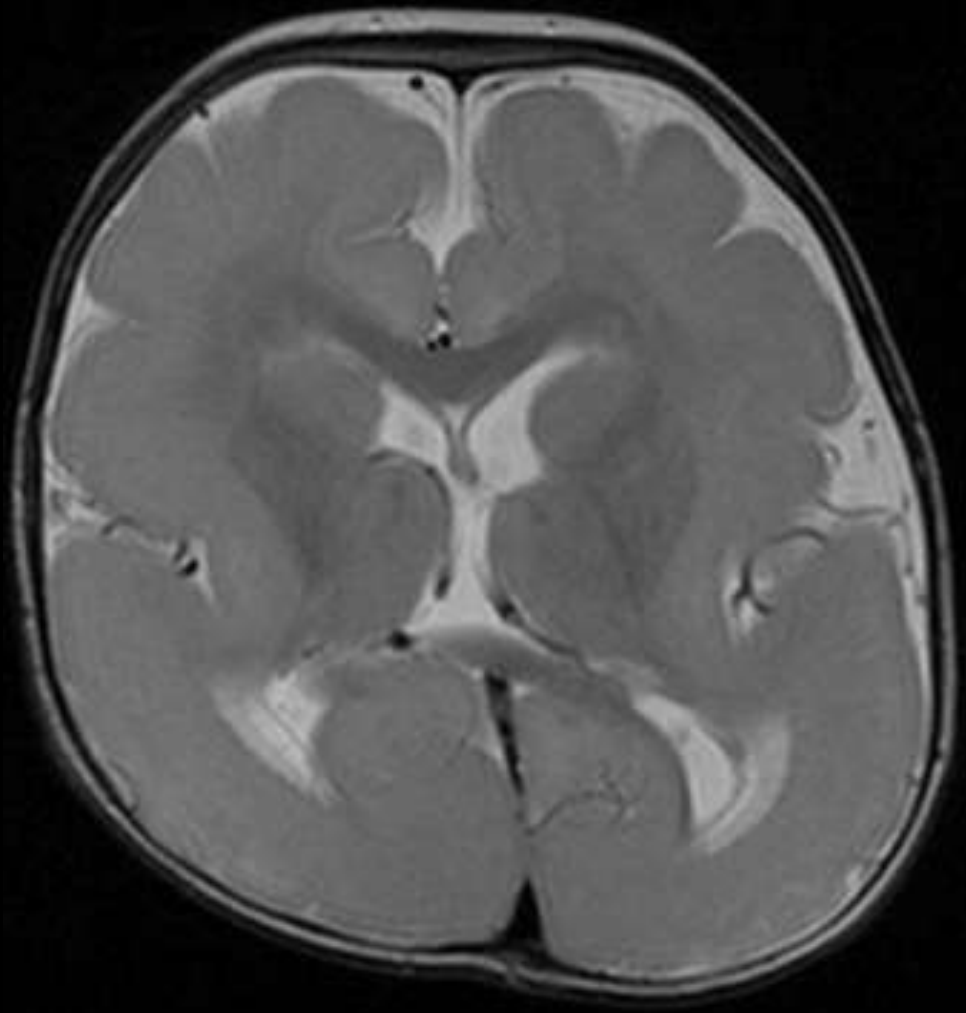
Normal

PMG

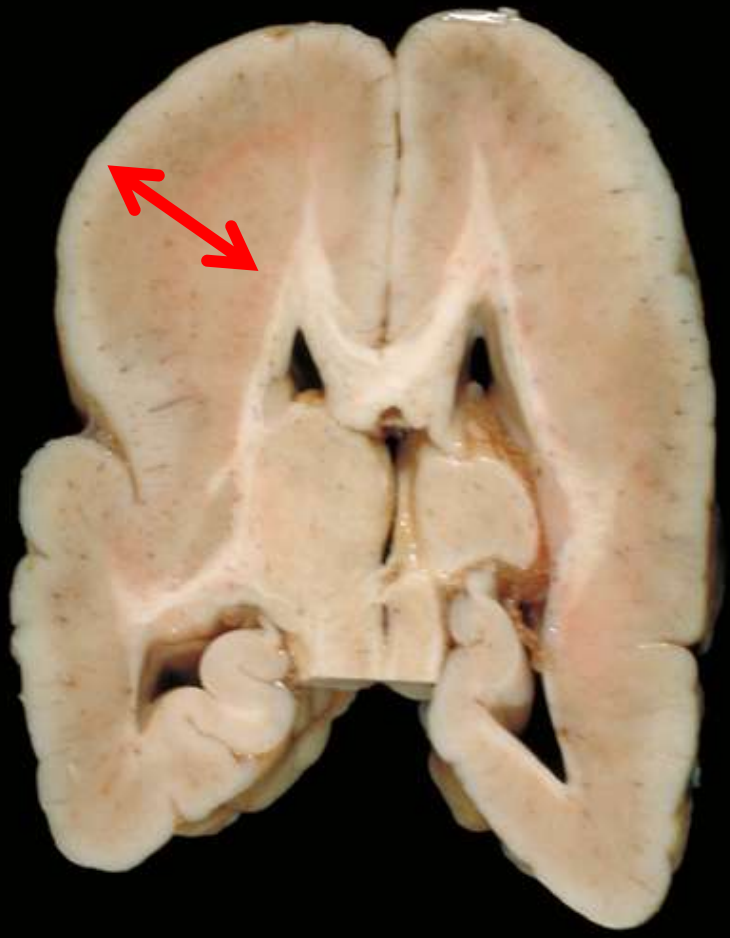


Courtesy of Dr Jeff Golden, Pen State Unv, Philadelphia

PMG is often confused with pachygyria (lissencephaly)

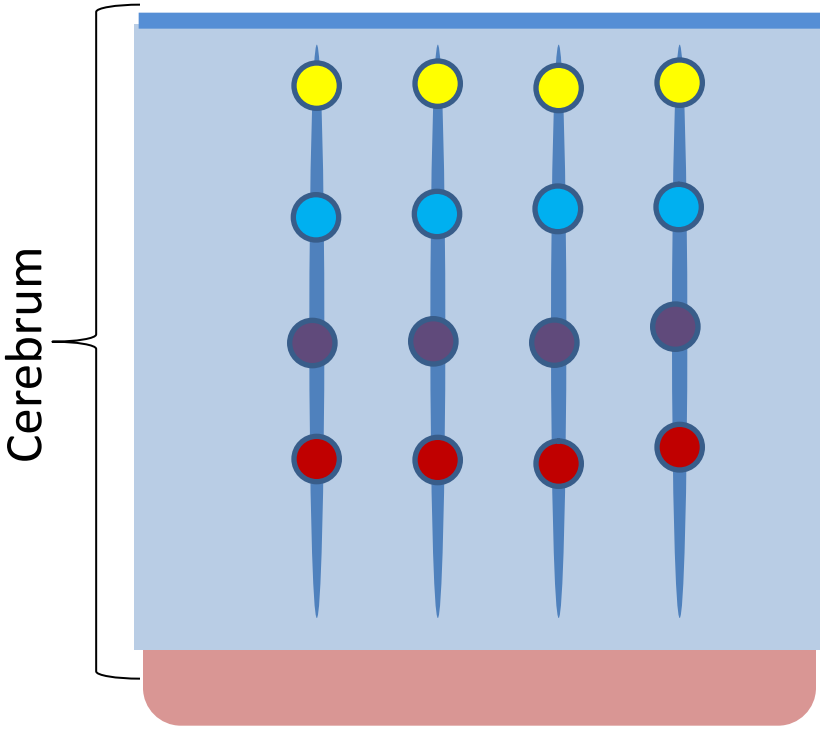


Axial MRI



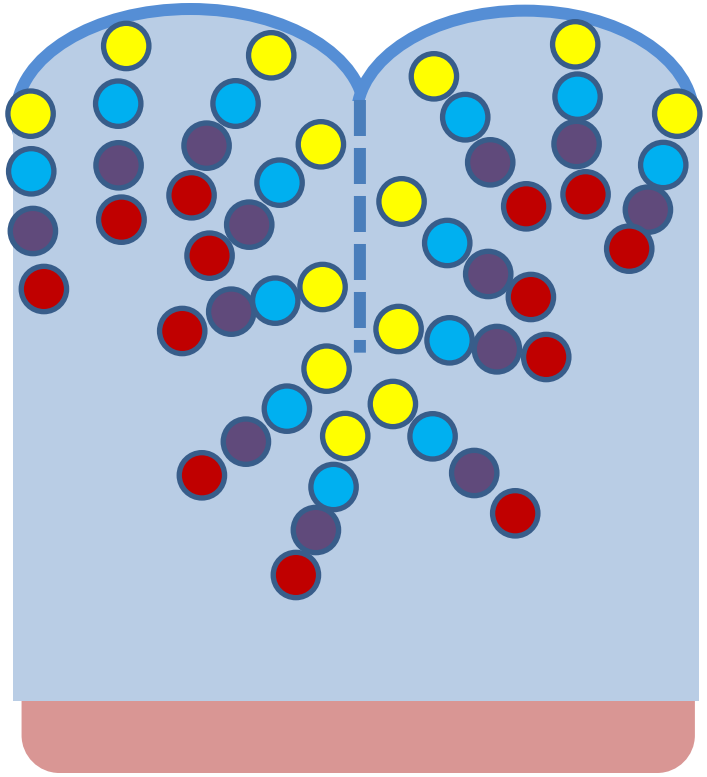
Thick cortex (10 – 20mm)
4 cortical layers

Lissencephaly

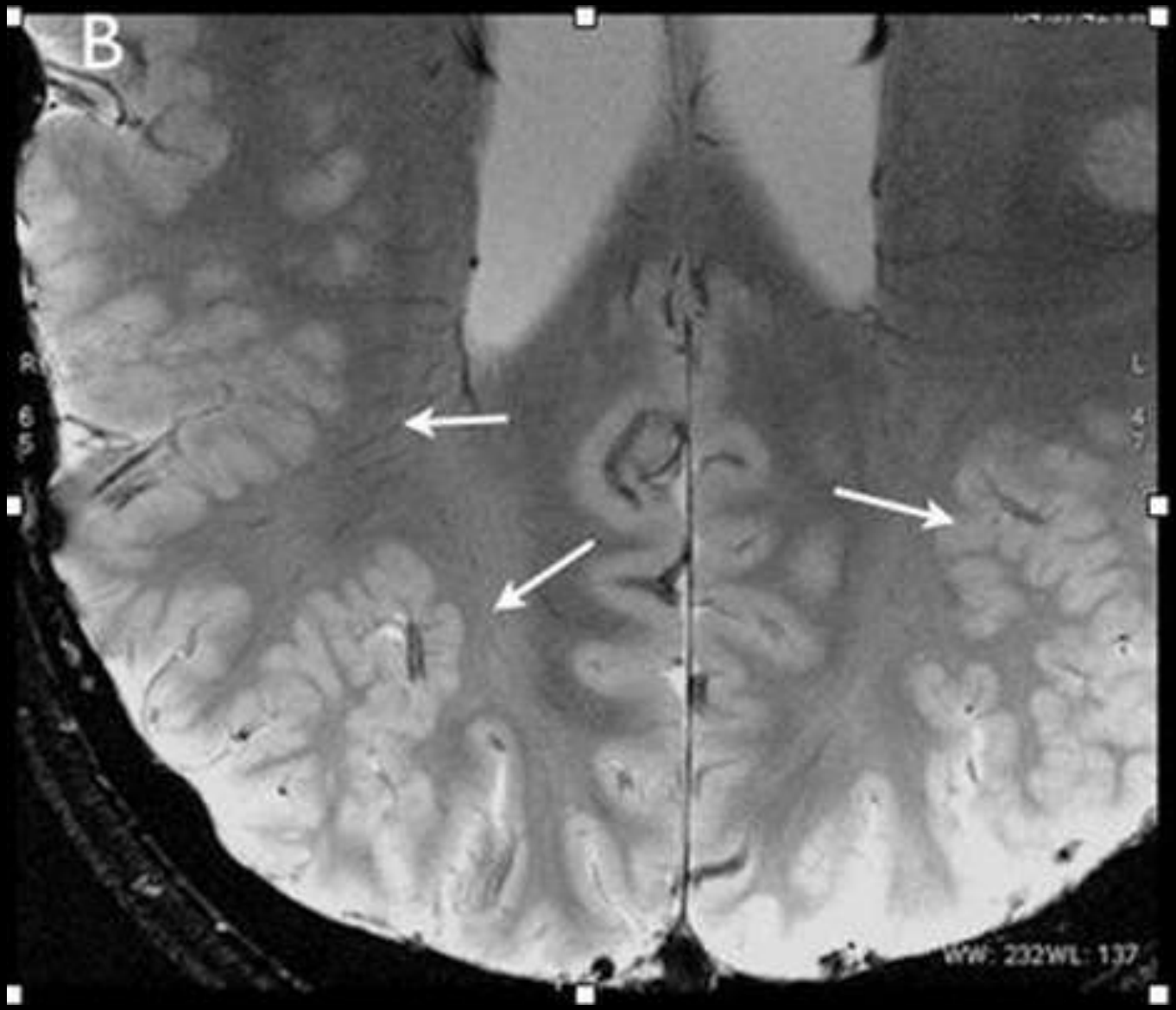


Classical lissencephaly is due to under-migration.

Polymicrogyria



Many small gyri – often fused together.



Axial MRI image at 7T showing morphological aspects of PMG.

Guerrini & Dobyns Malformations of cortical development: clinical features and genetic causes. Lancet Neurol. 2014 Jul; 13(7): 710–726.

PMG - aetiology

Pregnancy history

- Intrauterine hypoxic/ischemic brain injury (e.g. death of twin)
- Intrauterine infection (e.g. CMV, Zika virus)
  [+deafness & cerebral calcification]

TORCH, CMV PCR, CT scan

- Metabolic (e.g. Zellweger syndrome, glycine encephalopathy)

VLCFA, metabolic Ix

- Genetic:

Family history → Familial recurrence (XL, AD, AR)

Chromosomal abnormalities (e.g. 1p36 del, 22q11.2 del)

Examin-ation → Syndromic (e.g. Aicardi syndrome, Kabuki syndrome)

Monogenic (e.g. *TUBB2B, TUBA1A, GPR56)*

Array CGH

Gene test/Panel/WES/WGS

A cohort of 121 PMG patients

Aim: To explore the natural history of PMG and identify new genes.

Recruited:

- 99 unrelated patients
- 22 patients from 10 families

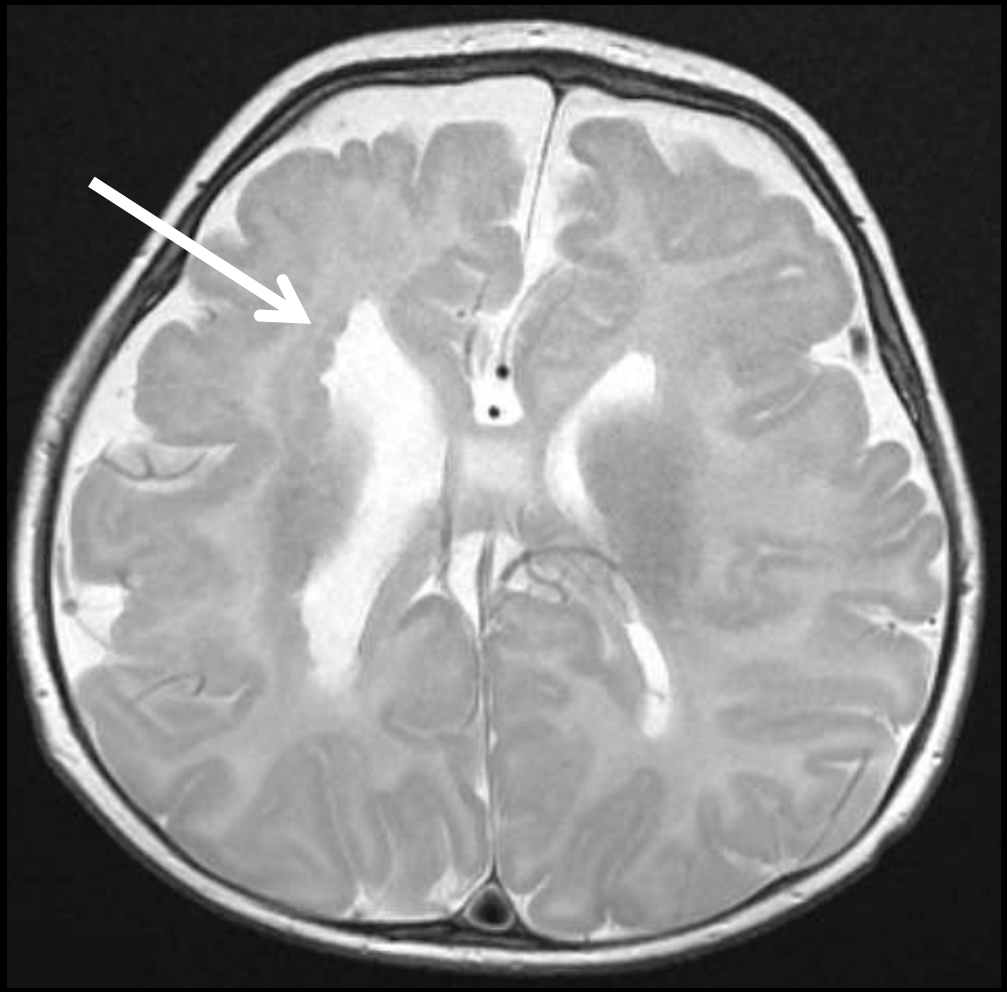
87% White British, 53% male

~92% sporadic cases (NB. ascertainment bias)

Sporadic PMG

- Array CGH, single gene and gene panel testing - then a subset (n=57) had trio-WES.
- 2/99 with pathogenic copy number variants (CNVs):
- 3/99 with possibly contributory CNVs
- 21/99 with pathogenic single nucleotide variants (SNVs)

PMG	Regions	Bi	Rt	Lt
Frontal		4	1	0
Frontoparietal		11	3	1
Perisylvian		55	9	4
Parieto-occipital		11	3	2
Generalized		12	3	2

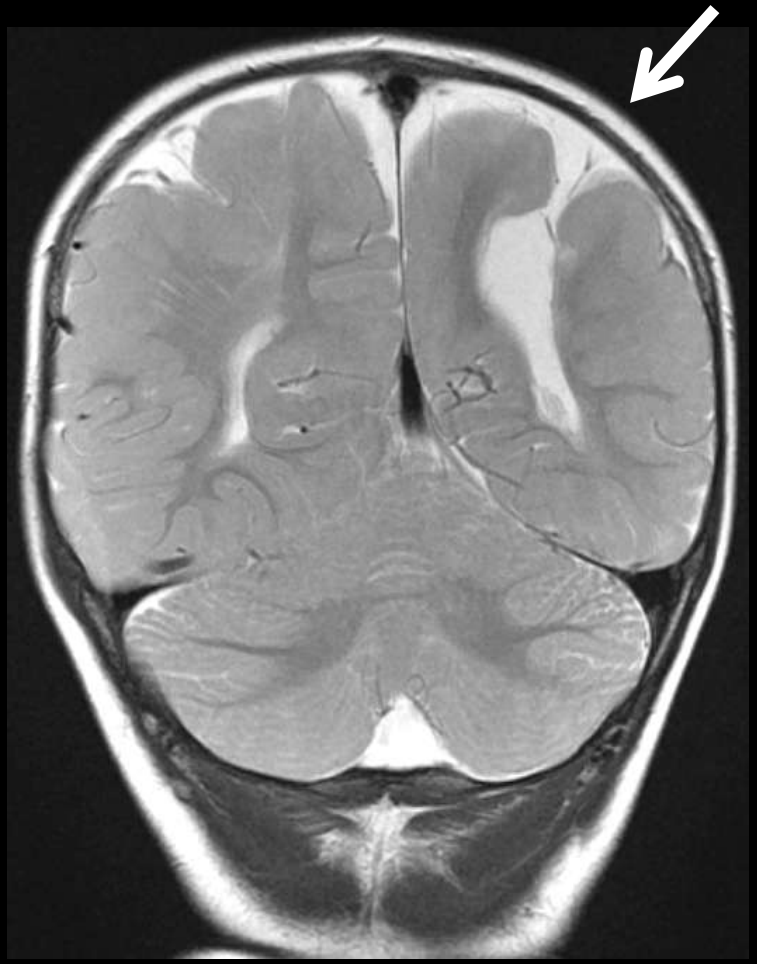


7 with periventricular heterotopia (PVNH)

7 with PMG-like cortical malformations

Schizencephaly

13 patients with schizencephaly (SCZ)



Lower genetic diagnostic rate , ? non-genetic causes (e.g. vascular)

Array CGH, consider eye exam, TORCH/CMV PCR

Cortical malformation gene panel: *COL4A1* and *COL4A2*
+/- congenital cataracts
+/- porencephaly

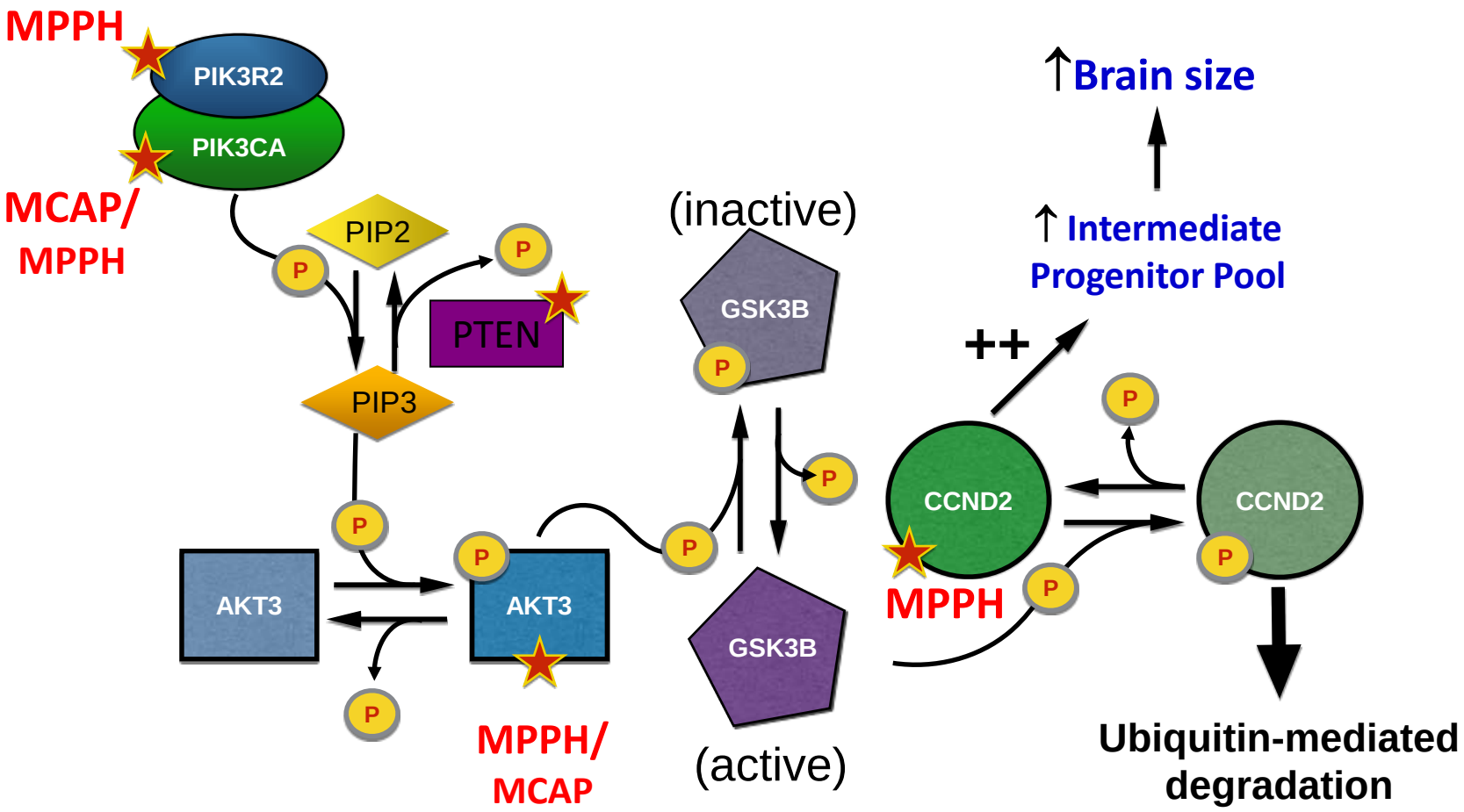
Rarely with *TUBB2B, SIX3, EMX2* and *SHH*

SCZ can be a feature of septo-optic dysplasia spectrum.

PMG patients:

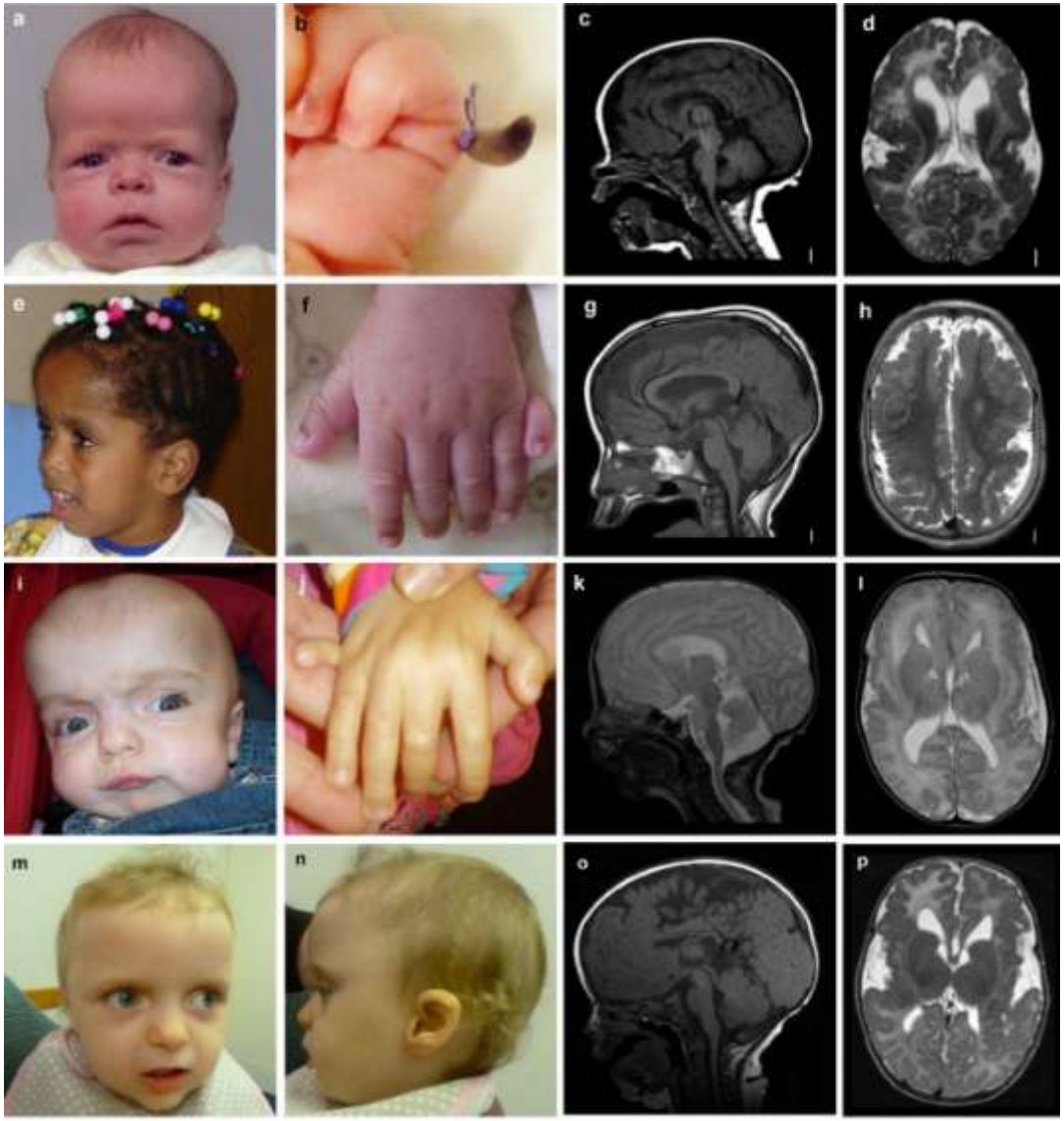
Microcephaly (<2SD)	51%	(57/111)
Macrocephaly (>2SD)	6%	(7/111)

MCAP, megalencephaly-capillary malformation syndrome
MPPH, megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome



PMG patients with large heads often have mutations in the PI3K-AKT pathway.

Megalencephaly-Polymicrogyria-Polydactyly-Hydrocephalus Syndrome (MPPH)

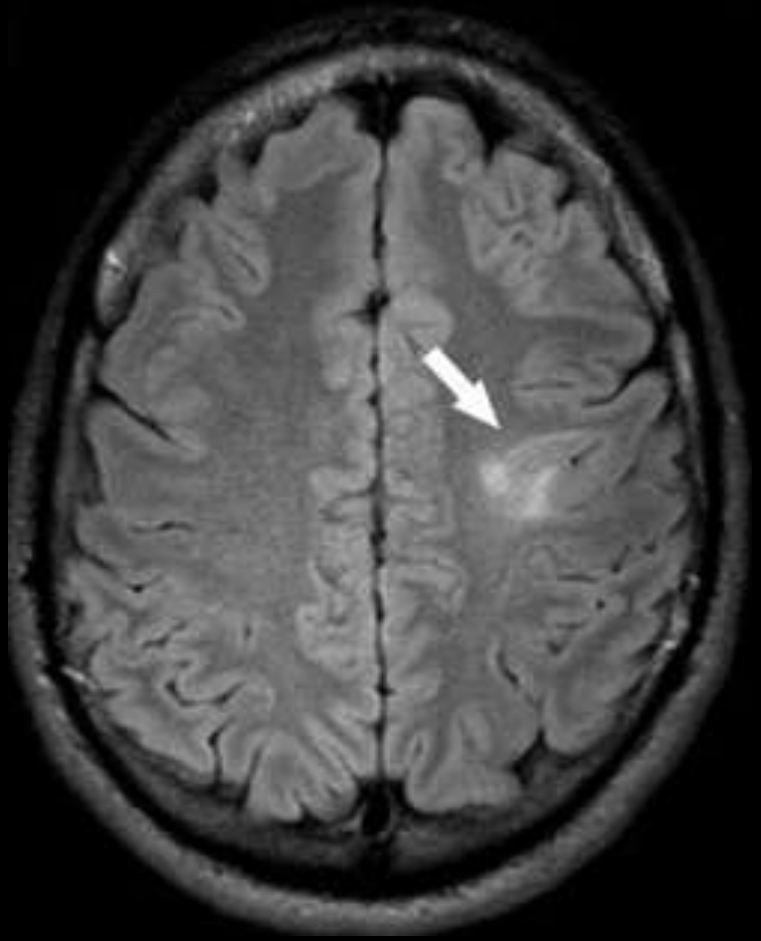


Brain overgrowth
- Megalencephaly
- Ventriculomegaly/
- Hydrocephalus

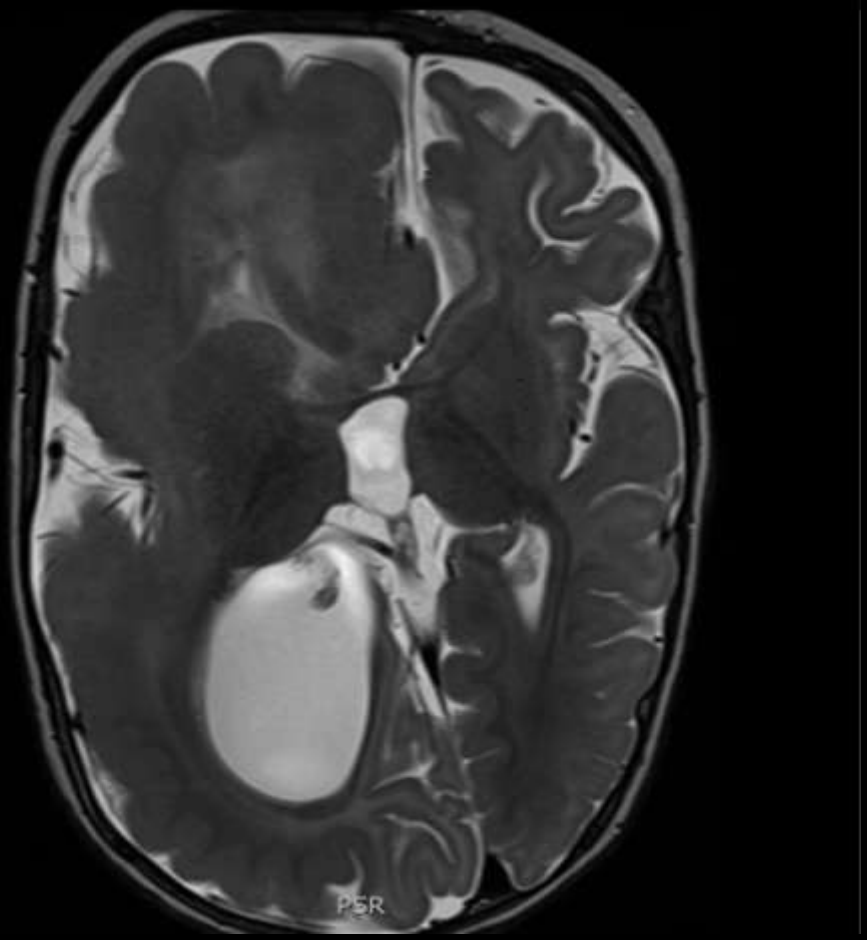
Cortical brain malformation
- Polymicrogyria

Limb anomalies
- Postaxial polydactyly

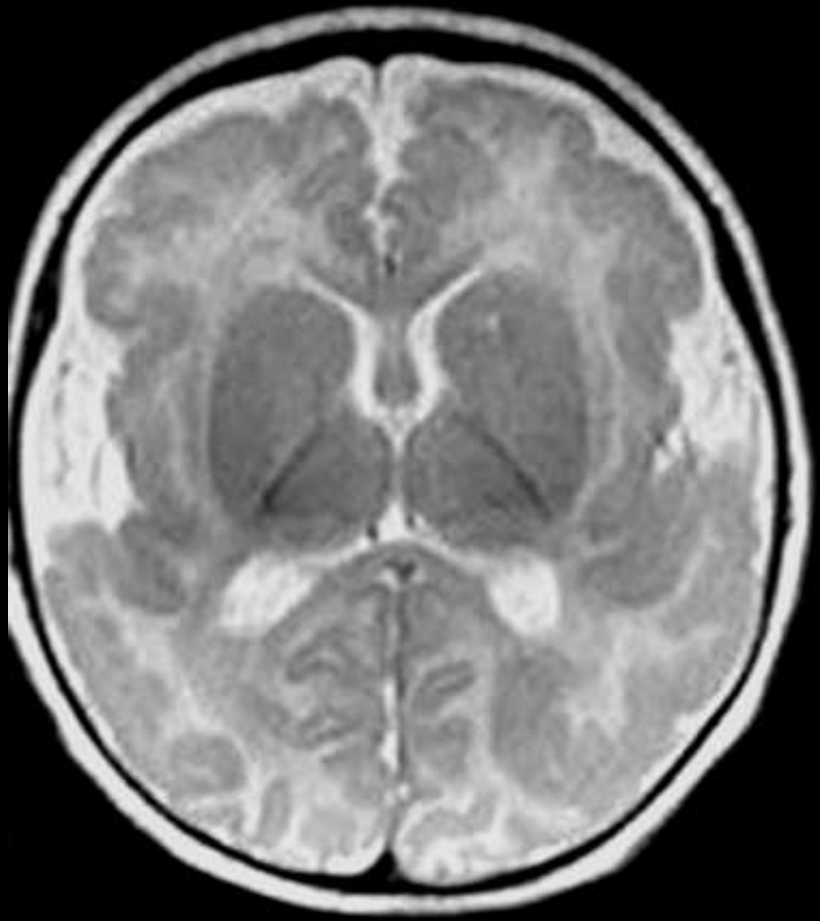
Mirzaa et al. De novo CCND2 mutations leading to stabilization of cyclin D2 cause megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome. Nat Genet. 2014 May;46(5):510-5.



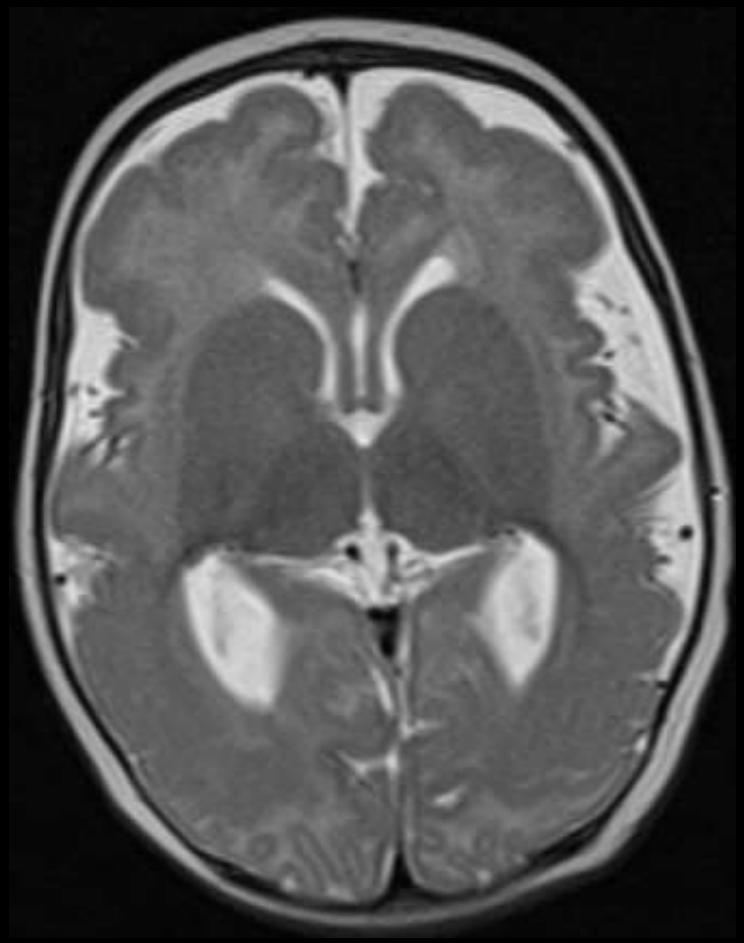
Focal cortical dysplasia
(Mosaic *PIK3CA, TSC1, TSC2, MTOR*)



Hemimegalencephaly
(Mosaic *AKT3, PIK3CA, MTOR*)



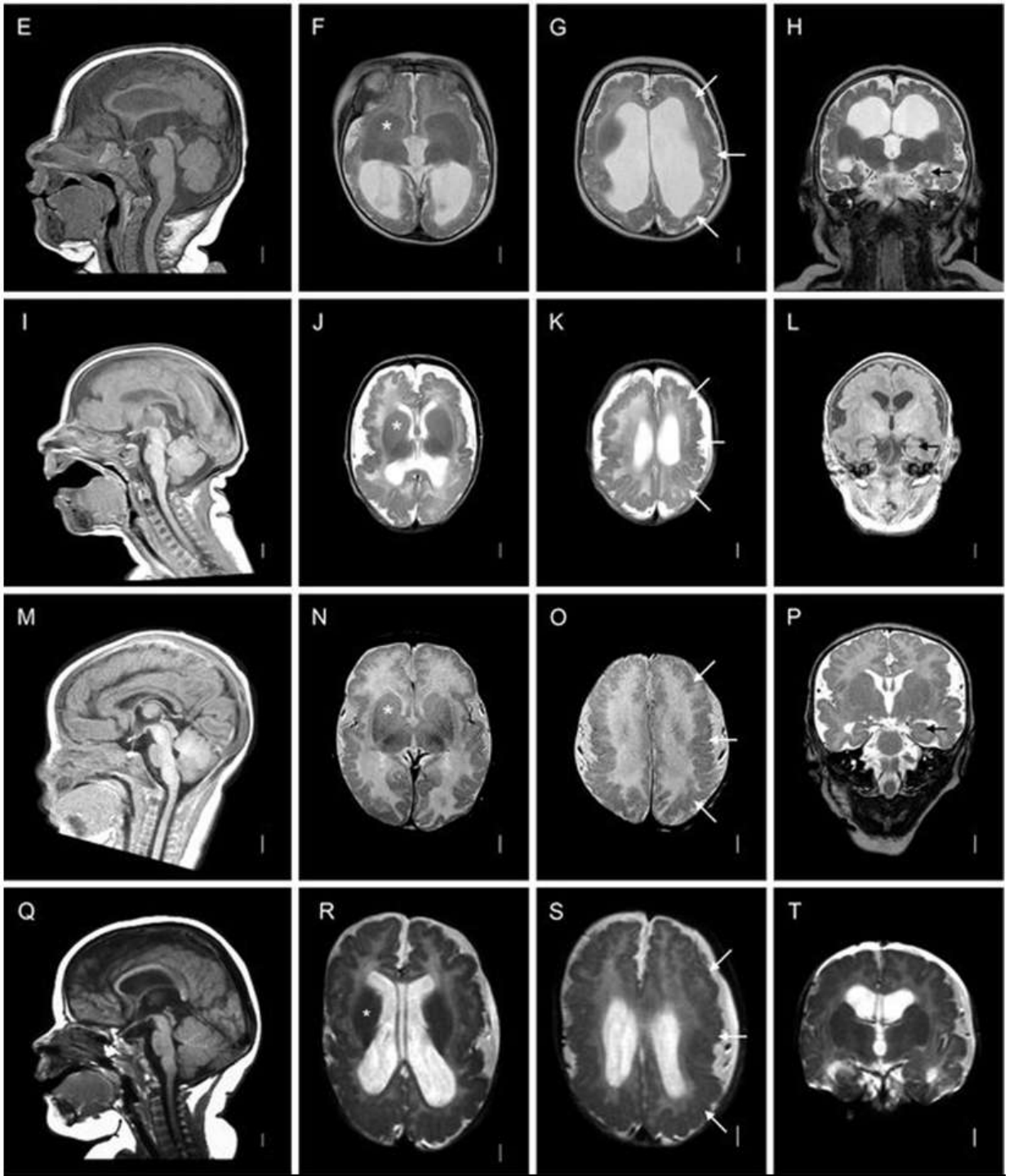
GRIN1, p.(Asn674Ile)



GRIN1, p.(Arg794Gln)

- Extensive bilateral PMG – occipital sparing.
- Profound developmental delay, early-onset epilepsy (1w-9m), spastic muscle weakness, cortical visual impairment. ~20 cases now - all *de novo* missense

Fry AE et al. De novo mutations in GRIN1 cause extensive bilateral polymicrogyria. Brain. 2018 Mar 1;141(3):698-712.

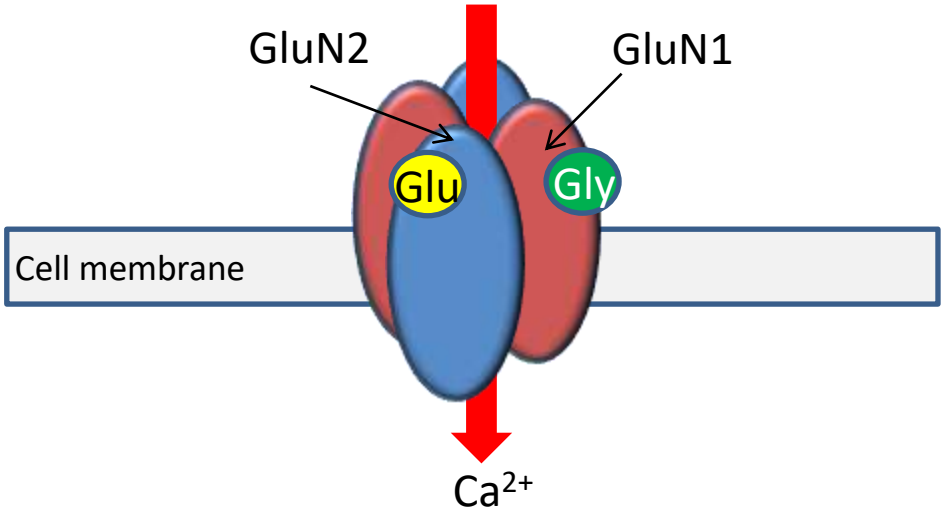


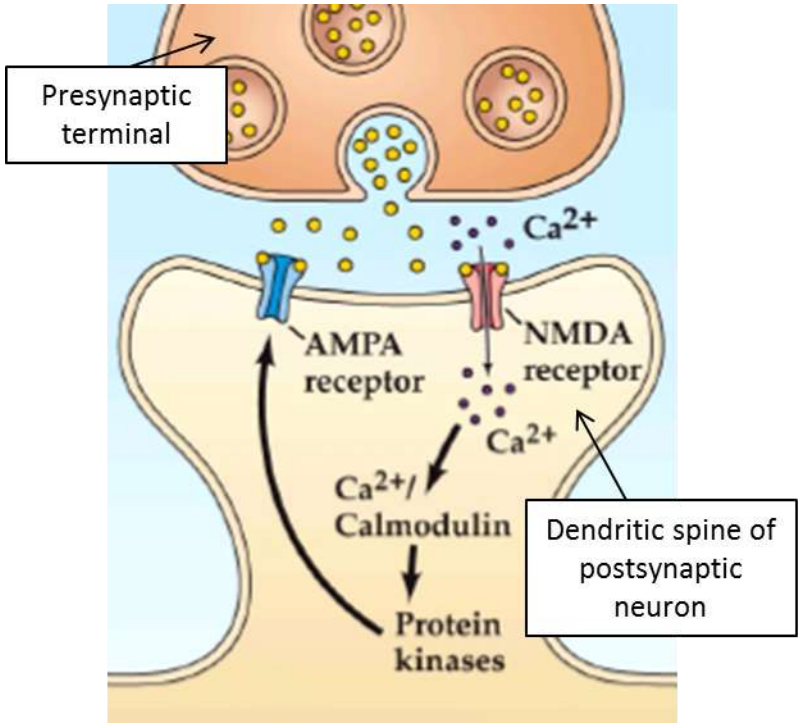
6 x GRIN2B patients with PMG-like malformations

- Volume loss
- Extensive dysgyria similar to cortical appearance of tubulinopathies
- hippocampal dysplasia In some

Platzer *et al.* GRIN2B encephalopathy: novel findings on phenotype, variant clustering, functional consequences and treatment aspects. J Med Genet. 2017 Jul;54(7):460-470.

GRIN1 (encoding GluN1) and GRIN2B (encoding GluN2B) are the components of the N-methyl-D-aspartate receptor (NMDAR).





- Key receptor for excitatory neurotransmission
- *GRIN1*, *GRIN2A* and *GRIN2B* mutations found in patients with Intellectual disability, autism, epilepsy, cortical visual impairment and schizophrenia.
- *GRIN1* and *GRIN2B* highly expressed in fetal brain.
- Why do only some GRIN1/2B mutations cause PMG?

Conclusions

- PMG – a heterogeneous MCD - genetic factors are a significant cause.
- Diagnostic rates are highest in PMG patients with bilateral disease and/or big heads and/or familial disease.
- Recurrence risk is typically low (but not always!)
- Fetal MRI can be considered for reassurance when a gene is not known.
- Further PMG genes remain to be discovered!

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