

Manchester ESHG Syndromology and Dysmorphology Course

14th - 16th October 2026

The **brain** as a clue to syndrome diagnosis

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**Please do not
panic.....**



Outline

- Background
 - Basics of MR imaging
 - Imaging examples
 - Pattern recognition (with N image adjacent in **red** border)
 - Non-specific to highly specific
 - Combining clues into overall diagnosis
 - No faces (but some animal signs)
- Examples from categories:
 - Cortex
 - White matter
 - Cerebellum
 - Brainstem
 - Calcium
 - Iron
 - **Multisystem**

B

R



D

G

E



Brain Imaging in Diagnosing Genetic Disorders

Date: 27 and 28 November 2019

Venue: Queen's Medical Centre, Nottingham

Nottingham
Children's
Hospital

NHS
Nottingham
University Hospitals
NHS Trust

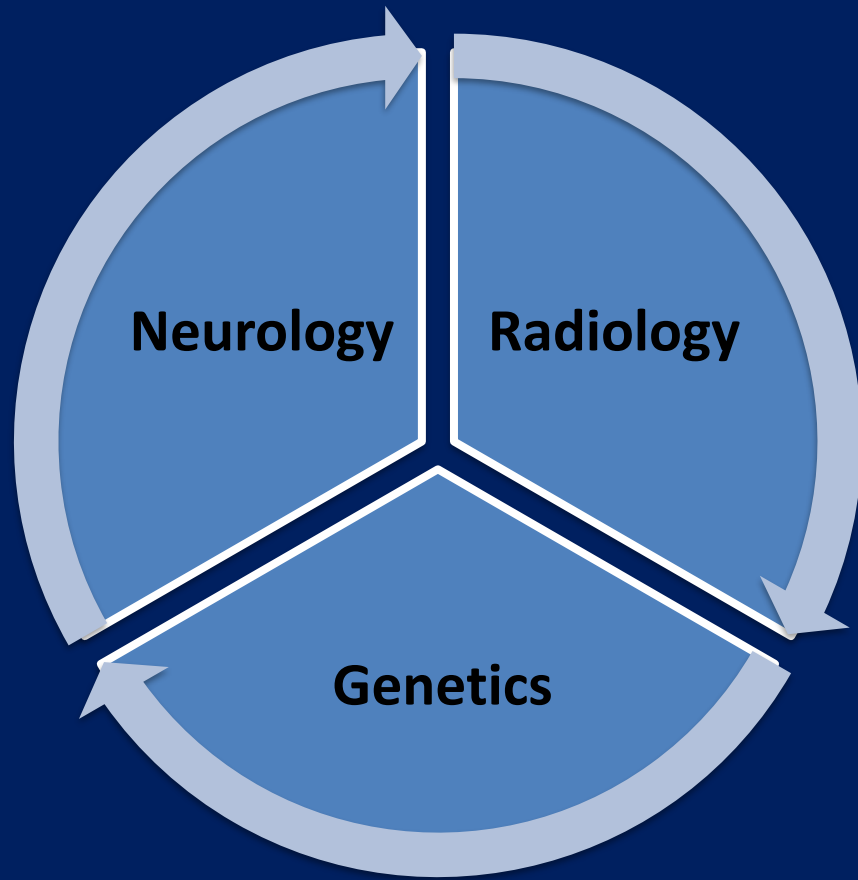
B R D G E - I I



Brain Imaging in Diagnosing Genetic Disorders

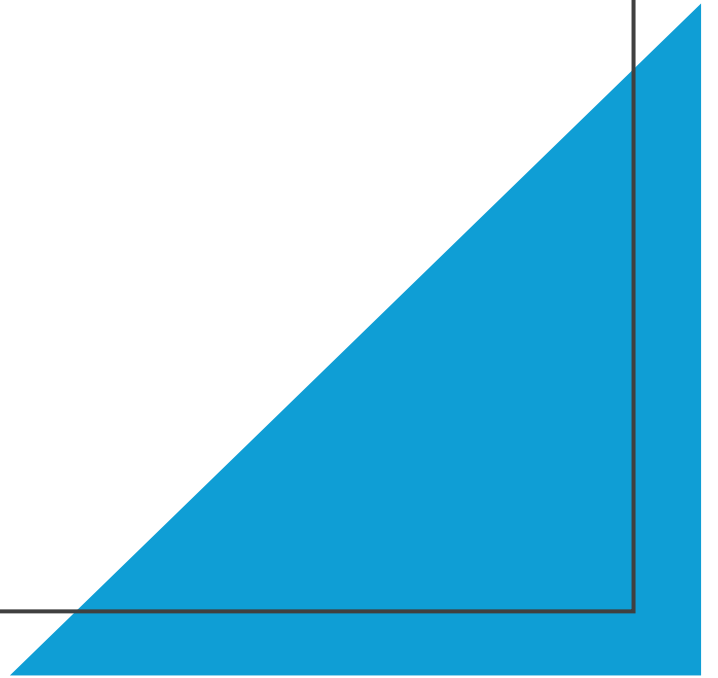
Date: 11 and 12 September 2025

Venue: Nottingham, United Kingdom



Improving diagnosis of
genetic disorders through
MRI pattern recognition

UK neurogenetics club





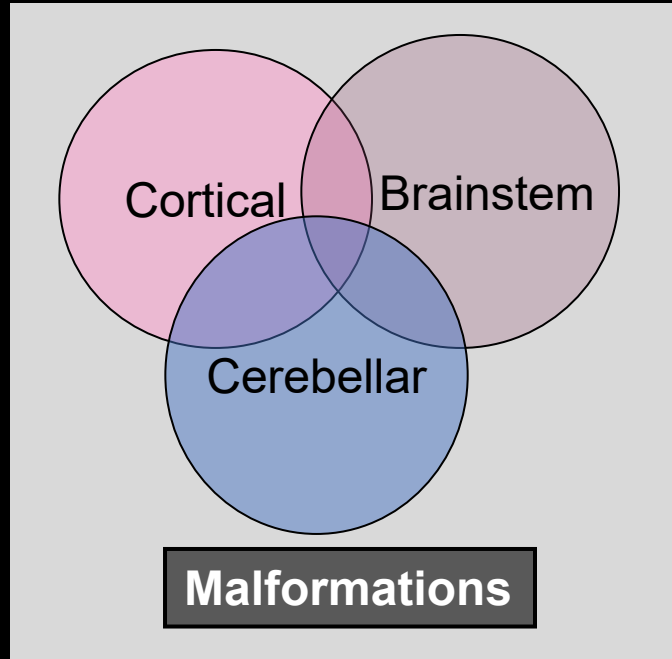
- **Over 750 cases** across 36 meetings
- pdf minutes for meetings
- Two meetings a year
- 2006 – 2019 in person meetings
- 2020 onwards virtual

Host centres

- GOS London – 7
- St George's London – 6
- Nottingham – 4
- Leeds – 4
- Manchester – 3
- Guy's London – 3
- Exeter – 2
- Birmingham – 2
- Bradford – 1
- Cardiff – 1
- Oxford – 1
- Glasgow – 1
- Imperial London – 1

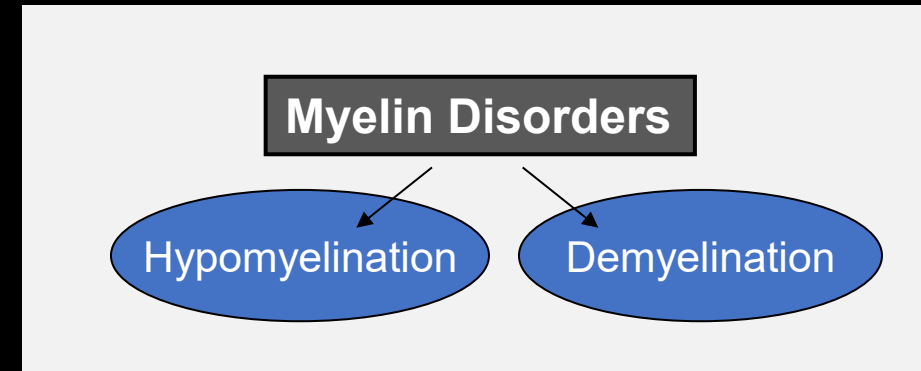
MRI basics

Abnormal findings on MRI



Intracranial
calcification

Brain iron
accumulation



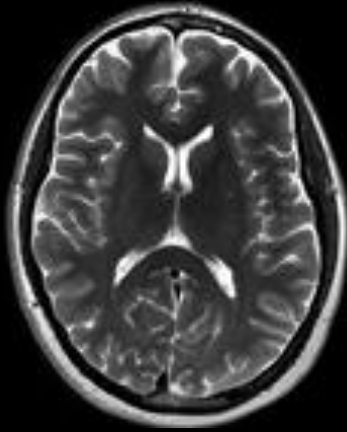
Metabolic disorders

Specific disorders
or syndromes

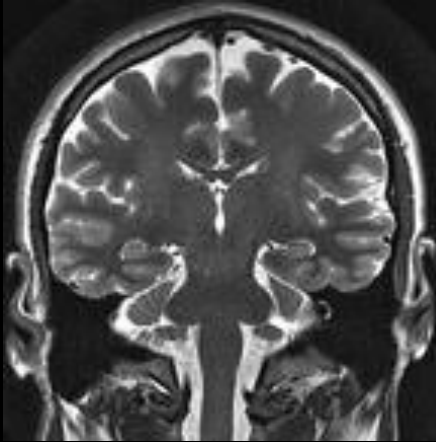
Infections
Tumours
Vascular

Imaging planes

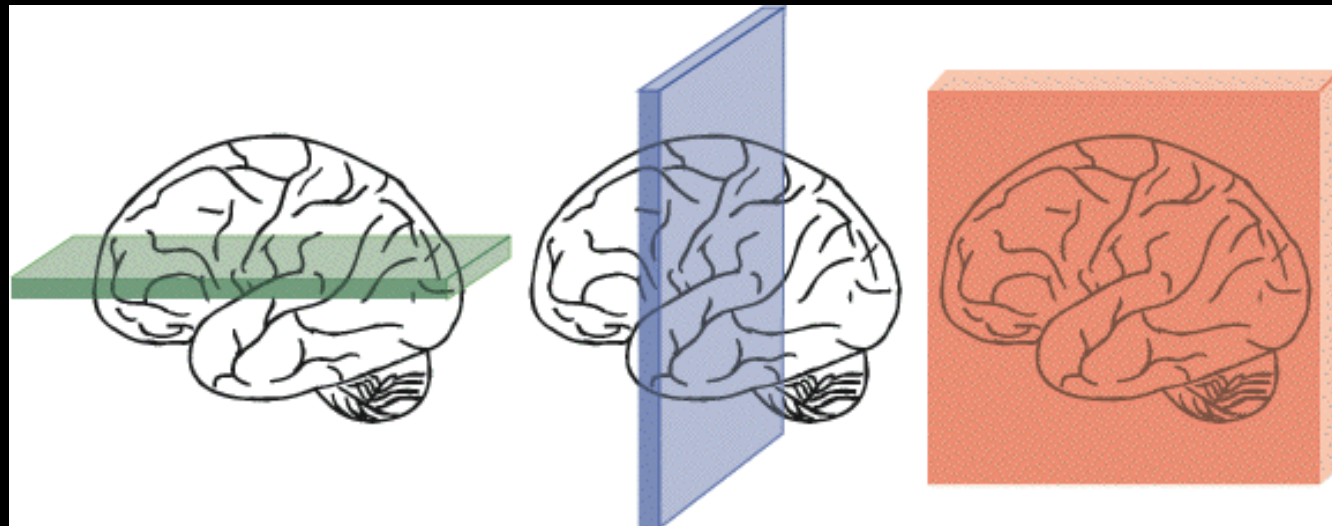
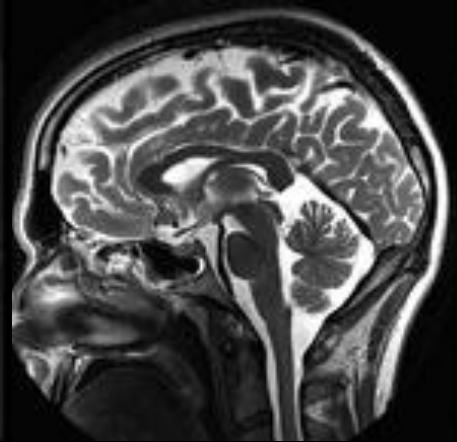
AXIAL



CORONAL



SAGITTAL



The jargon

- USS —————> echogenicity

- CT scan —————> density

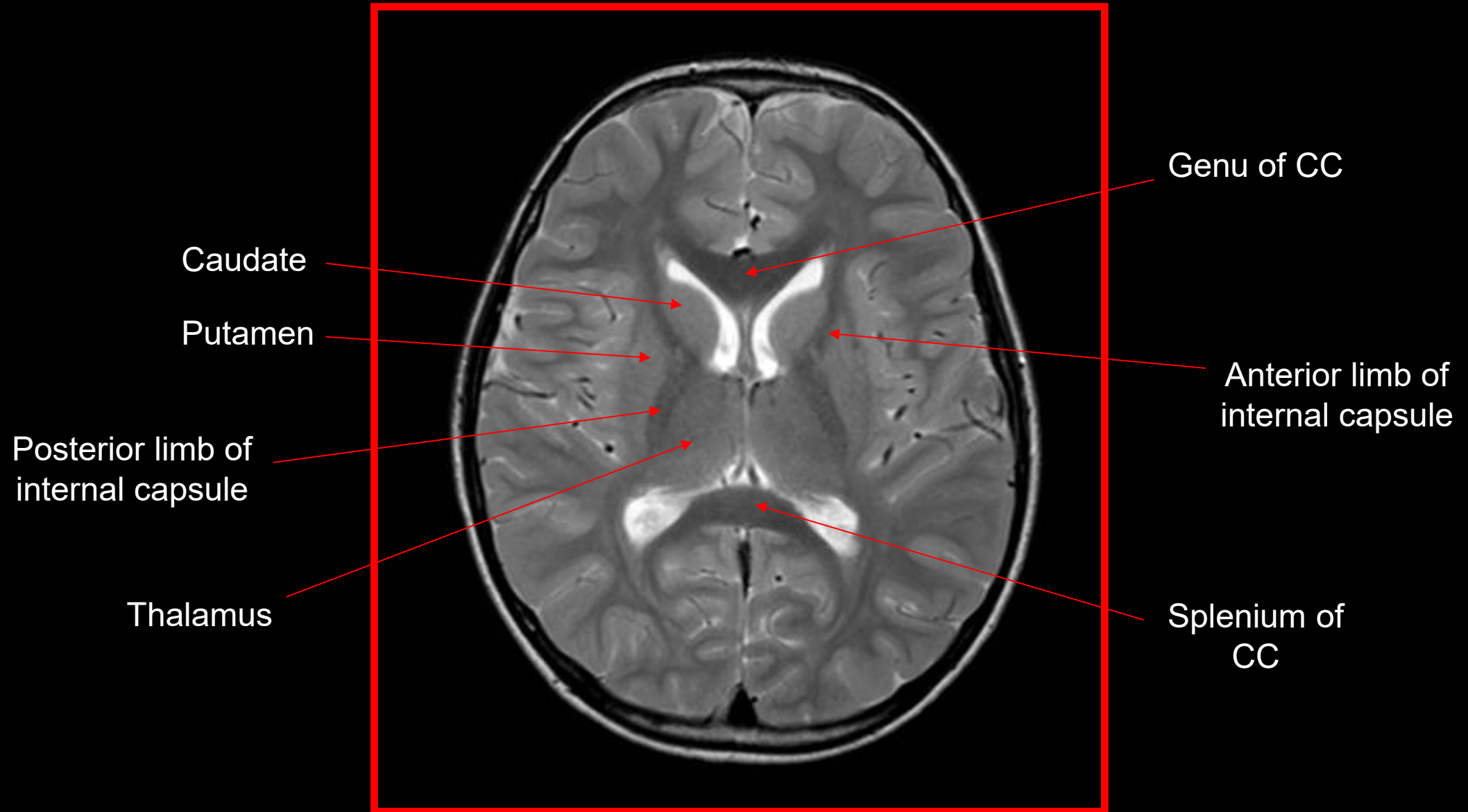
- **MRI scan** —————> **intensity**

'bright'

'high signal'

'WM changes'

Axial T2



Sagittal T1

Corpus
callosum



Cerebellar
vermis

Pons

Medulla

Diagnosis on MRI brain

- Four broad categories
 - **'Spot' diagnosis**
 - No other Ix required
 - **Main clue to diagnosis**
 - No need to see face
 - **Narrows down the ballpark diagnosis**
 - Makes accurate diagnosis easier/cheaper
 - Supportive features
 - Other clues are more important

Hard handles

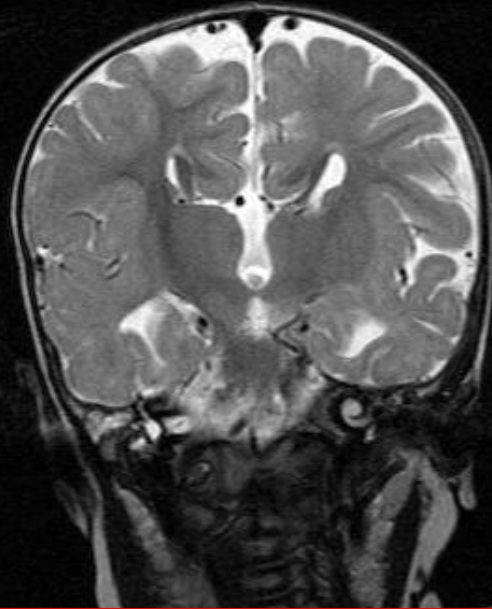
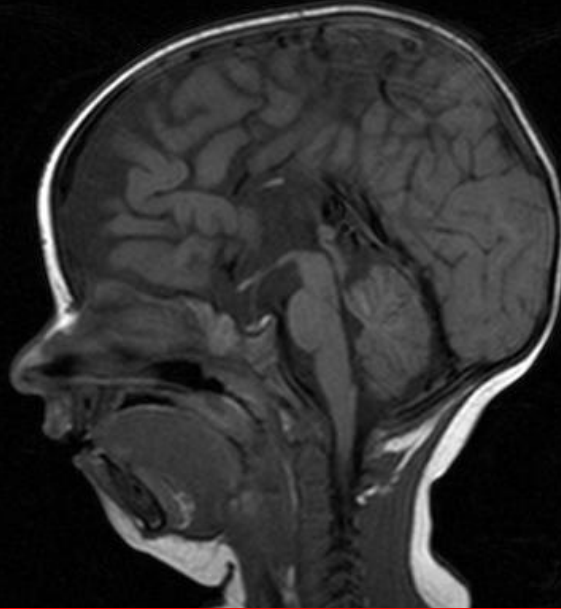
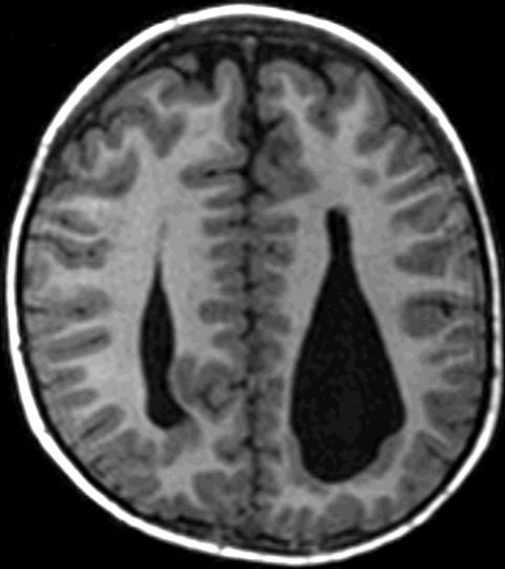


Soft pointers

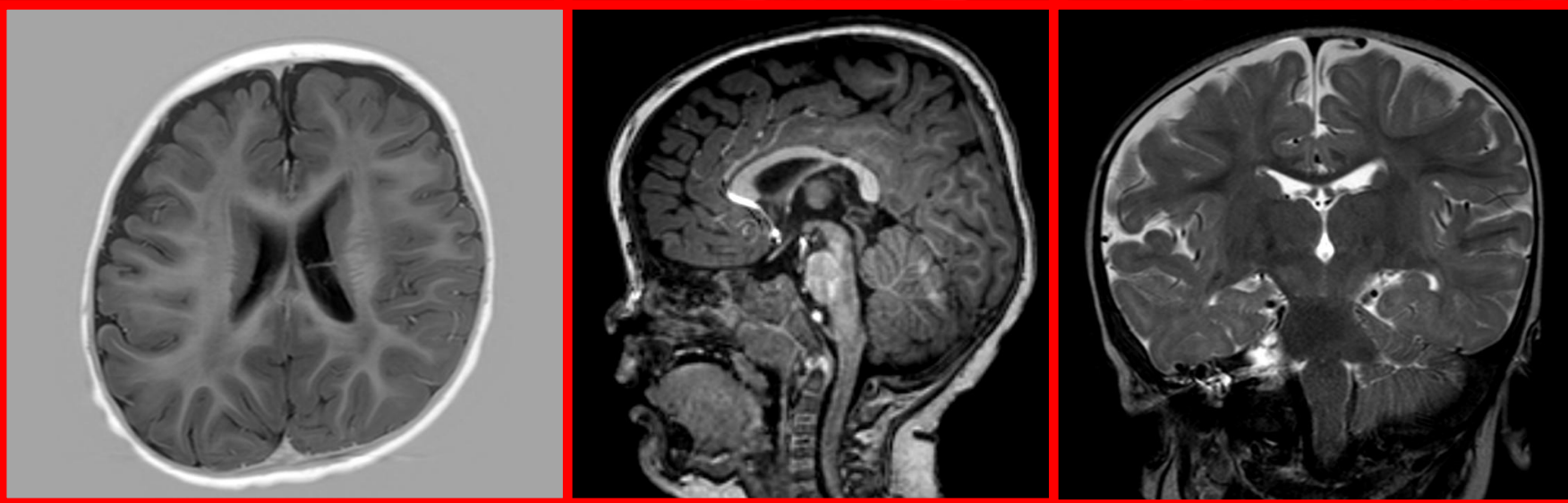
The background of the slide is a composite of medical images. It features several axial MRI slices of a human brain, showing the characteristic gyri and sulci. Overlaid on these images is a network of white lines, likely representing a diffusion tensor imaging (DTI) tractography or a similar structural connectivity map. The entire image has a color gradient, transitioning from a deep blue on the left to a vibrant red on the right. In the lower-left corner, there is a solid orange rectangular bar. The text 'MR imaging examples' is written in a large, white, sans-serif font across the middle of the image.

MR imaging examples

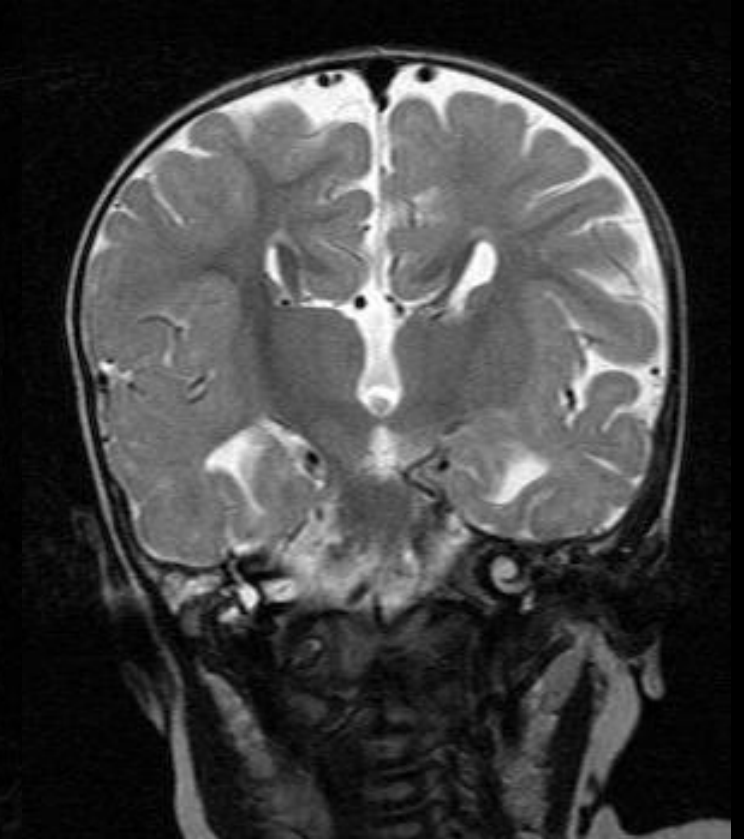
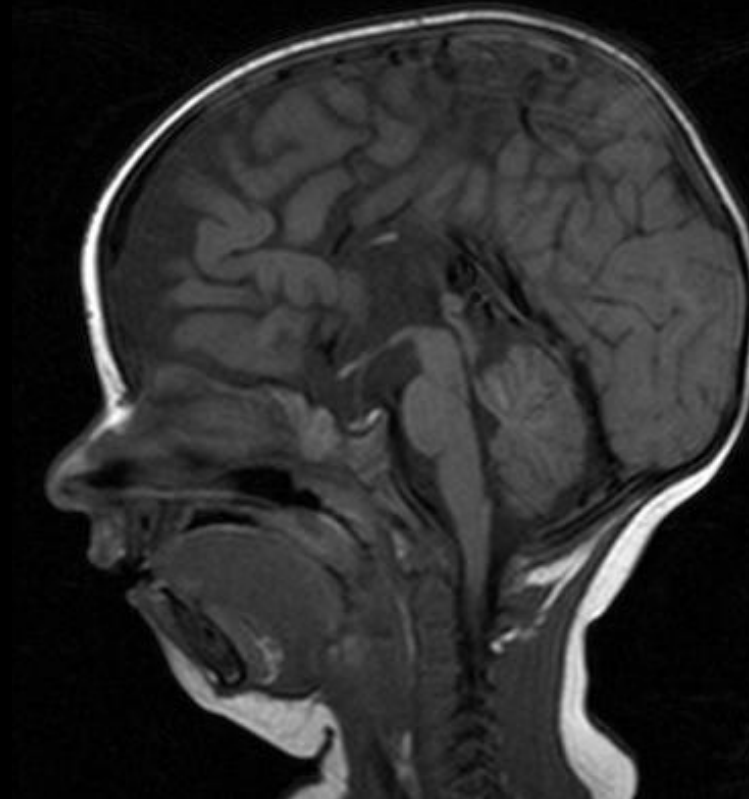
Agenesis of corpus callosum



moose head sign

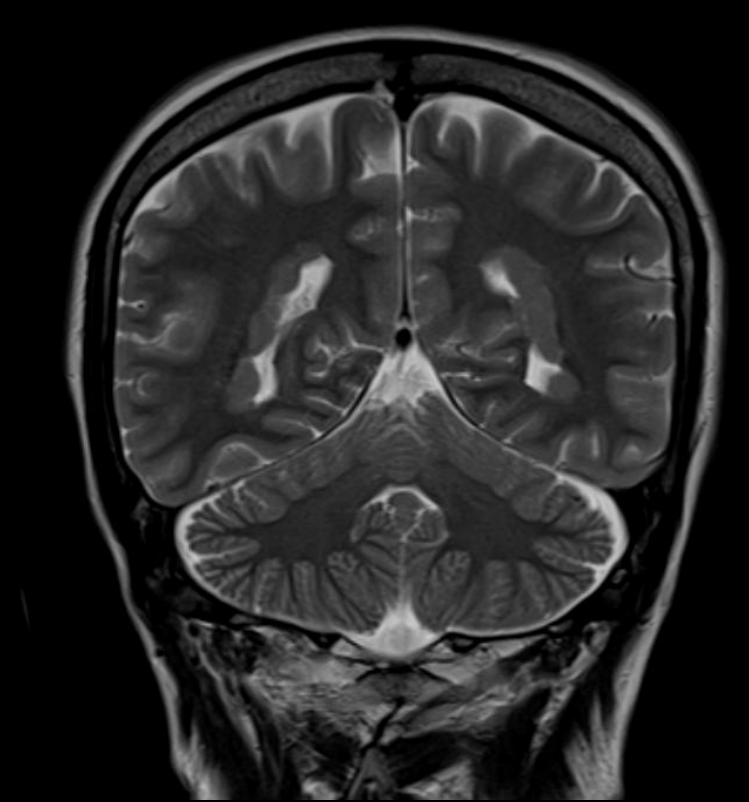
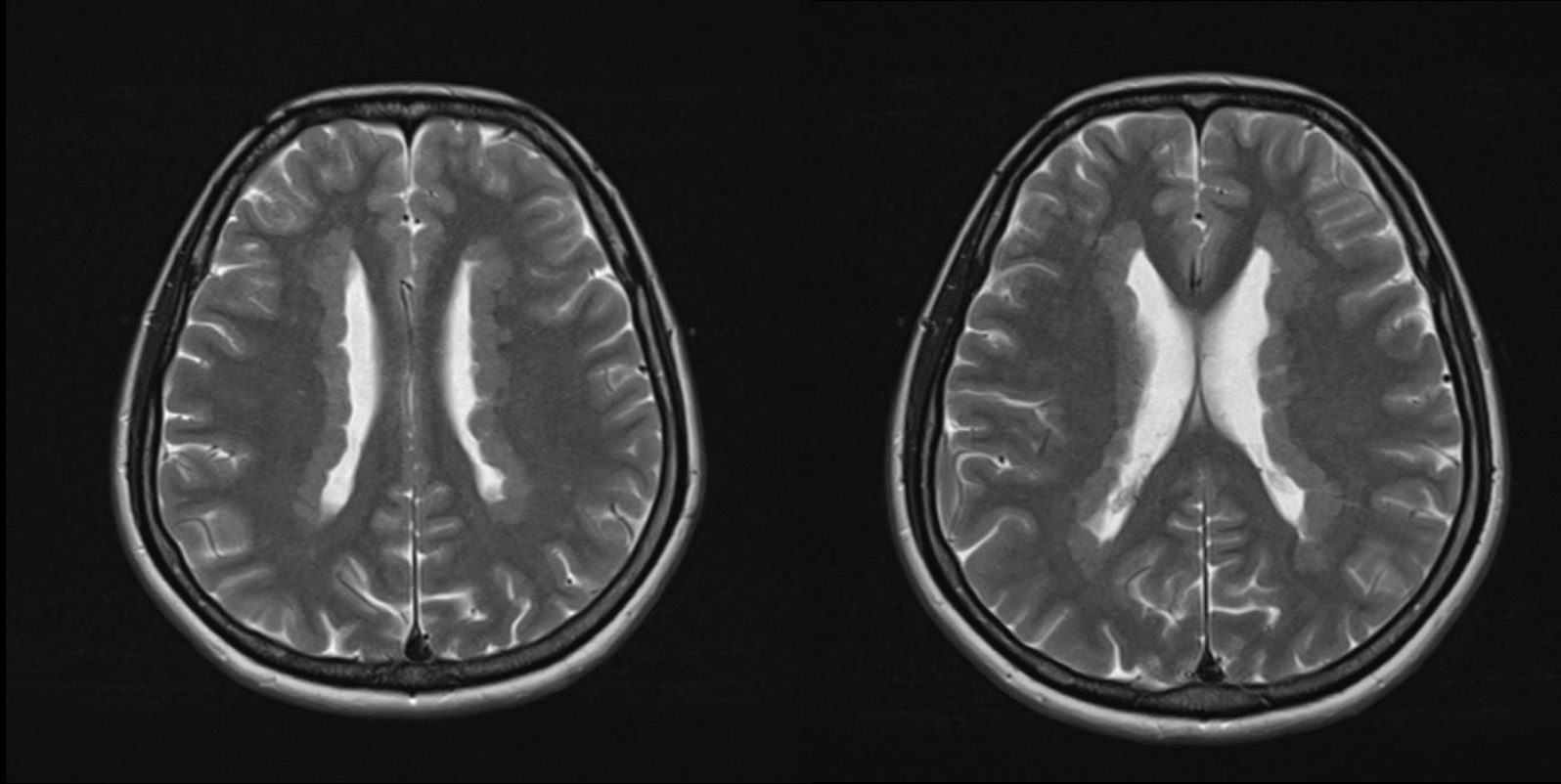


Agenesis of corpus callosum



Isolated, Mosaic +8, Acrocallosal, Andermann, Opitz-Kaveggia, Vici, XLAG, Aicardi
KIF7 *SLC12A6* *MED12* *EPG5* *ARX*

CDK13, DCC, L1CAM, GPSM2, LRP2

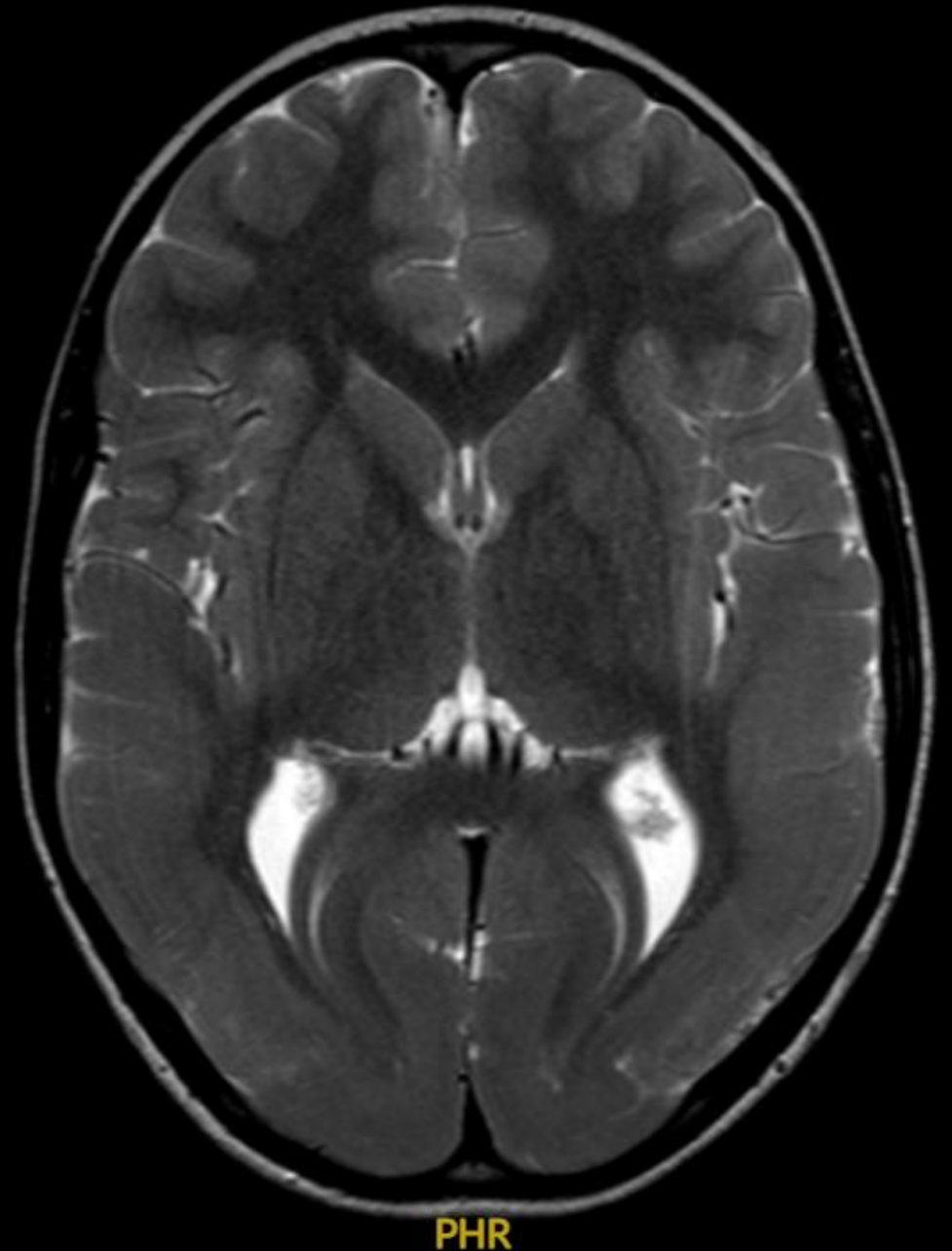


Periventricular nodular heterotopia
LoF variants in *FLNA* in women

Distribution of nodules quite specific

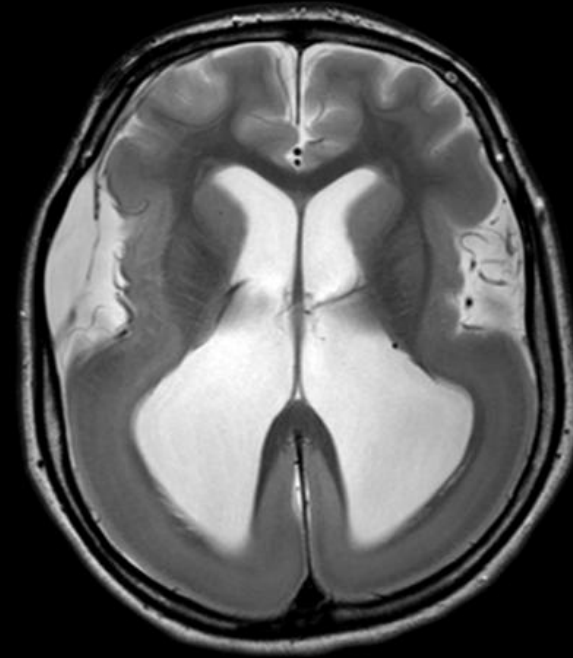
Lissencephaly

- 24-year-old man
 - Visual impairment
 - Epilepsy onset at 12 years
 - Mild learning difficulties
 - Growth parameters – N
- *LIS1* and *DCX* analysis – negative
- Recruited to DDD study – no diagnosis
- 59 gene cortical malformation panel – negative
- Trio WGS – requested in April 2021
- De novo *CEP85L* c.1A>T; p.(Met1?)



***CEP85L*-lissencephaly**

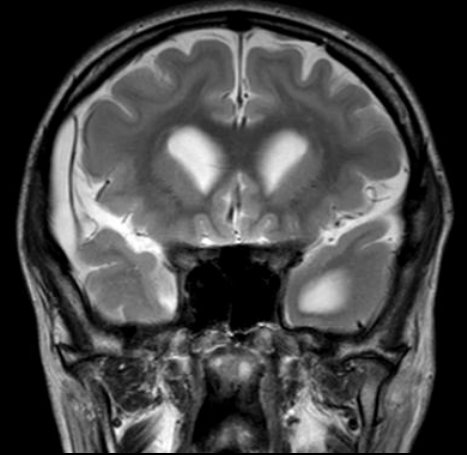
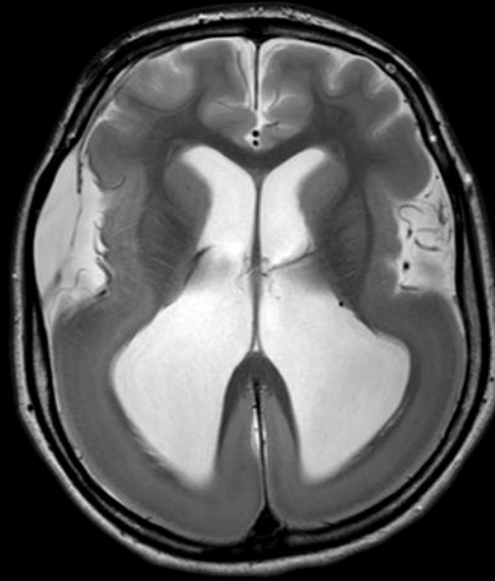
- Initially described in 2018
 - Only 30-odd patients in published literature
 - Posterior lissencephaly – 100%
 - Subcortical band heterotopia – 55%
- ID/NDD very common, but variable severity
- Epilepsy – 93%
- Visual impairment – 92%



Quite specific

Question 28

BRIDGE II quiz
Sept 2025



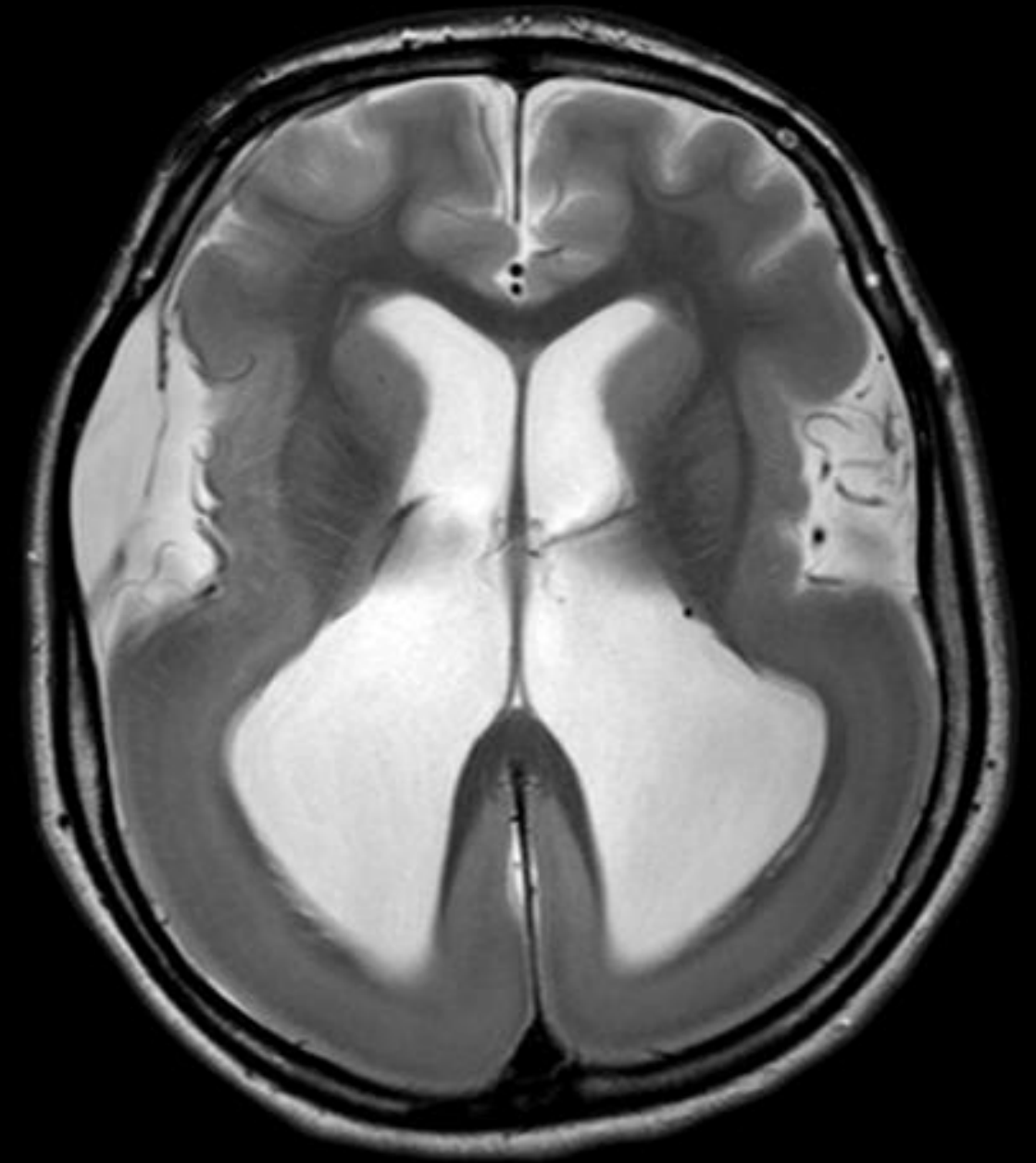
This teenage girl has severe learning disability and epilepsy. What is the most likely genetic basis for her presentation?

- a. ARX
- b. TUBA1A
- c. CEP85L
- d. RELN

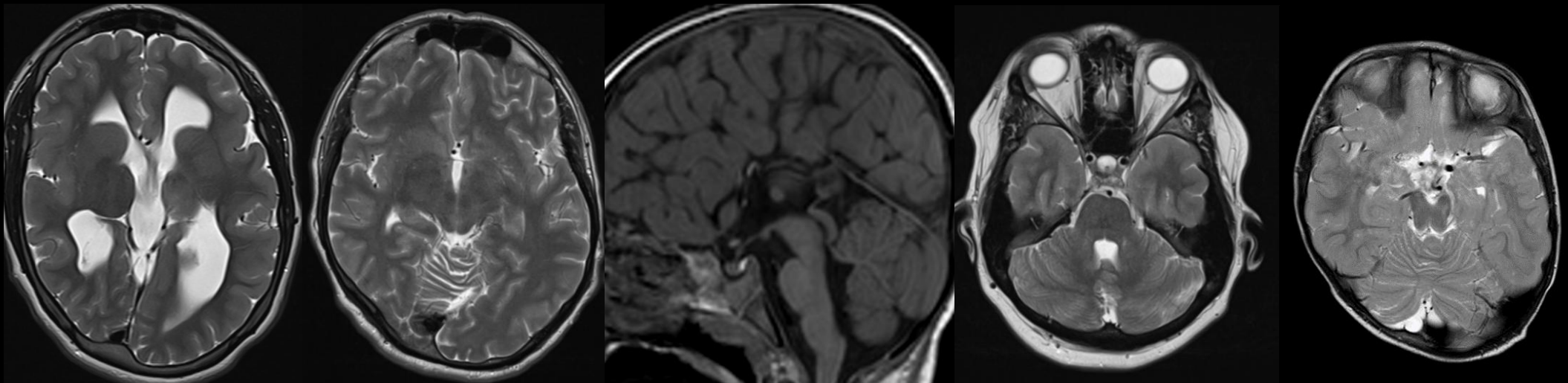


***CEP85L*- lissencephaly**

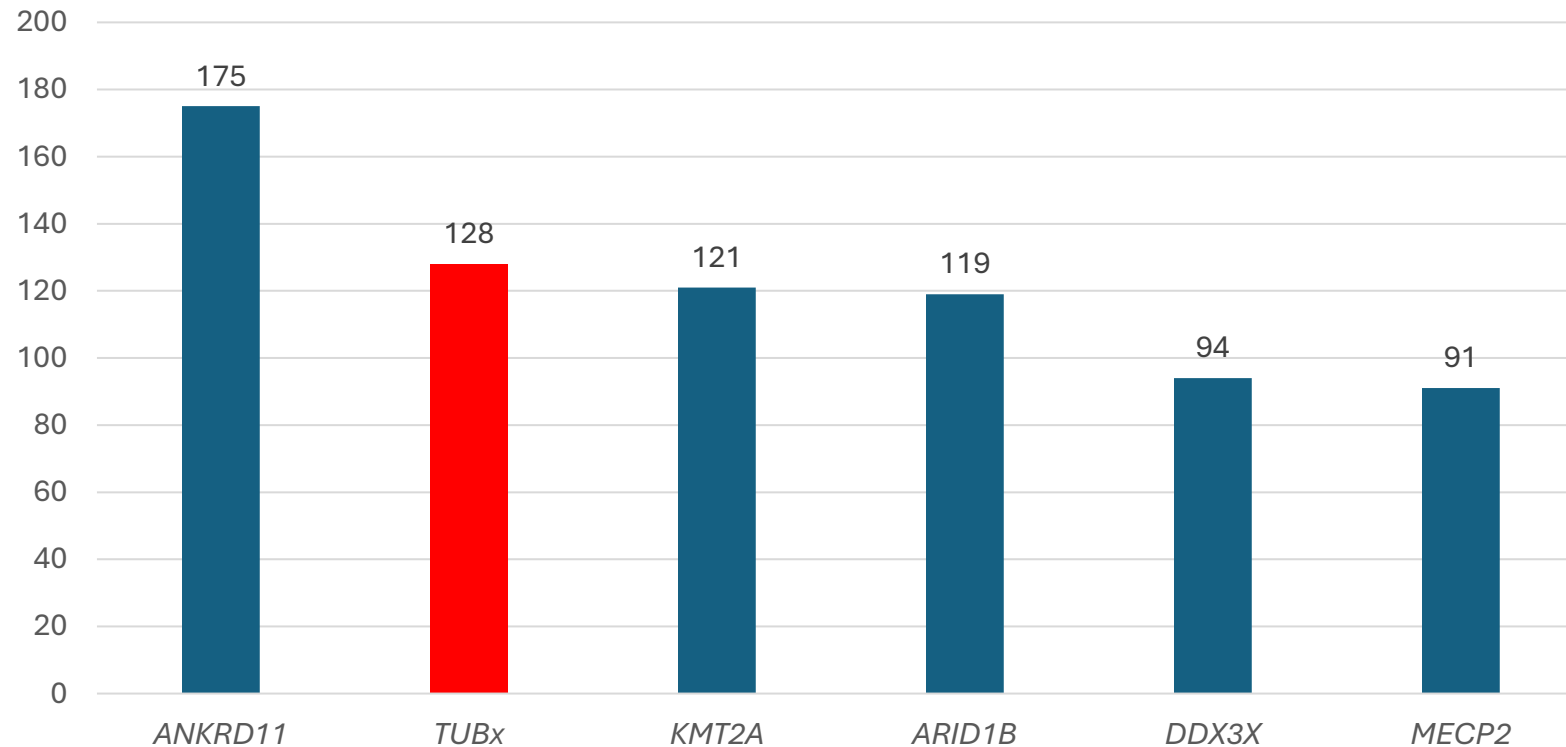
- 27-year-old woman
 - Severe intellectual disability and epilepsy
 - Hydrocephalus in infancy (no shunt)
 - In foster care from age 2 years
 - Mother has refractory epilepsy and intellectual disability
- LIS1 – negative (14 years)
- 8 gene cortical malf panel – negative (16 years)
- WGS – 42.8kb deletion involving exon 2 of CEP85L



Recognising **tubulinopathies** on MRI



How common are tubulinopathies?



Data query 07/01/26

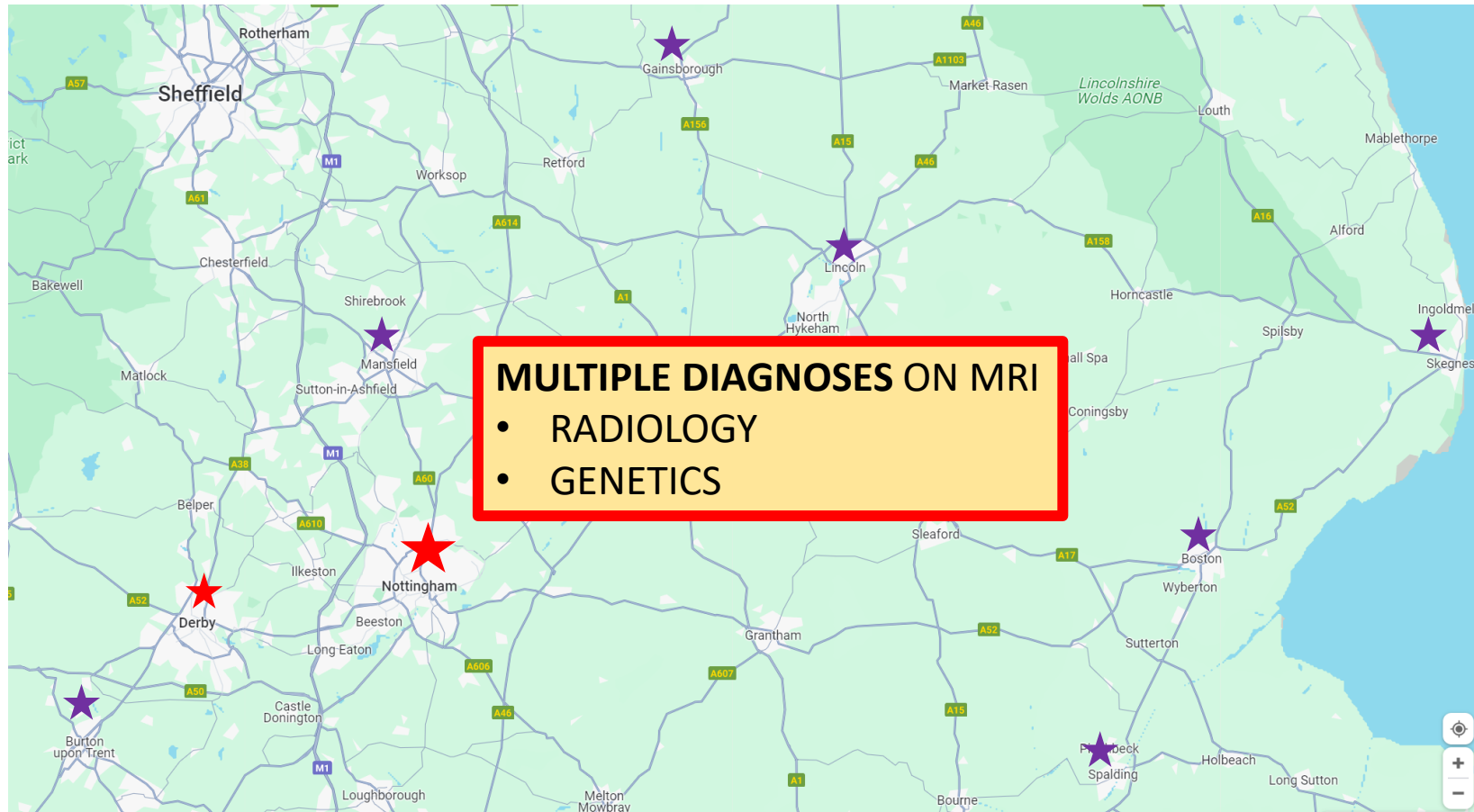
P and LP SNVs

- DDD consortium
- NHS consortium

TUBx includes

- *TUBA1A* – 60
- *TUBB3* – 34
- *TUBB* – 15
- *TUBB2B* – 9
- *TUBB2A* – 6
- *TUBG1* – 4

East Midlands region of England – pop ~2.5 million



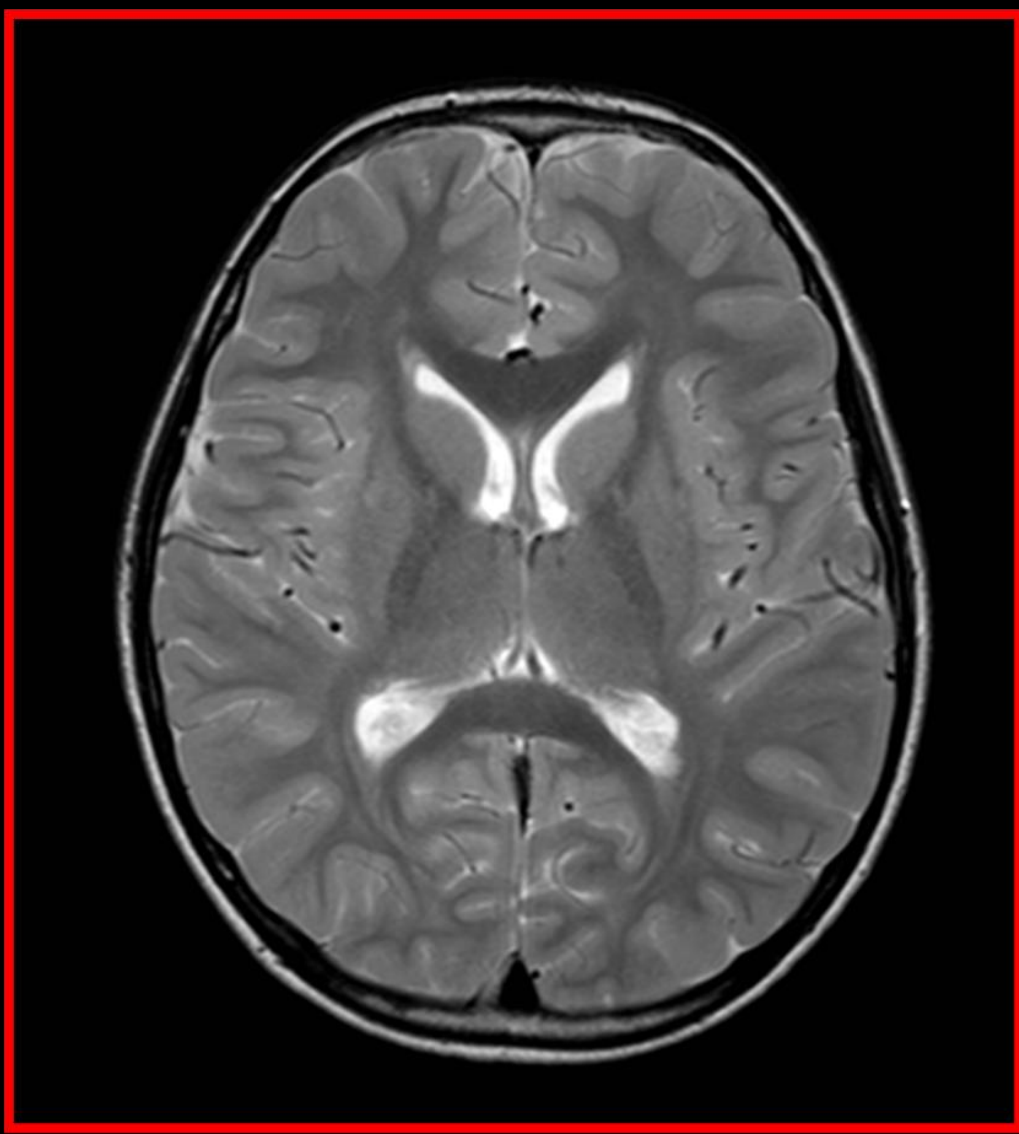
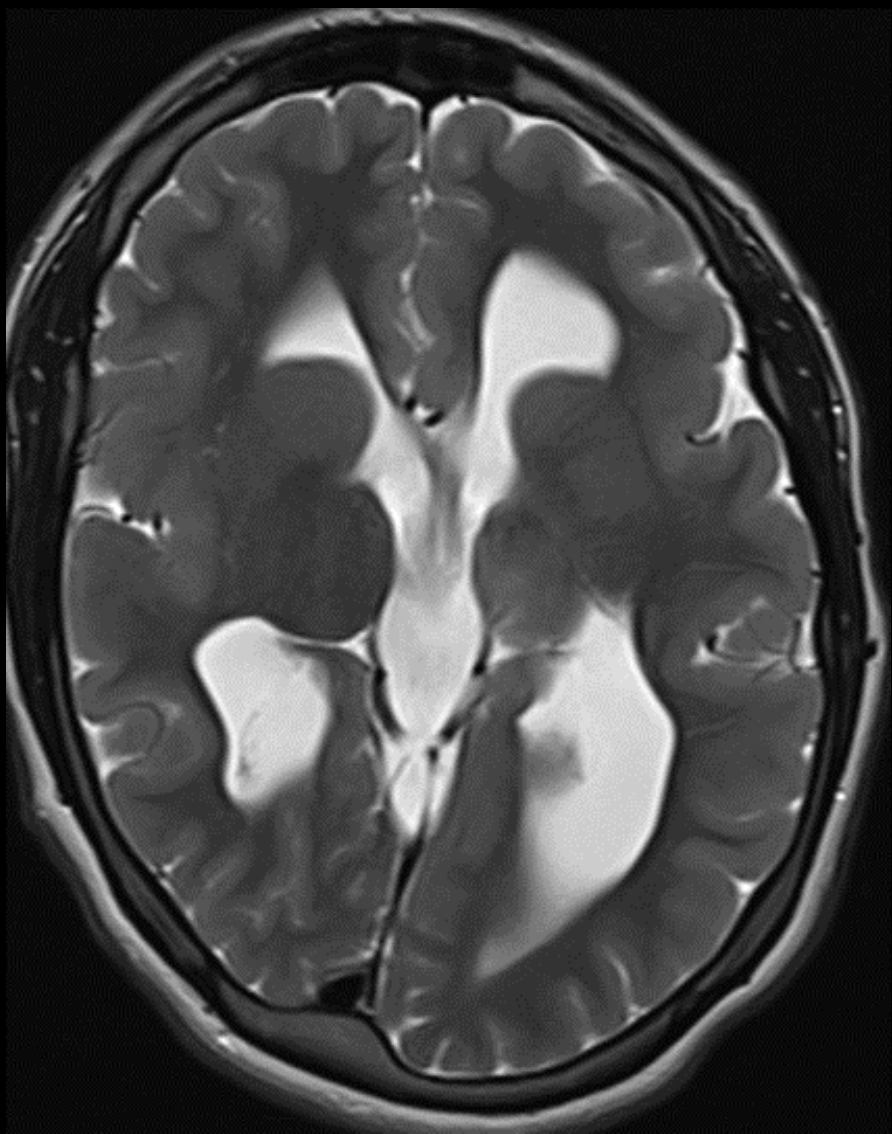
MULTIPLE DIAGNOSES ON MRI

- RADIOLOGY
- GENETICS

35 patients

- *TUBA1A* – 11
- *TUBB* – 17 (!)
- *TUBB3* – 4
- *TUBB2B* – 1
- *TUBB2A* – 1
- No testing – 1

- One large *TUBB* family
- Prenatal diagnosis
- Older adults
- *TUBB3* E410K syndrome

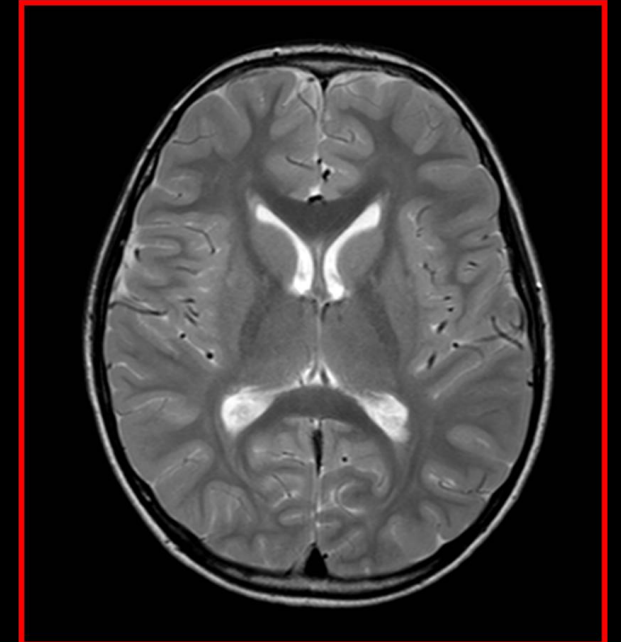
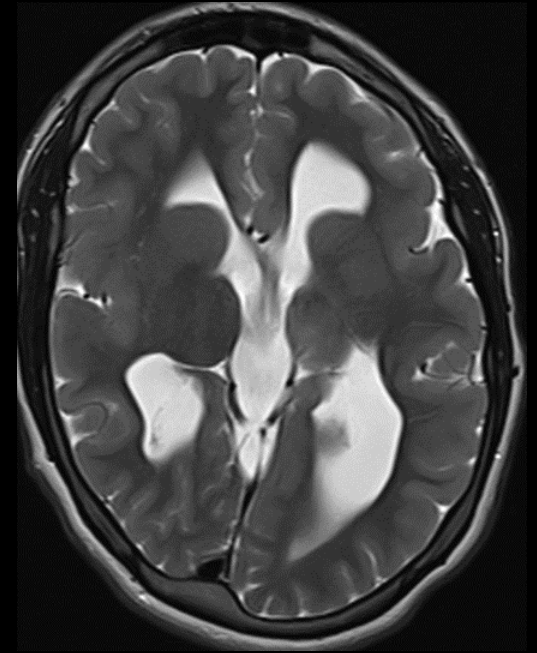


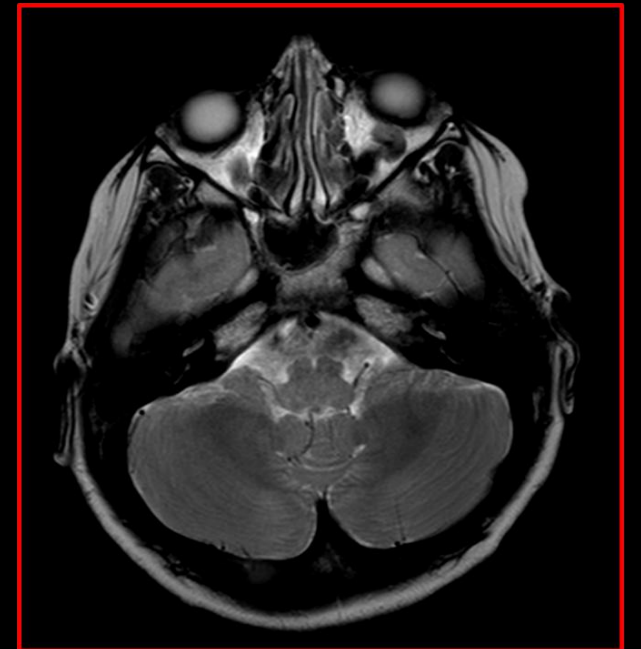
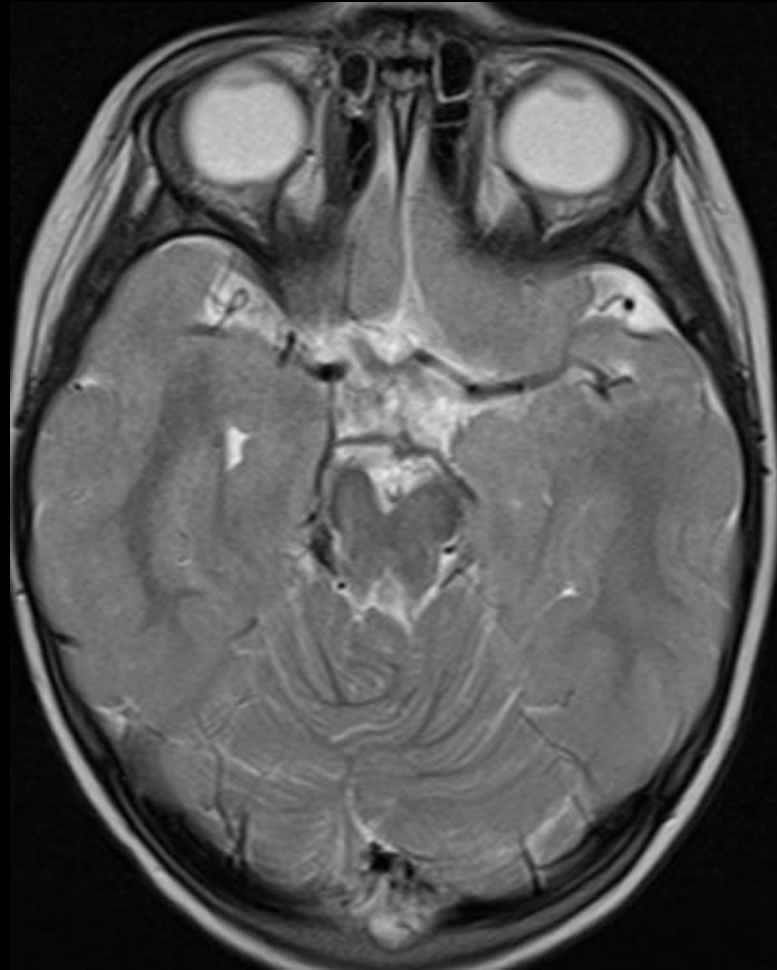
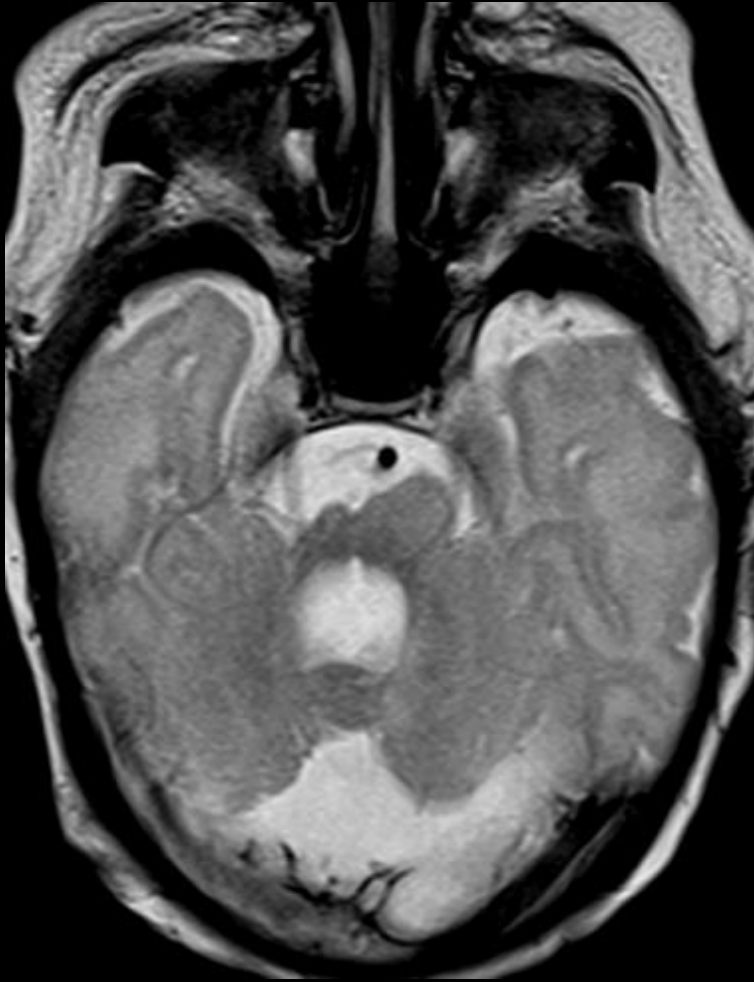
Characteristic features

- **Dysgyria***
 - Polymicrogyria, simplified gyral pattern, pachygyria, lissencephaly
- **Dysmorphic (malrotated) basal ganglia**
 - Asymmetric
 - ALIC not visible in axial views
 - Appear enlarged, fused and rounded
 - Anterior horn of lateral ventricle appears hooked over caudate head

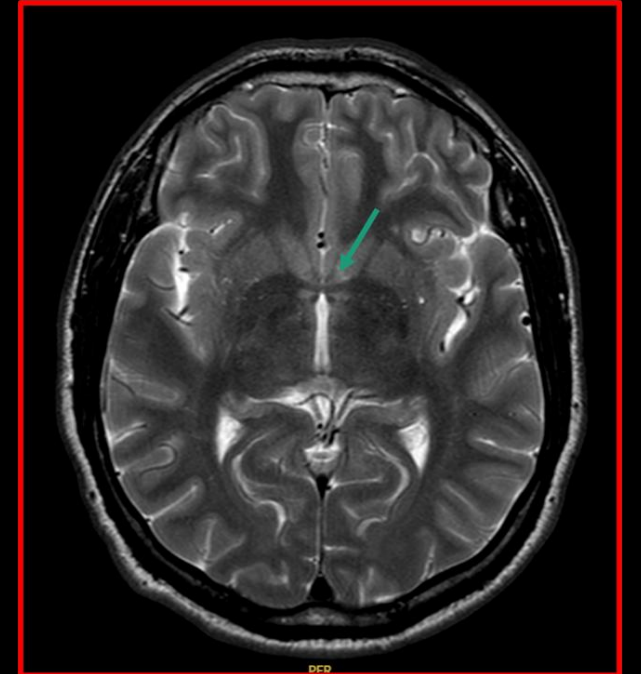
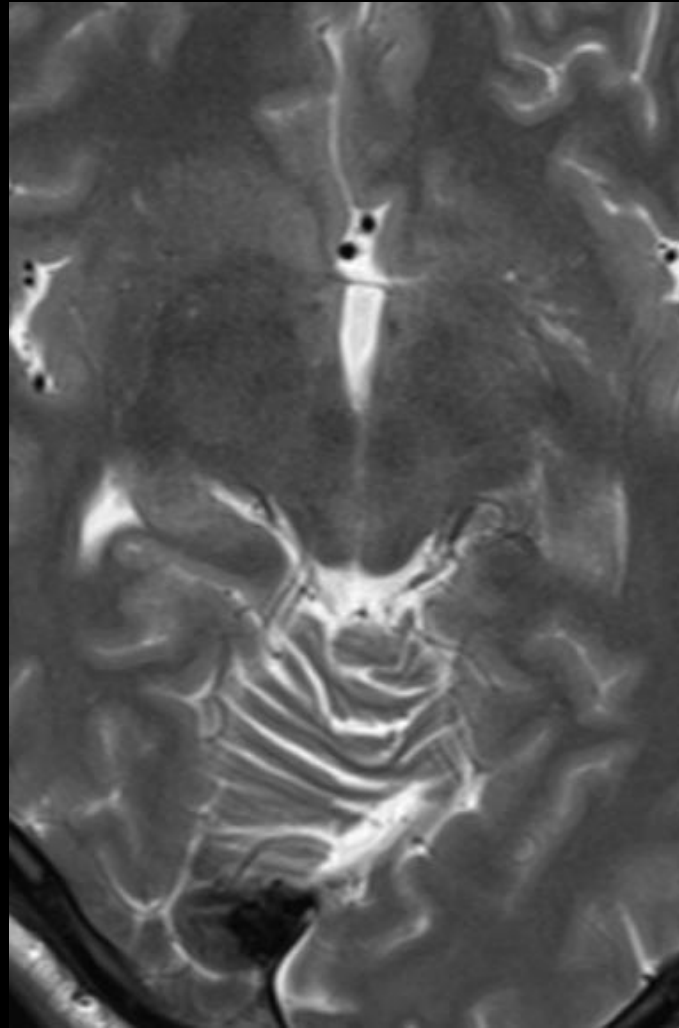
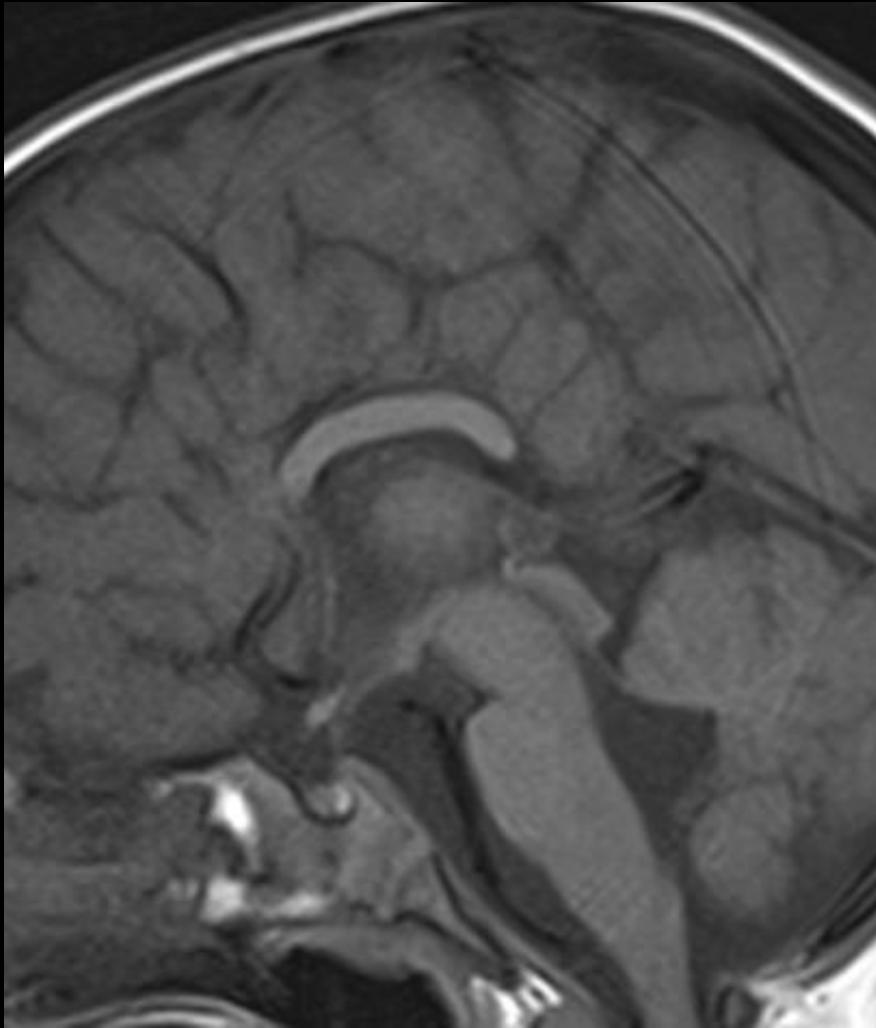
*Dysgyria – no easy definition; can be diffuse or focal

- Cortex thickness is normal
- Sulcal depth and orientation abnormal
- Narrow gyri with abnormally deep or shallow sulci
- Radial or irregular orientation of sulci not s/o PMG or SGP

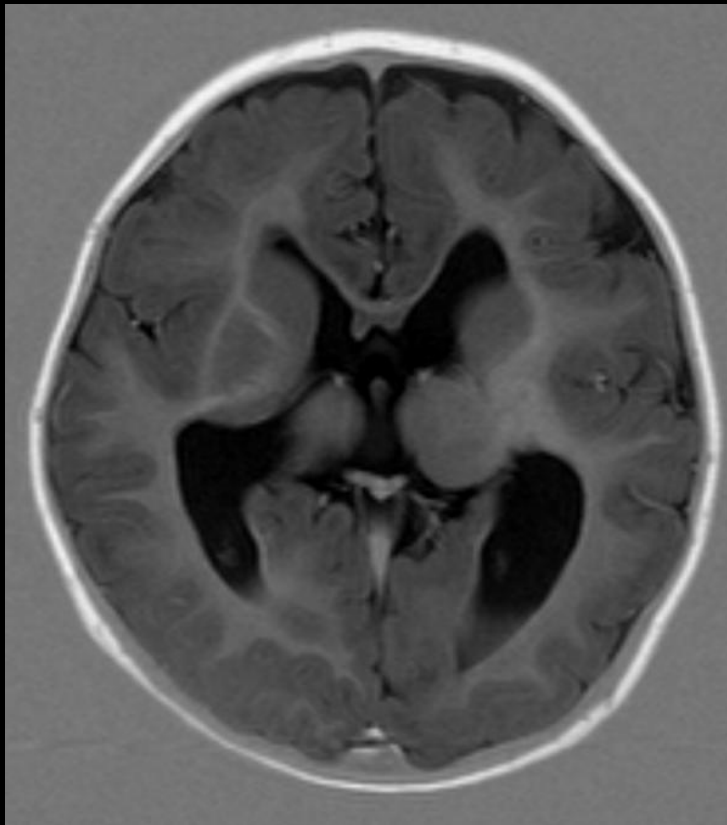




Asymmetry of brainstem, dysplastic cerebellar hemispheres but no cysts
Diagonal folia in superior cerebellum

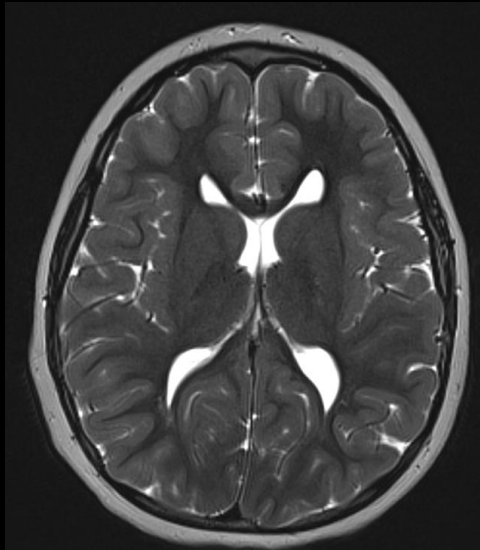
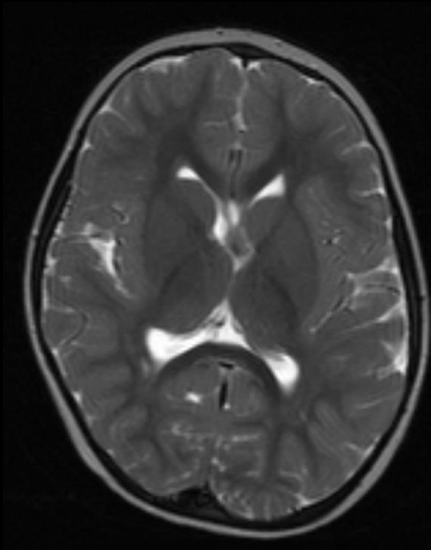
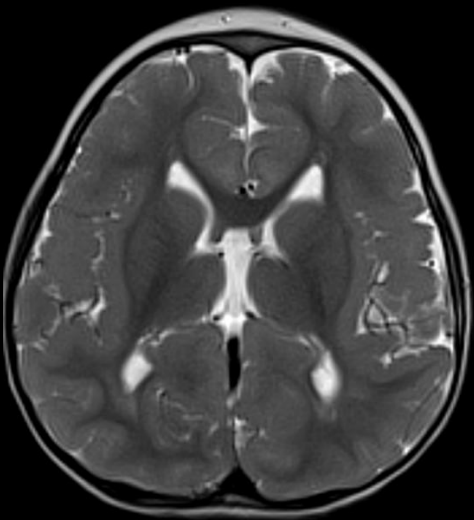
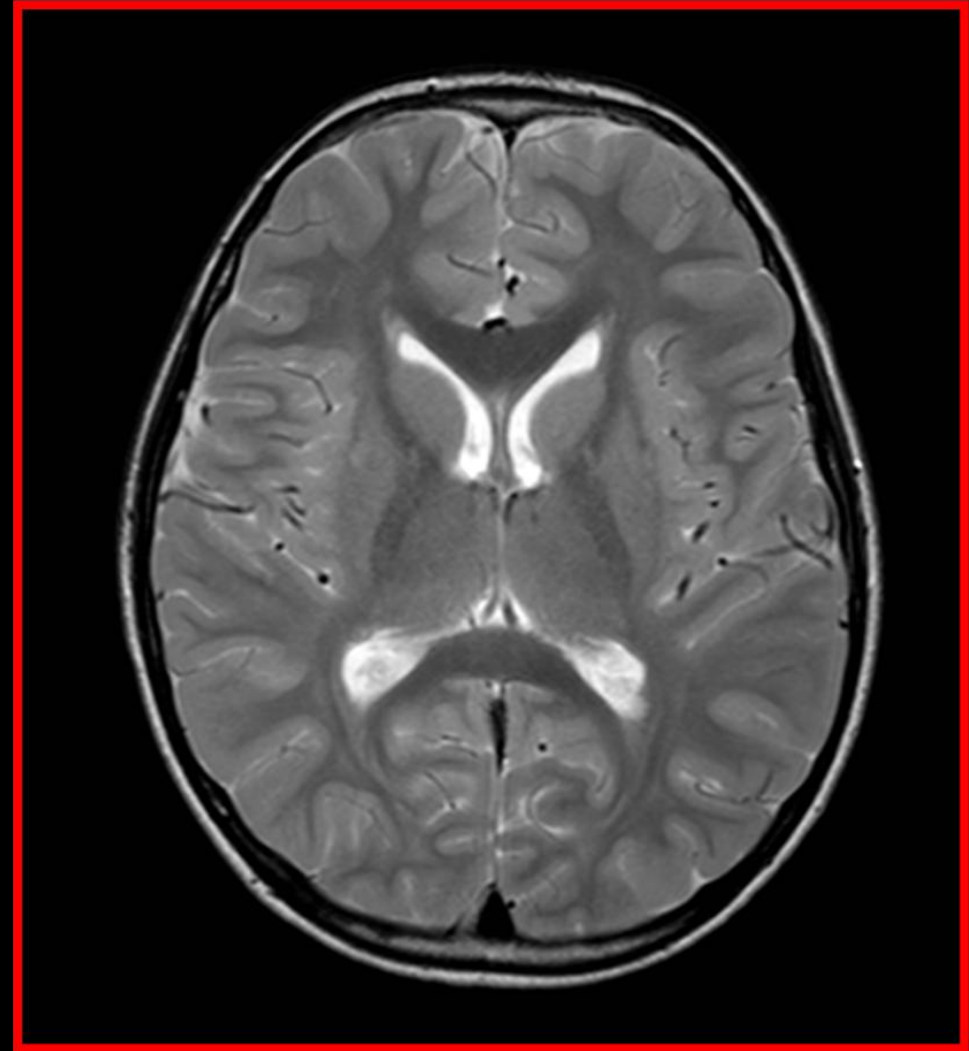


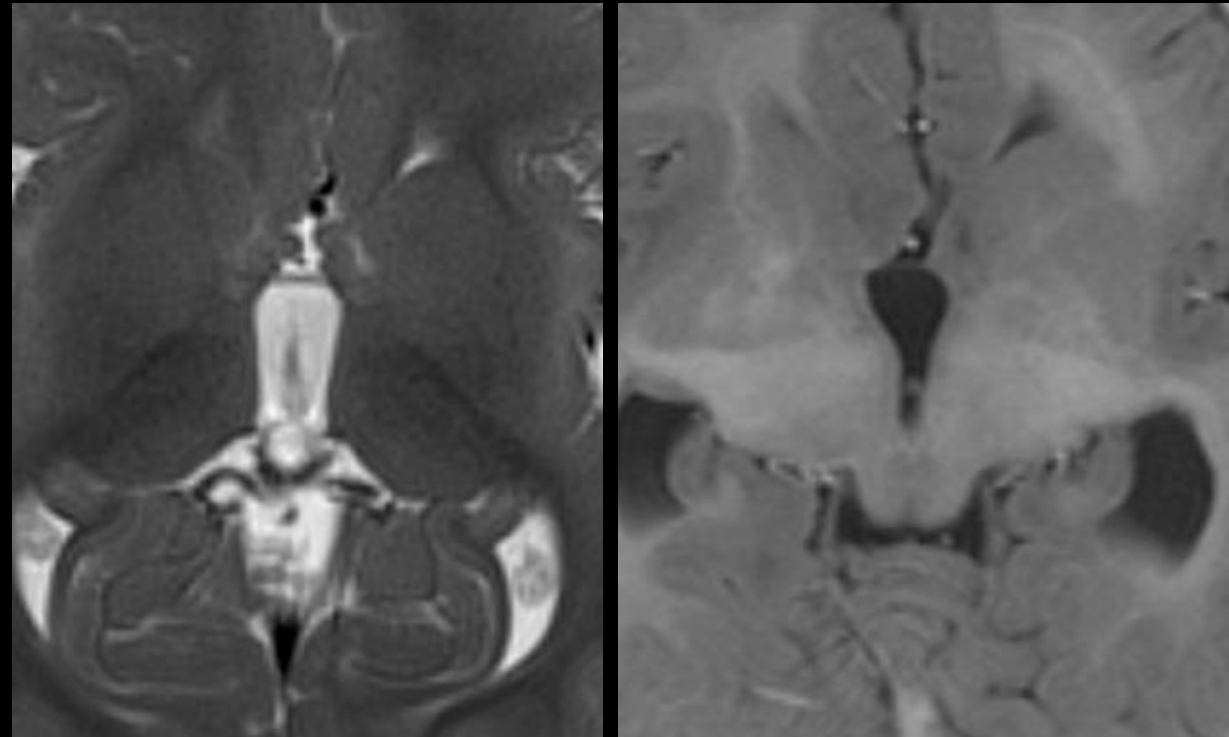
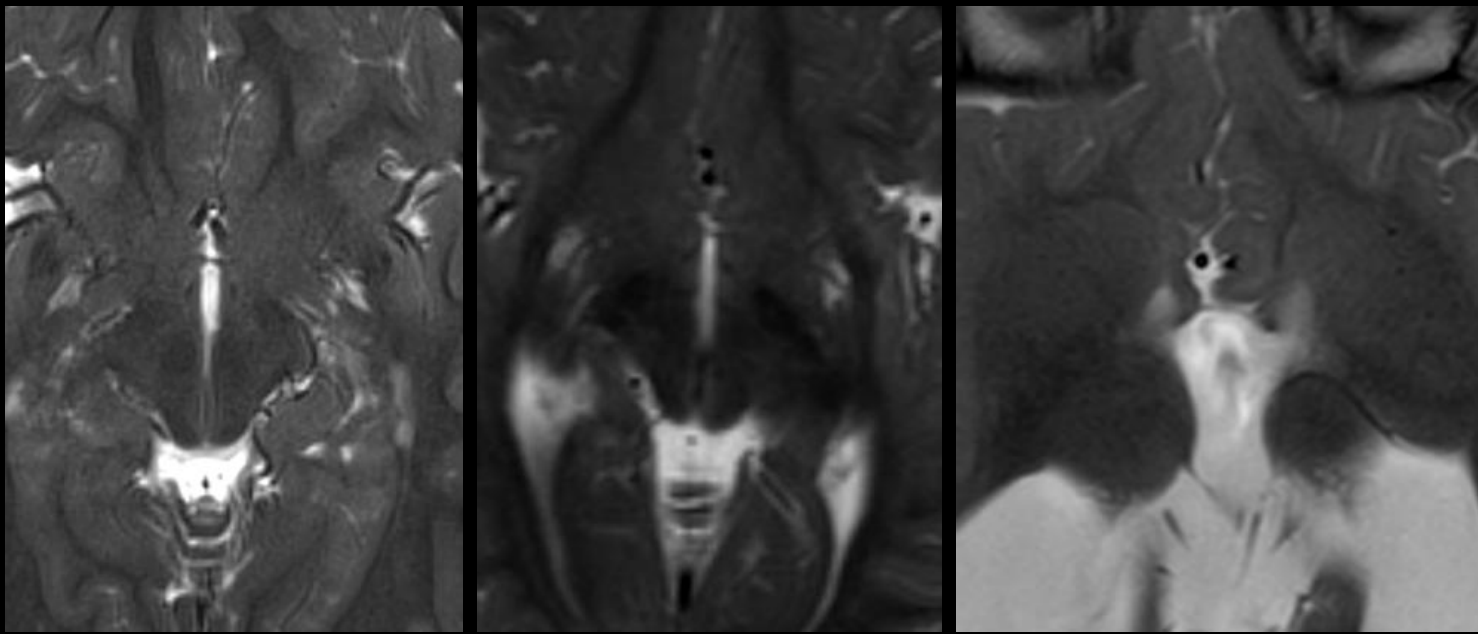
Corpus callosum abn (any) – short, thin, absent, dysgenetic **PLUS**
absent or hypoplastic anterior commissure



TUBA1A

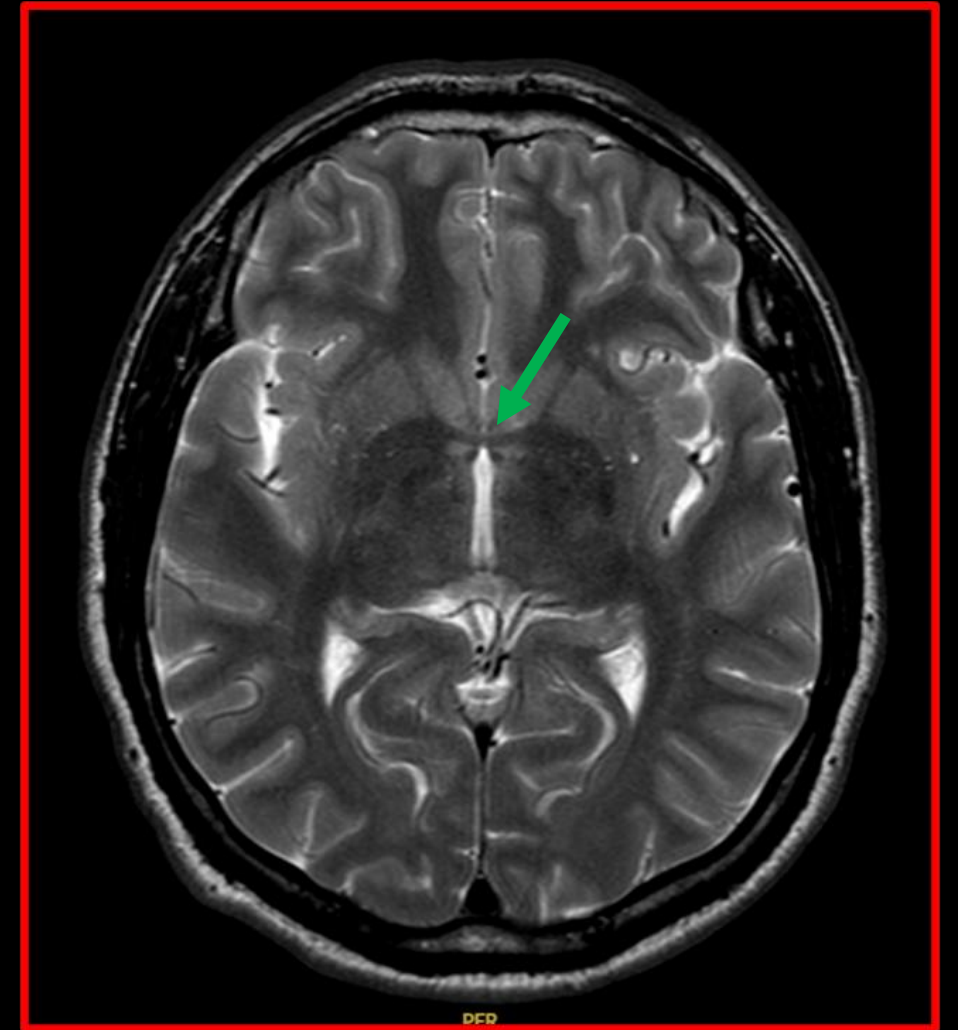
- Basal ganglia malrotation – severe to mild

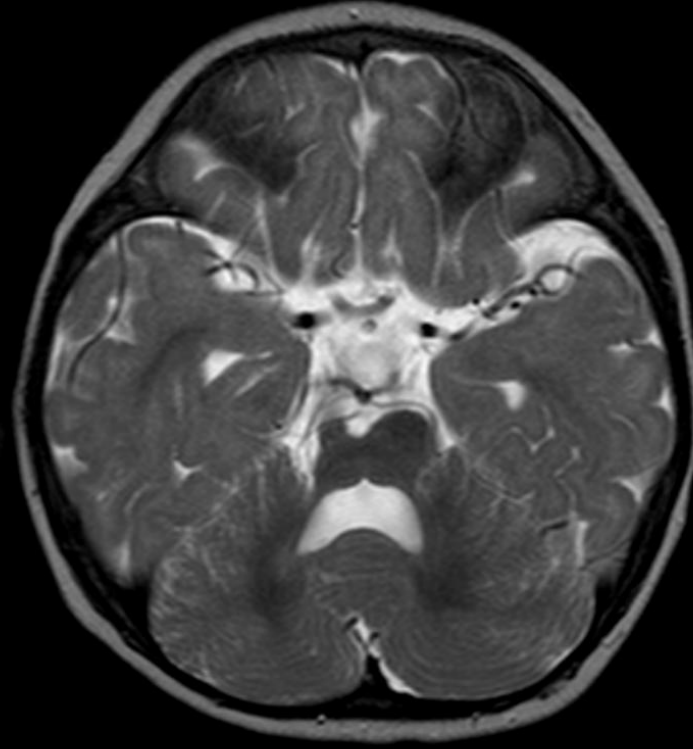




TUBA1A

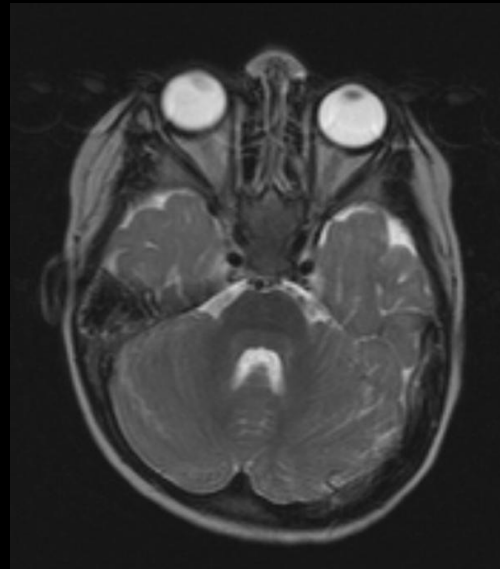
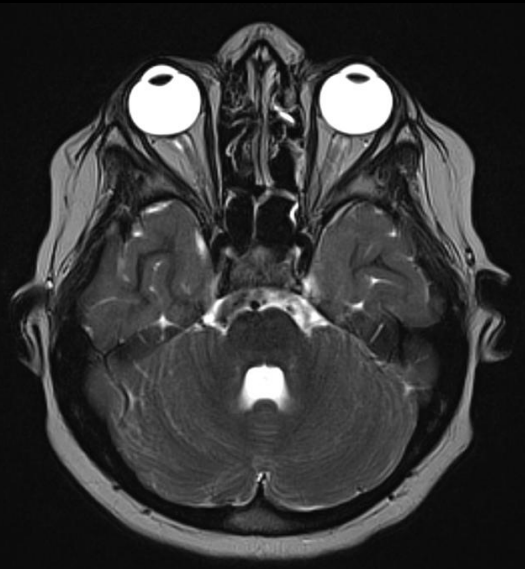
- Hypoplastic anterior commissure

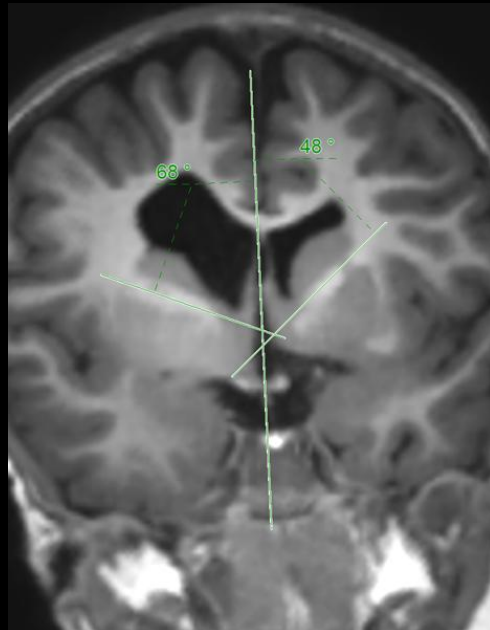
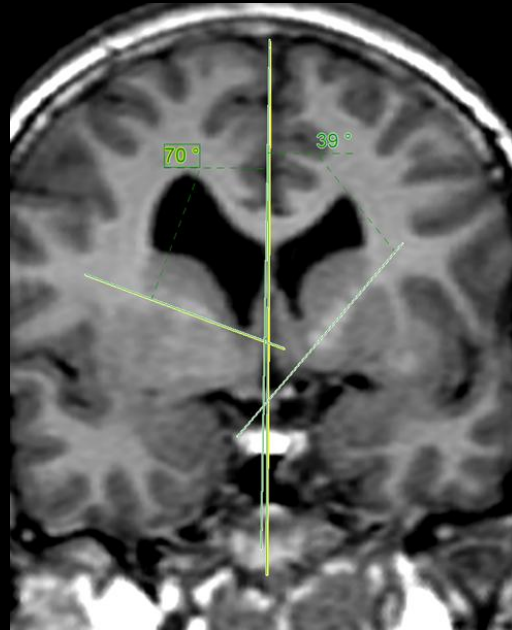
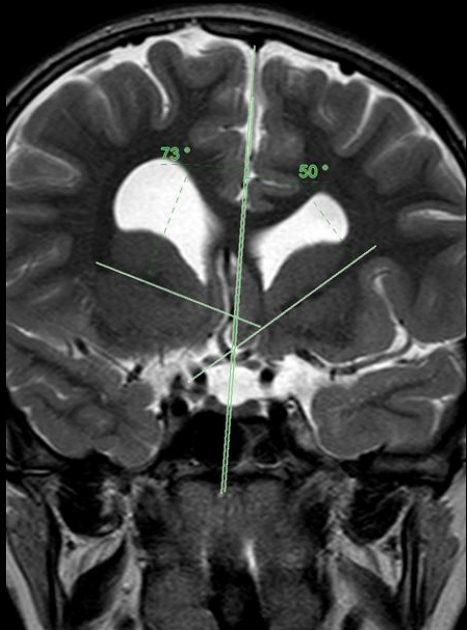
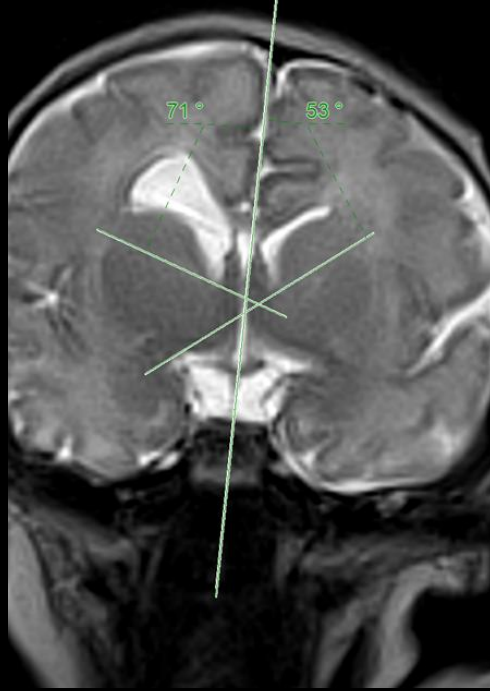
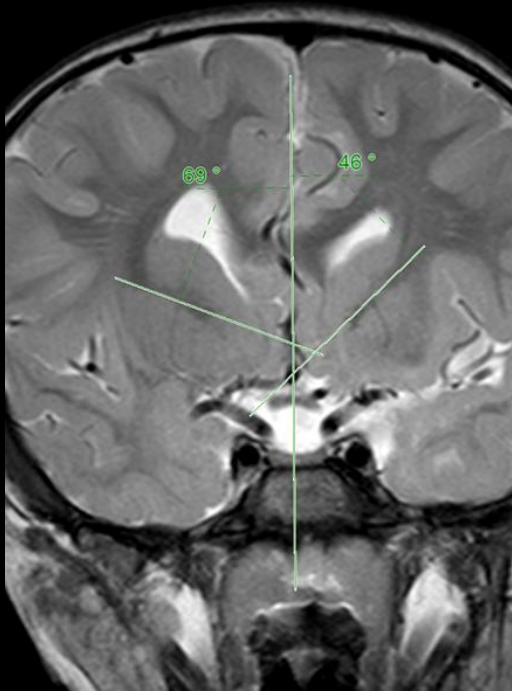
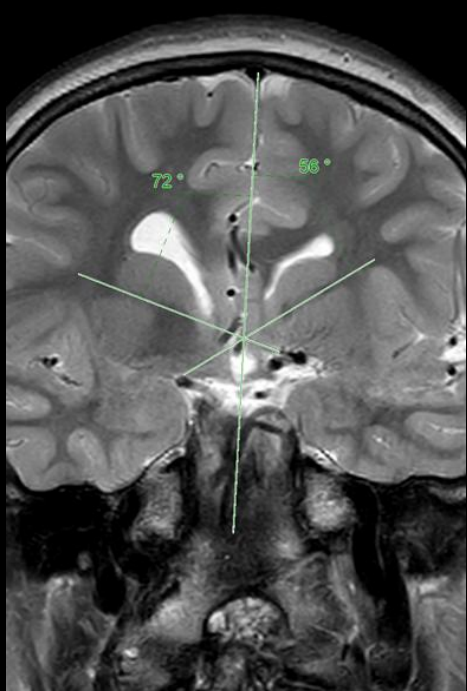




TUBA1A

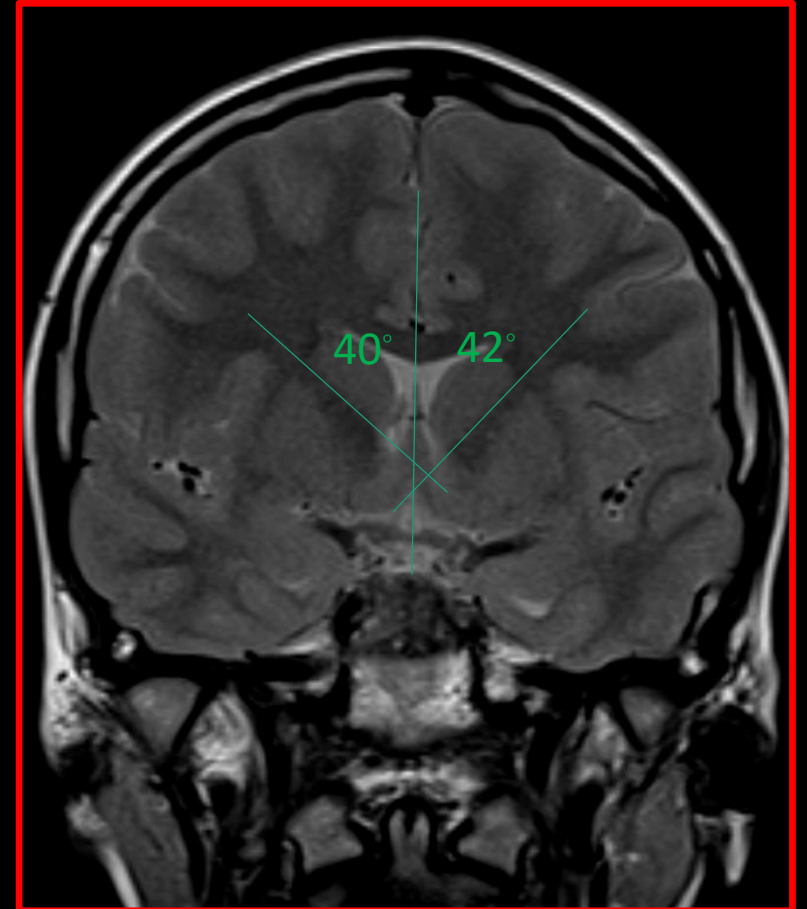
- Cerebellar and brainstem findings





TUBB

- Internal capsule angle



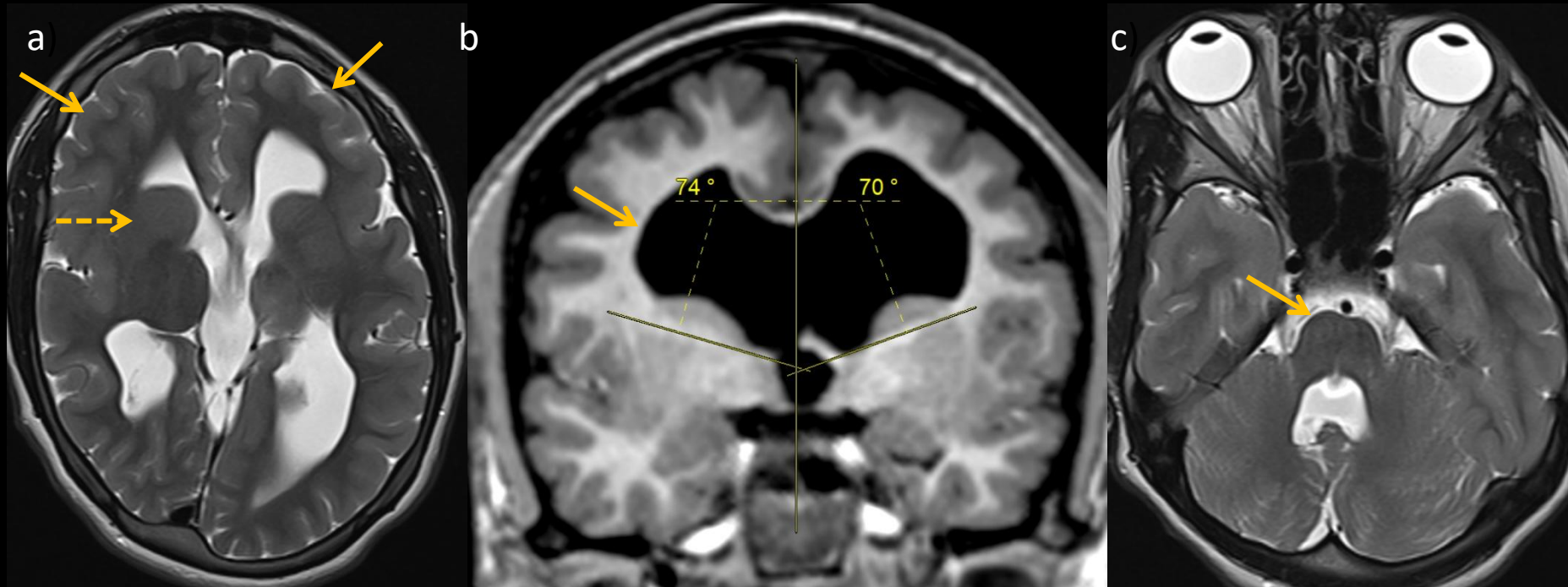
Scoring system for tubulinopathies

Feature				
Cortex	0 – normal	1 – mild	2 – moderate	3 – severe
Basal ganglia	0 – normal	1 – mild	2 – moderate	3 – severe
Corpus callosum	0 – normal	1 – mild	2 – moderate	3 – severe
Anterior commissure	0 – normal		2 – moderate	3 – severe
Cerebellum	0 – normal	1 – mild	2 – moderate	3 – severe
Brainstem	0 – normal	1 – mild	2 – moderate	3 – severe

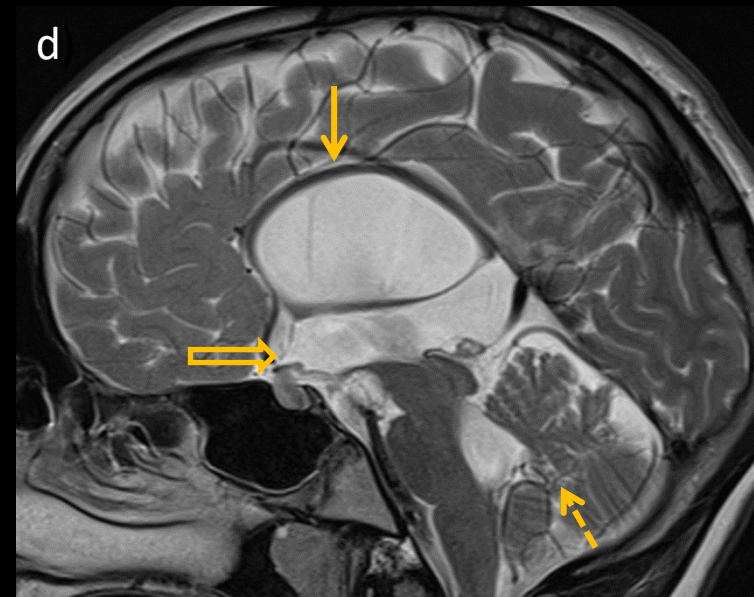
Maximum score – 18

- Mild – 0 to 6
- Moderate – 7 to 12
- Severe – 13 to 18

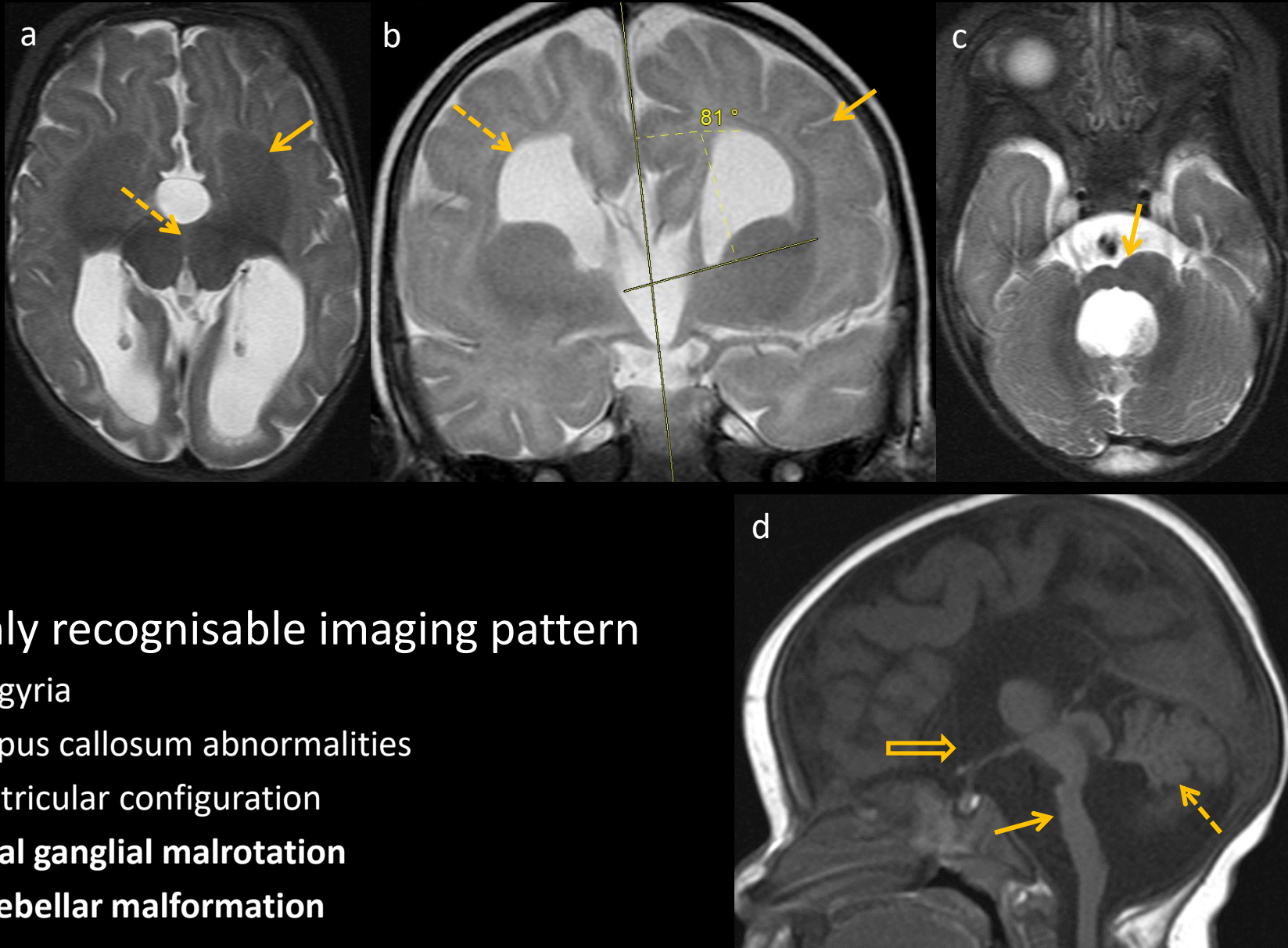
Score of ≥ 5 , including points for basal ganglia and/or anterior commissure, will be a sensitive and specific marker for tubulinopathies



- A highly recognisable imaging pattern
 - Dysgyria
 - Corpus callosum abnormalities
 - Ventricular configuration
 - **Basal ganglia malrotation**
 - **Cerebellar malformation**
 - Brainstem asymmetry

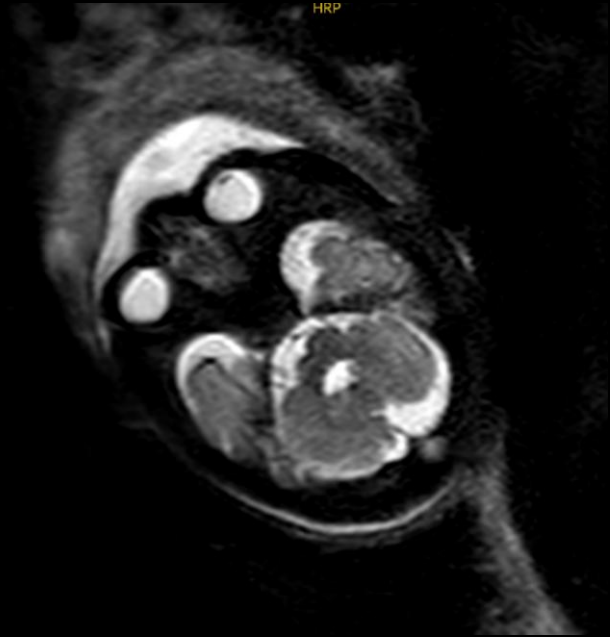
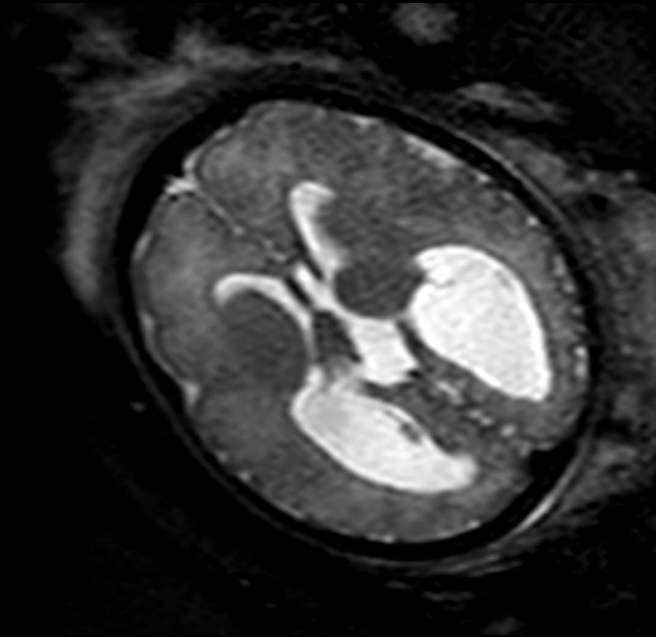


TUBA1A
moderate



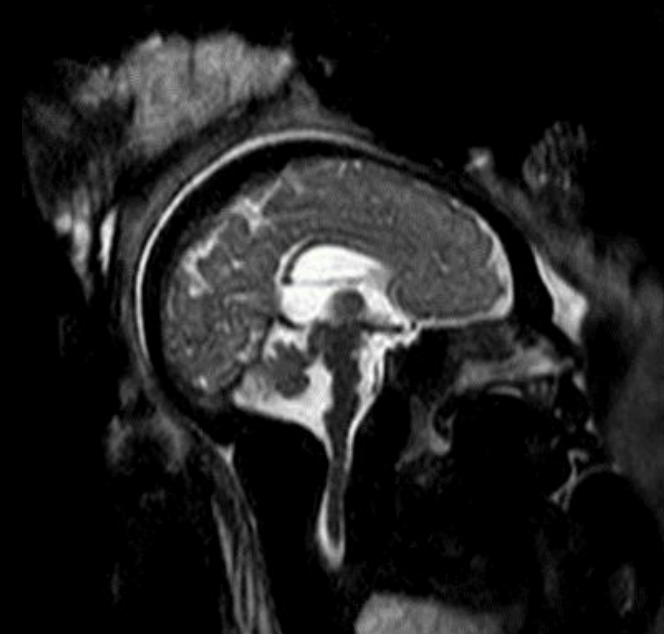
- A highly recognisable imaging pattern
 - Dysgyria
 - Corpus callosum abnormalities
 - Ventricular configuration
 - **Basal ganglia malrotation**
 - **Cerebellar malformation**
 - Brainstem asymmetry

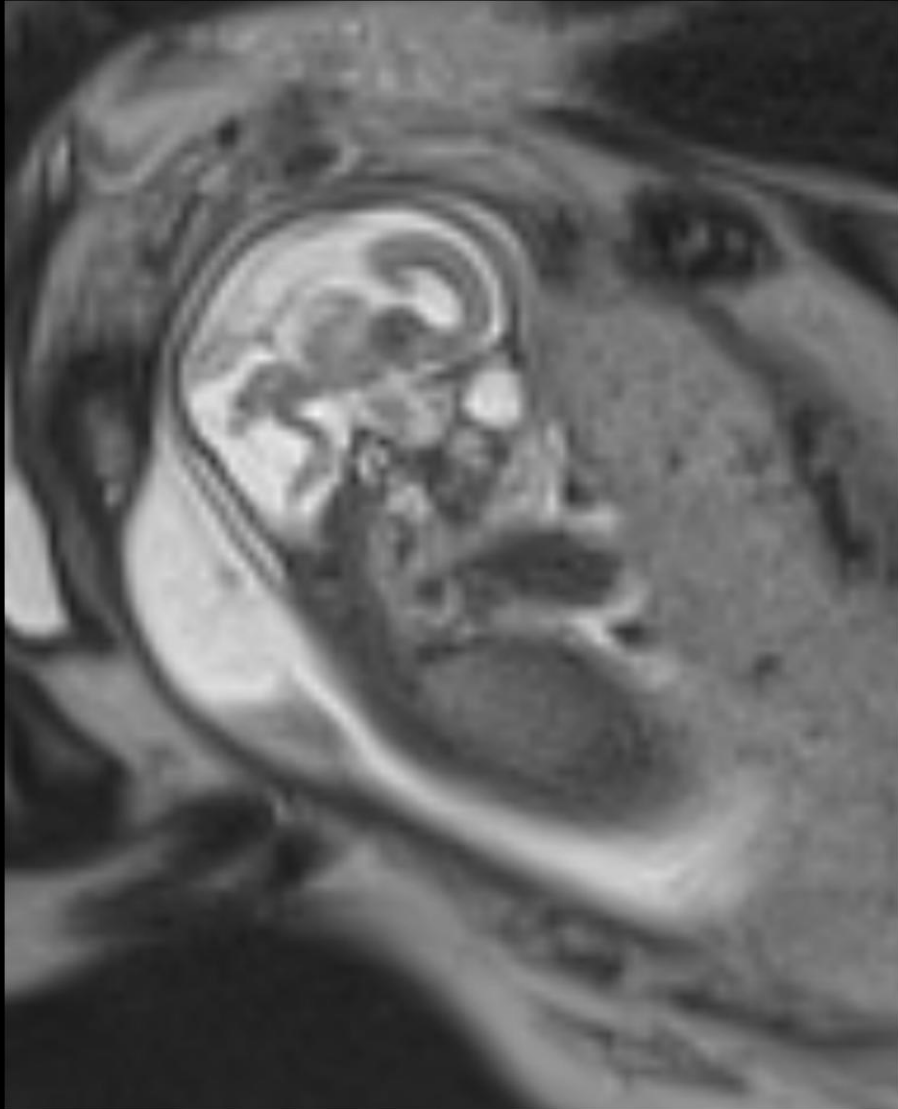
TUBA1A
severe



Asymmetric ventricular dilatation
Malrotation of basal ganglia
Brainstem asymmetry
Flat pons

Fetal tubulinopathy





Fetal MR at 22⁺⁴ weeks

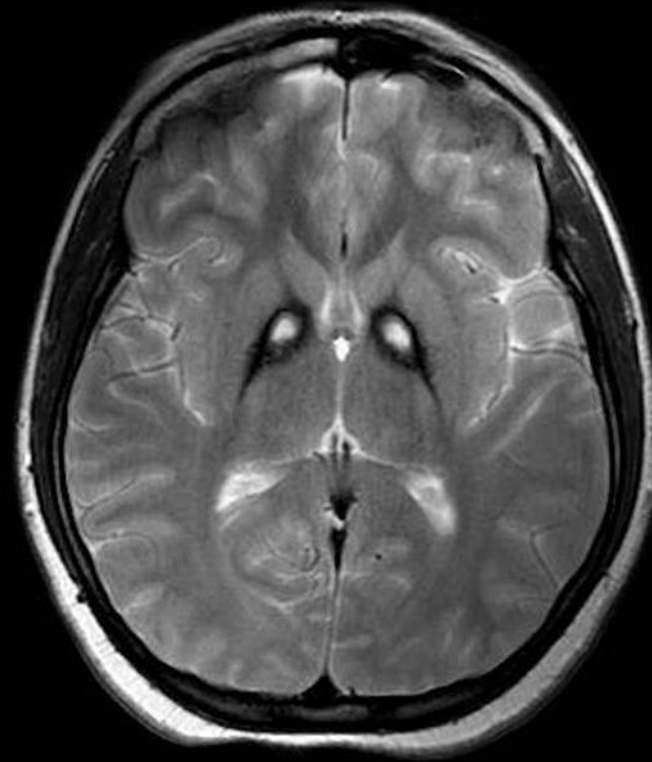
- Microcephaly
- Agenesis of CC
- No sylvian fissure
- **Kinked brainstem**
- Highly suggestive of severe tubulinopathy
- Pregnancy terminated

Urgent trio WGS – as pregnant again

- *De novo* *TUBA1A* 791G>A p.(Arg264His)
- Known recurrent variant associated with microlissencephaly

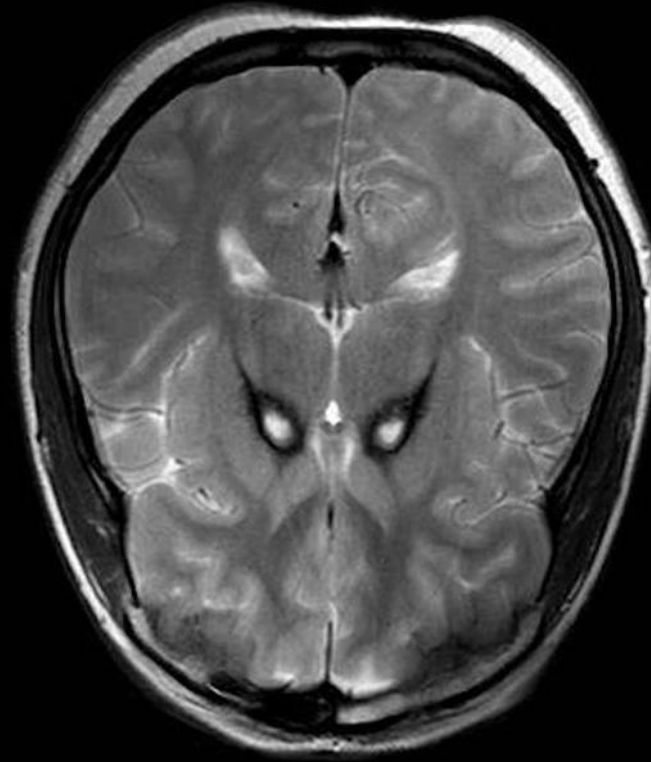
Non-tubulinopathy cases

Neurodegeneration with brain iron accumulation type 1 or Pantothenate kinase associated neurodegeneration (PKAN)

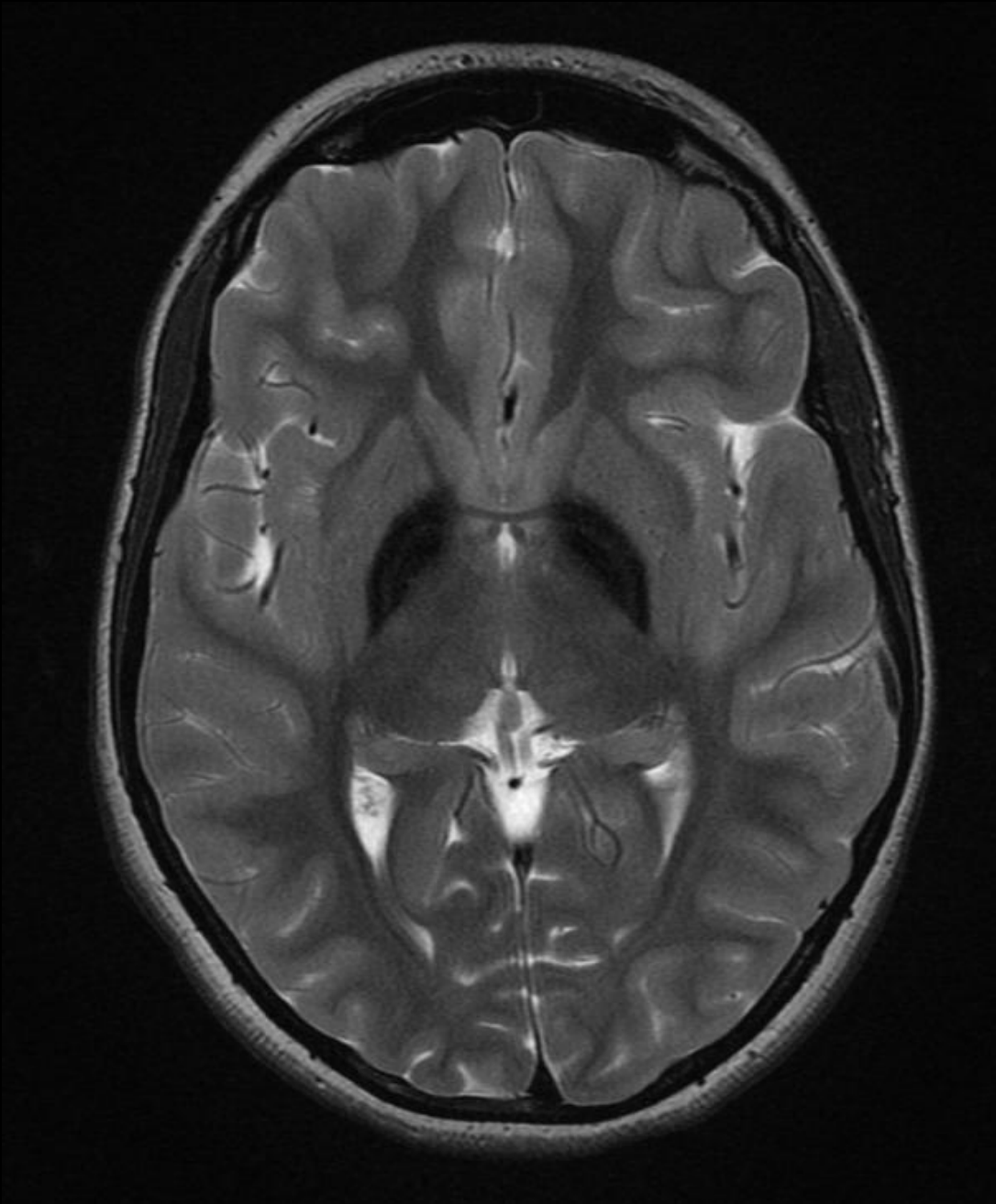


'Eye of the tiger' sign

Neurodegeneration with brain iron accumulation type 1 or Pantothenate kinase associated neurodegeneration (PKAN)



'Eye of the tiger' sign on T2WI

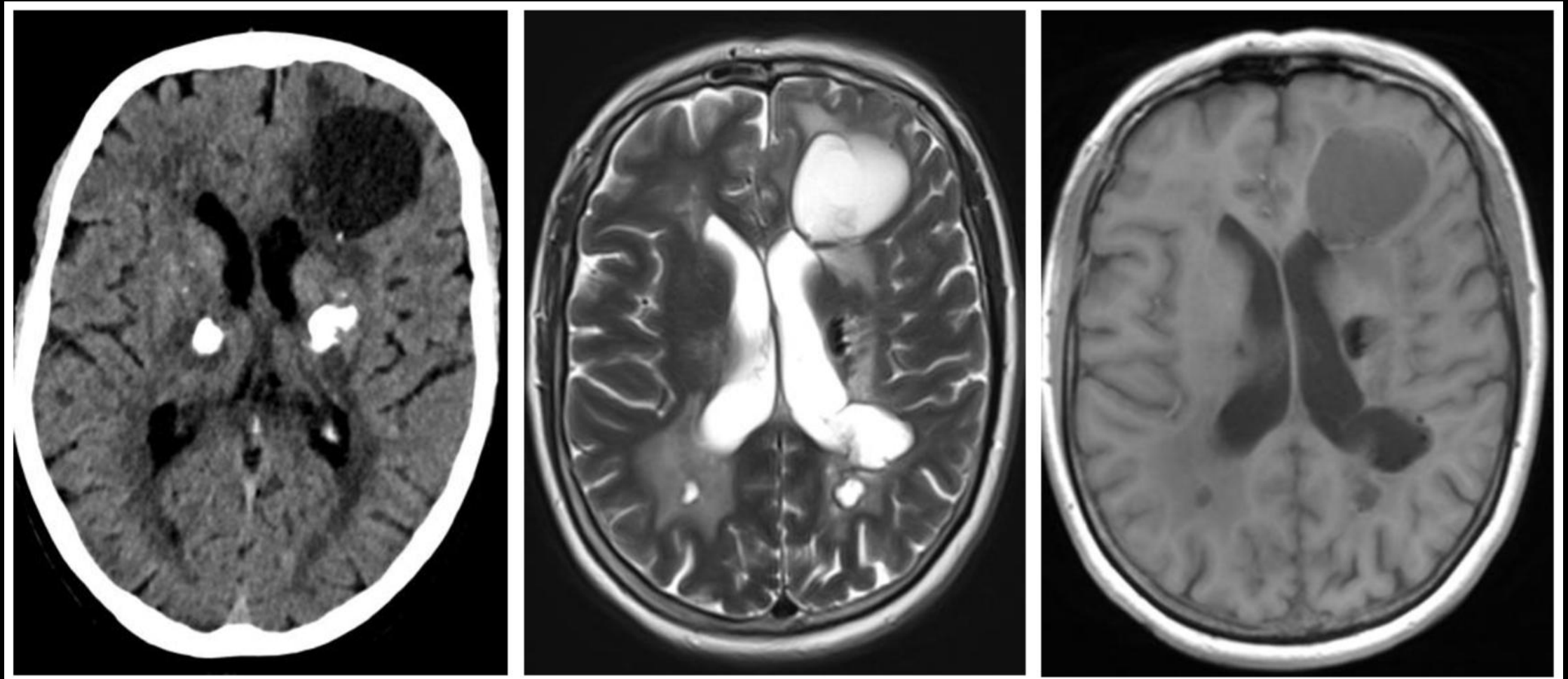


15-year-old girl, speech delay, mild autism spectrum disorder

Iron deposition in bilateral globus pallidus with streaky hyperintensity due to sparing of medial medullary lamina

Heterozygous for c.238C>T p.(Gln80*) variant in *C19orf12*
Mitochondrial Membrane Protein-Associated Degeneration

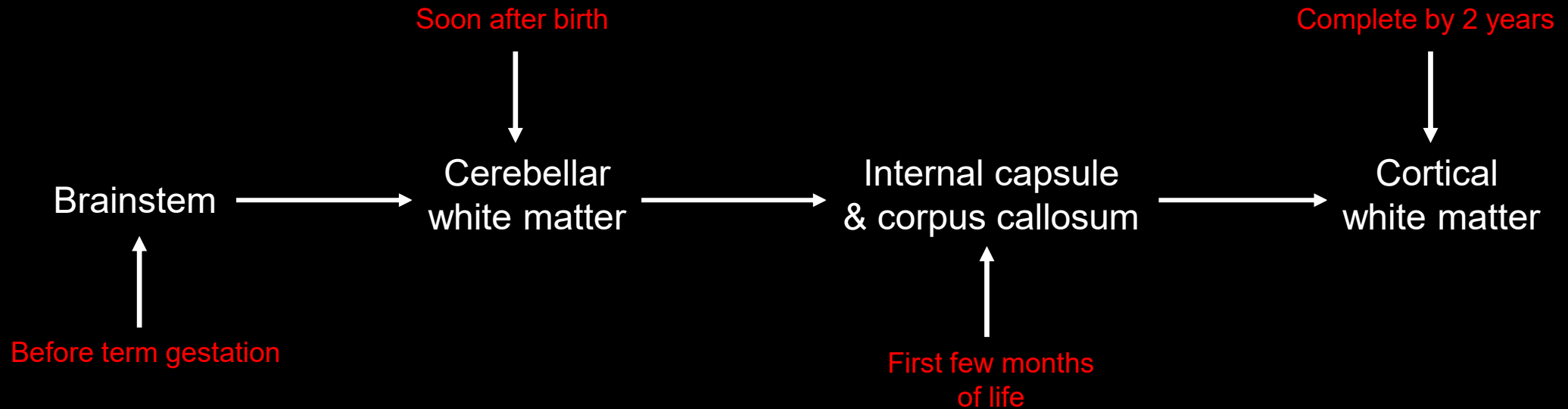
61-year-old woman walking difficulty, foot drop over 5-10 years. On exam, reduced power in R upper and lower limbs. Cognitively normal, mobilises with single stick and ankle splint.



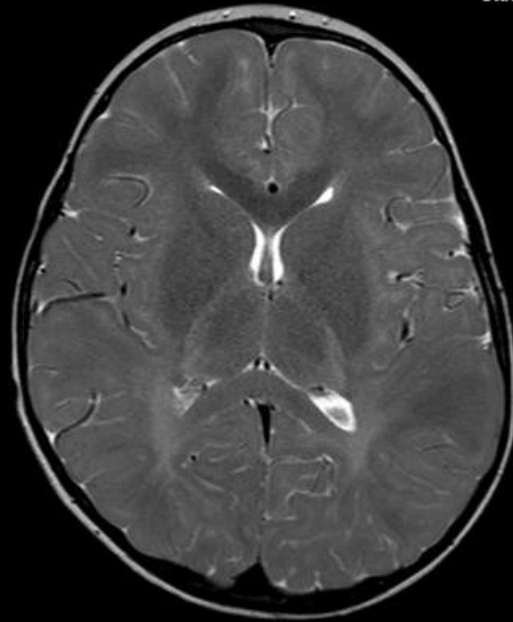
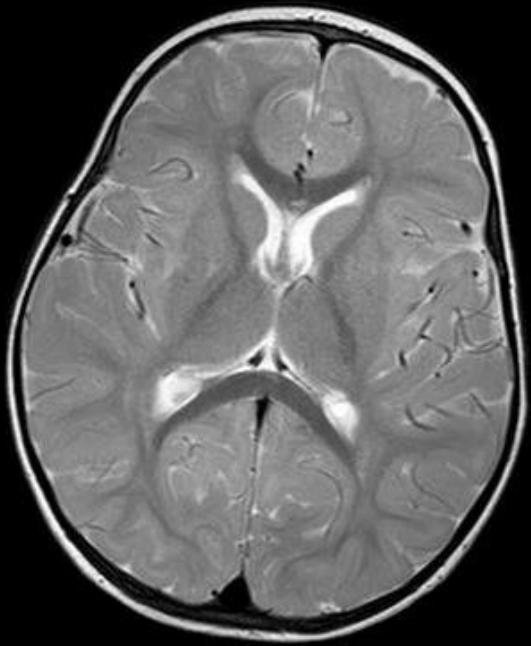
Leukoencephalopathy with calcification and cysts
AR – *SNORD118*

Myelination disorders

Normal sequence of myelination



Delayed myelination

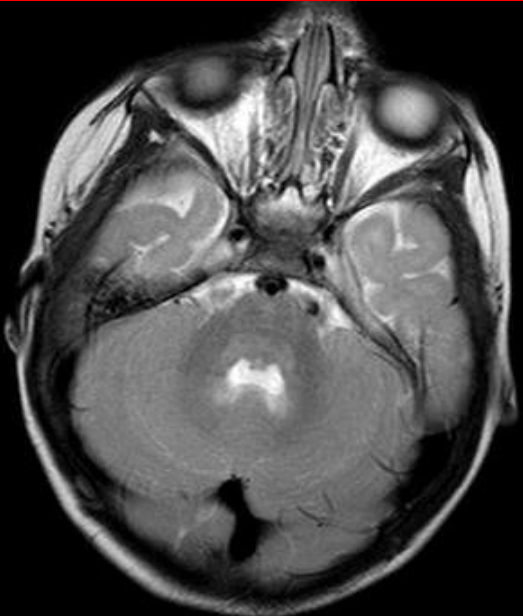


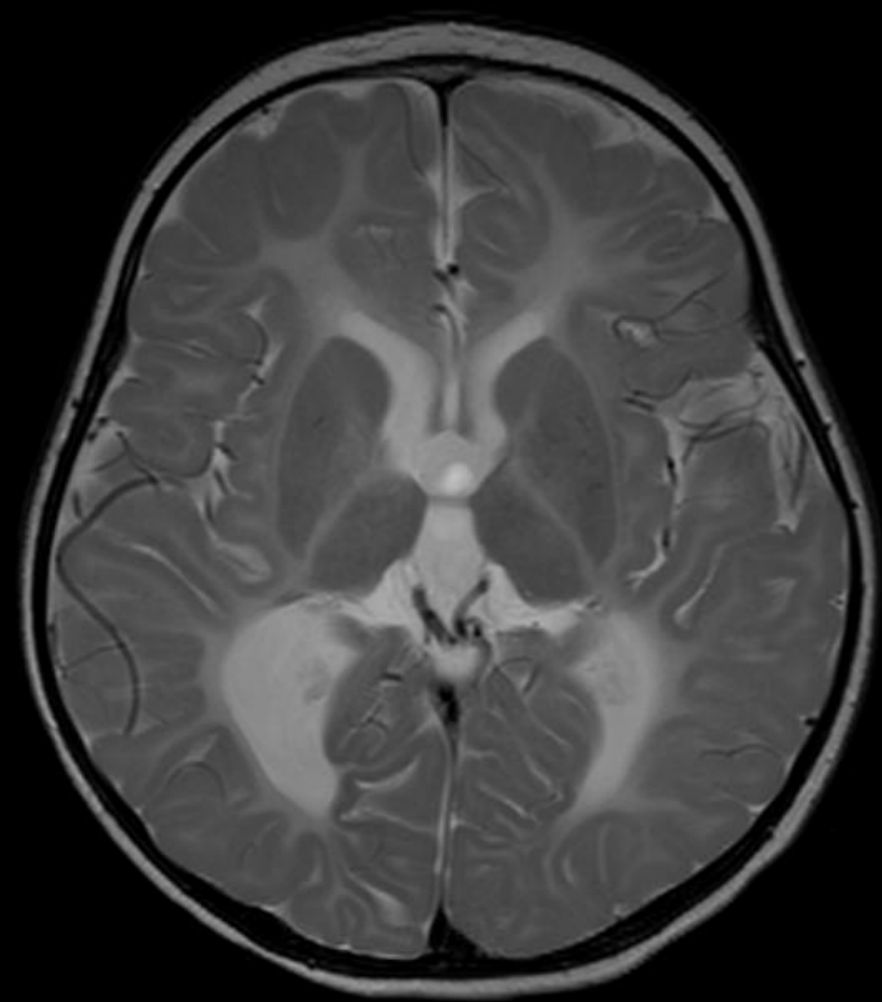
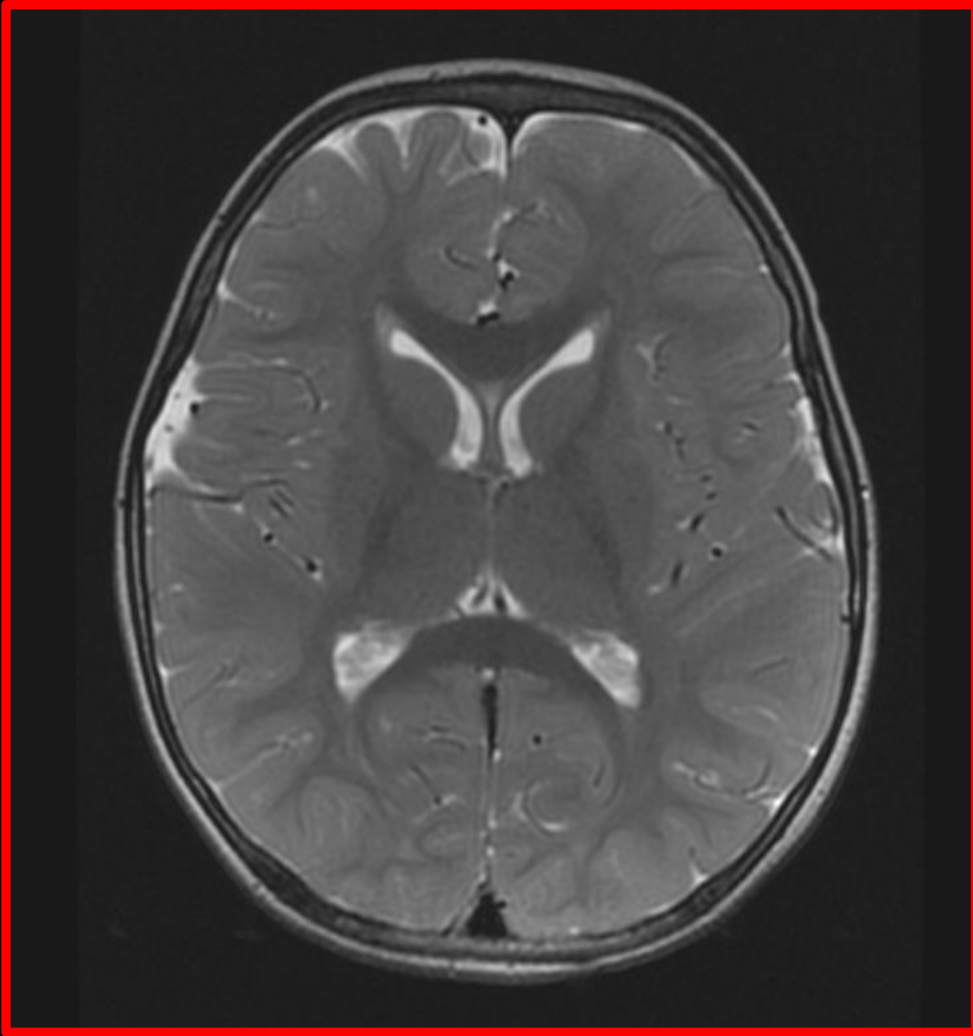
Pelizaeus-Merzbacher
 Pelizaeus-Merzbacher like type 1
 Allan-Herndon-Dudley
 4H or ADDH or TACH
 (POLR3-related disorders)

PLP1
GJC2
SLC16A2
POLR3A
POLR3B
POLR1C
SLC17A5
TUBB4A

Salla disease
 HABC

NACC1
RARS
FAM126A

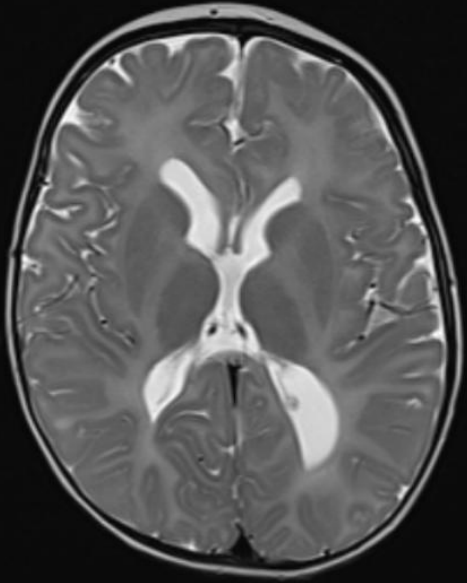




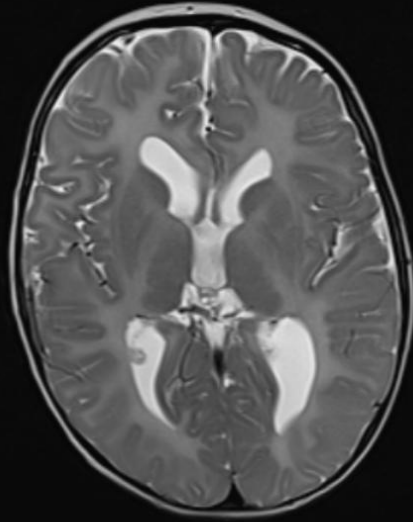
Congenital hypotonia, and global developmental delay

Metabolic screen – elevated sialic acid

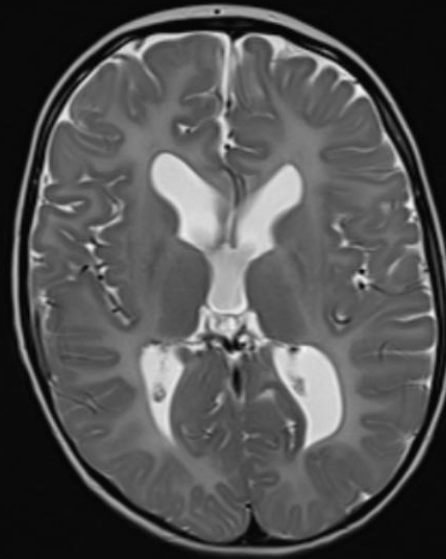
Intermediate-severe sialic acid storage disorder



11 months

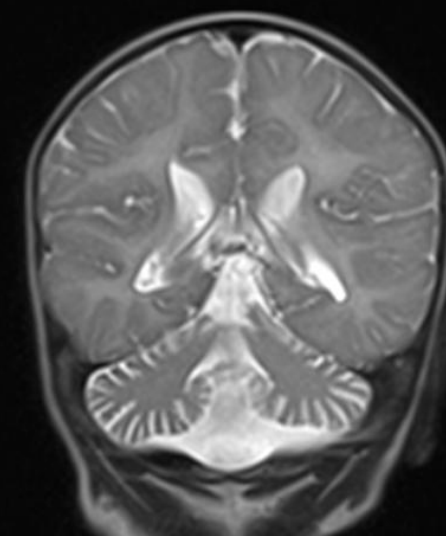
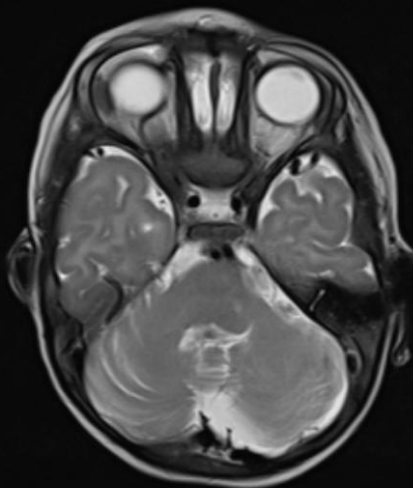
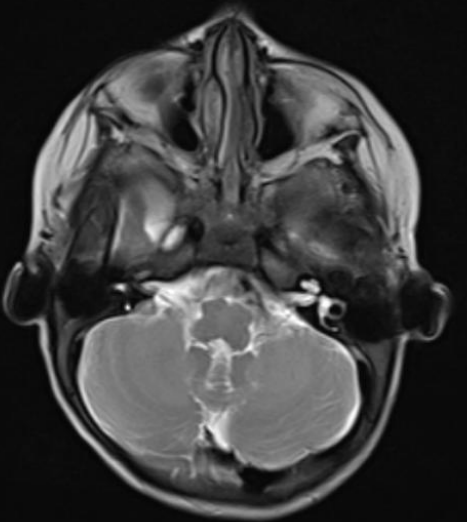


18 months

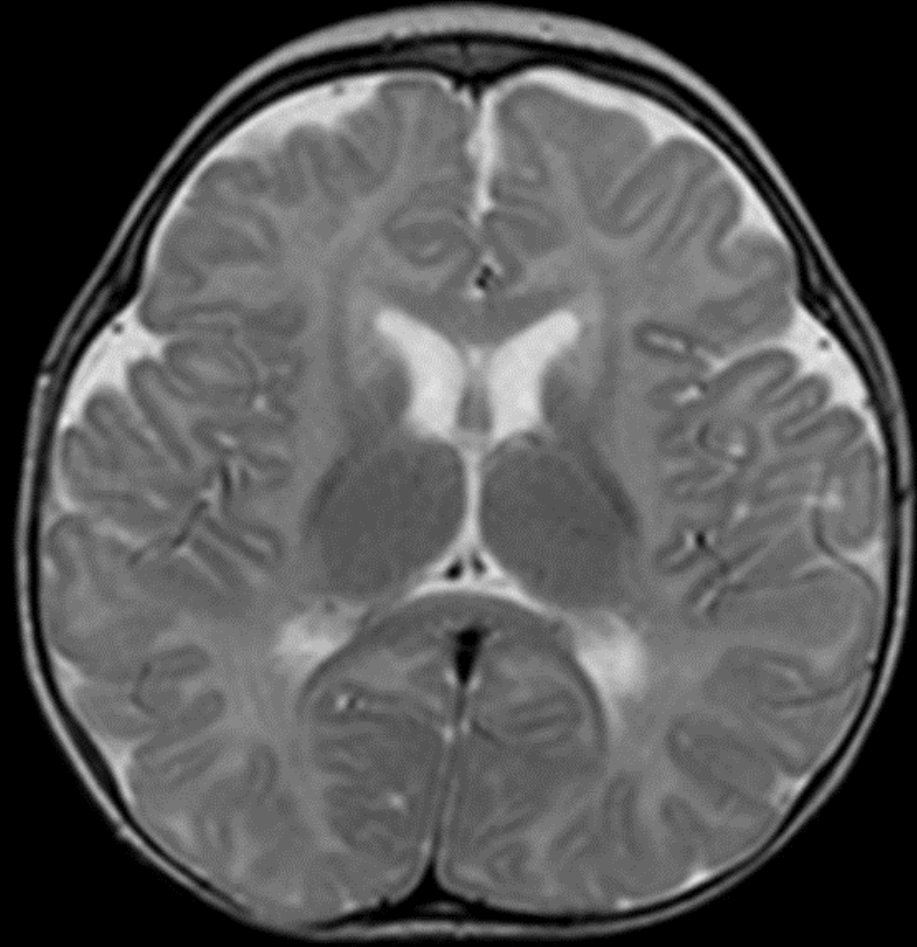
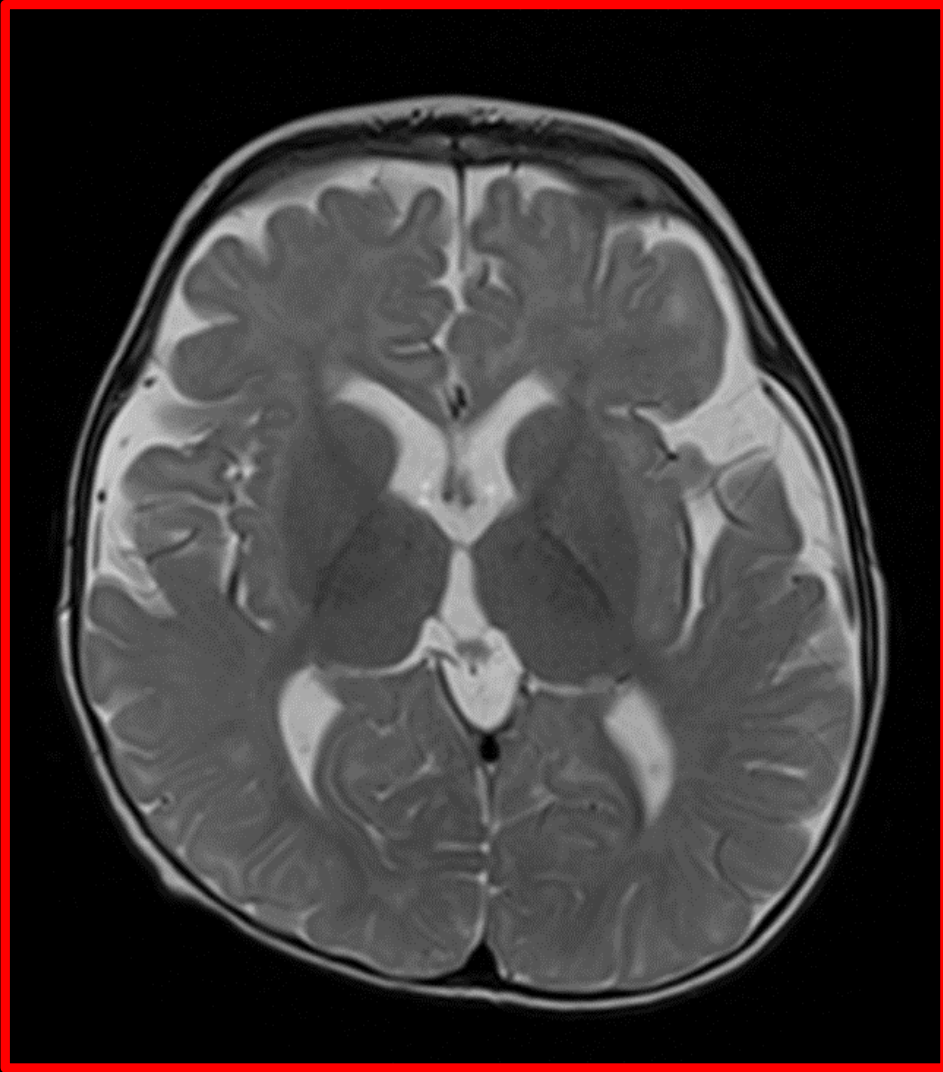


4 years

**Hypomyelination with
atrophy of basal ganglia
and cerebellum (HABC)**

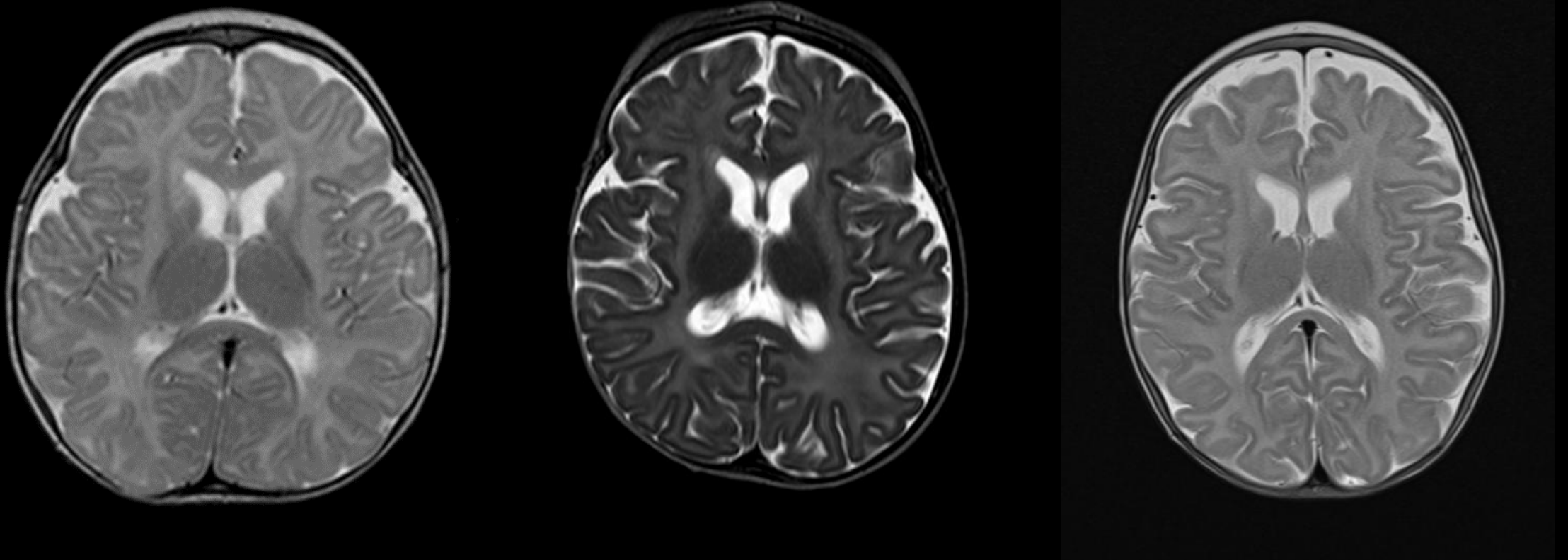


De novo *TUBB4A* variant
c.730G>A p.(Gly244Ser)

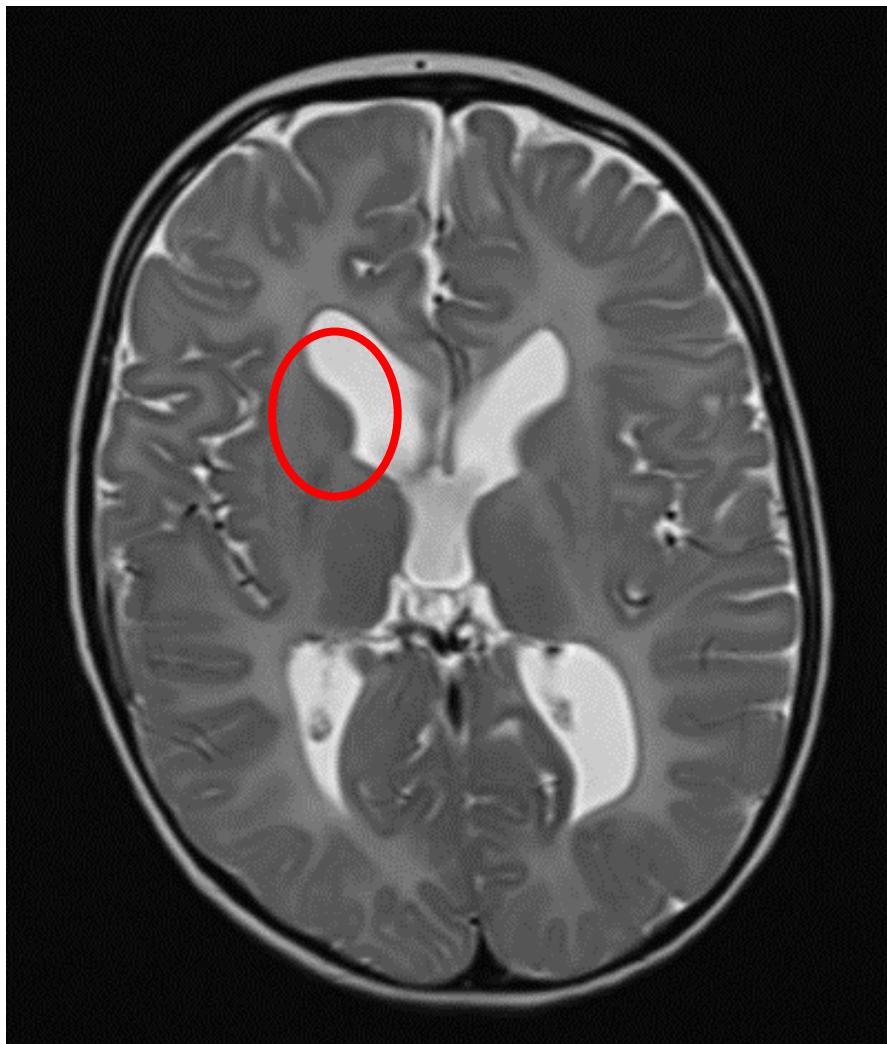


UFM1-related HABC

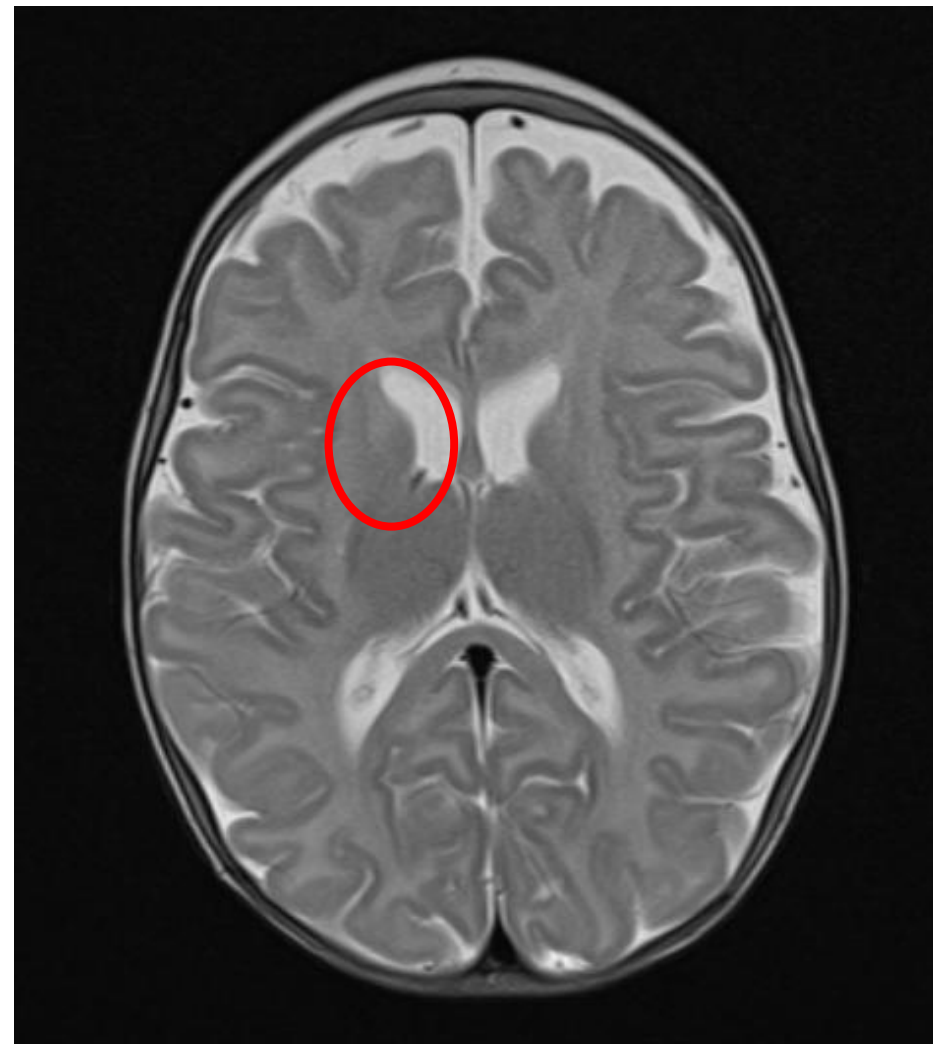
UFM1-related HABC



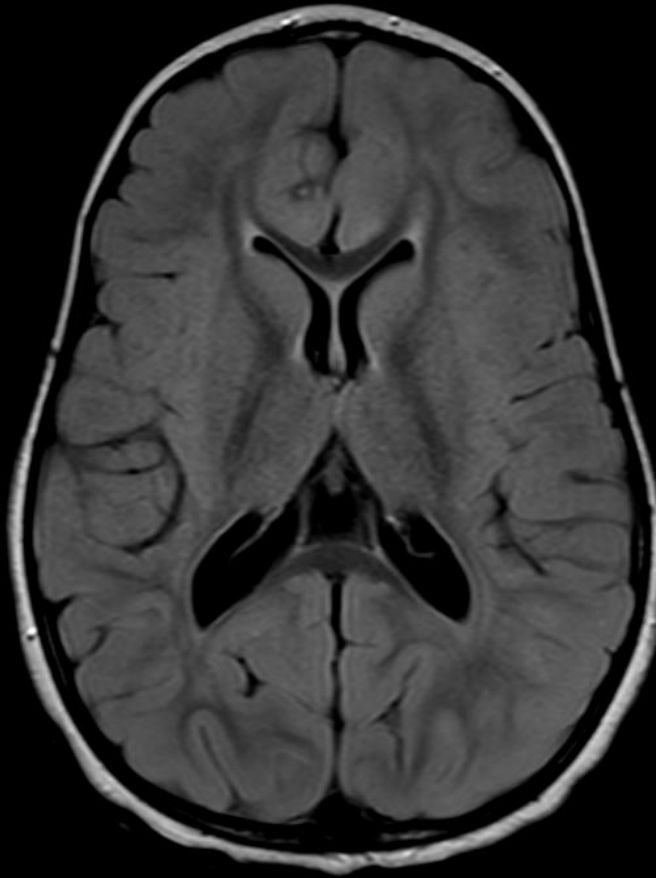
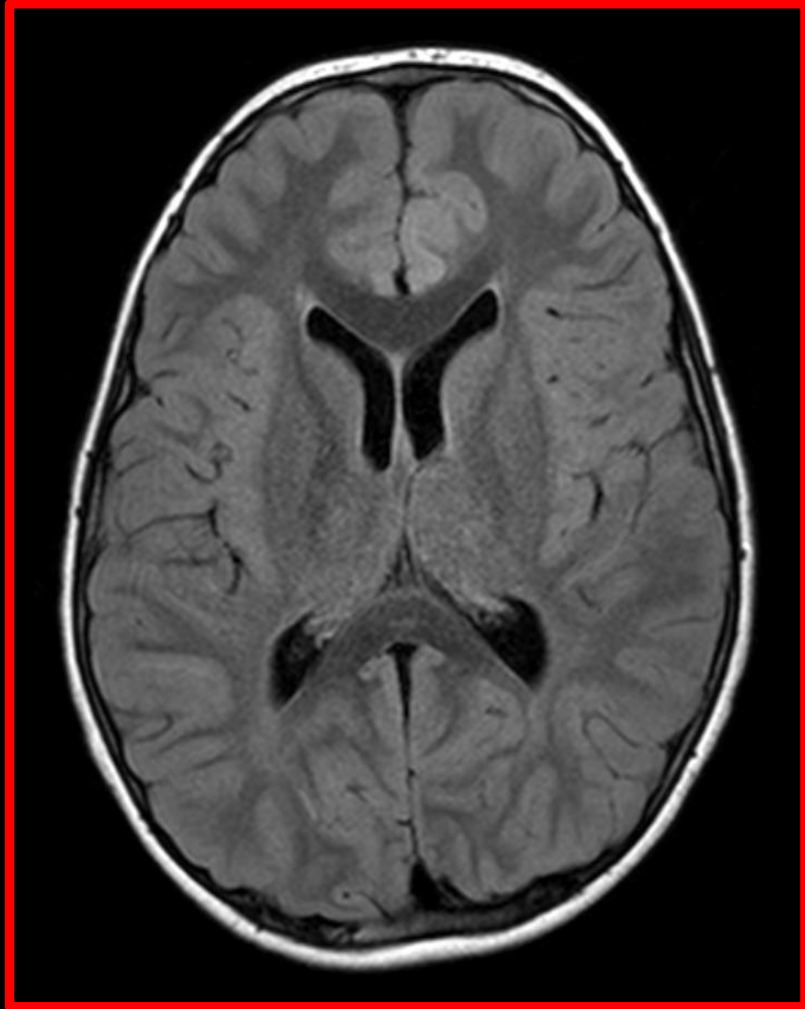
c.-155_-153delTCA deletion in the promoter region of *UFM1* is a founder variant in the Roma population



TUBB4A



UFM1

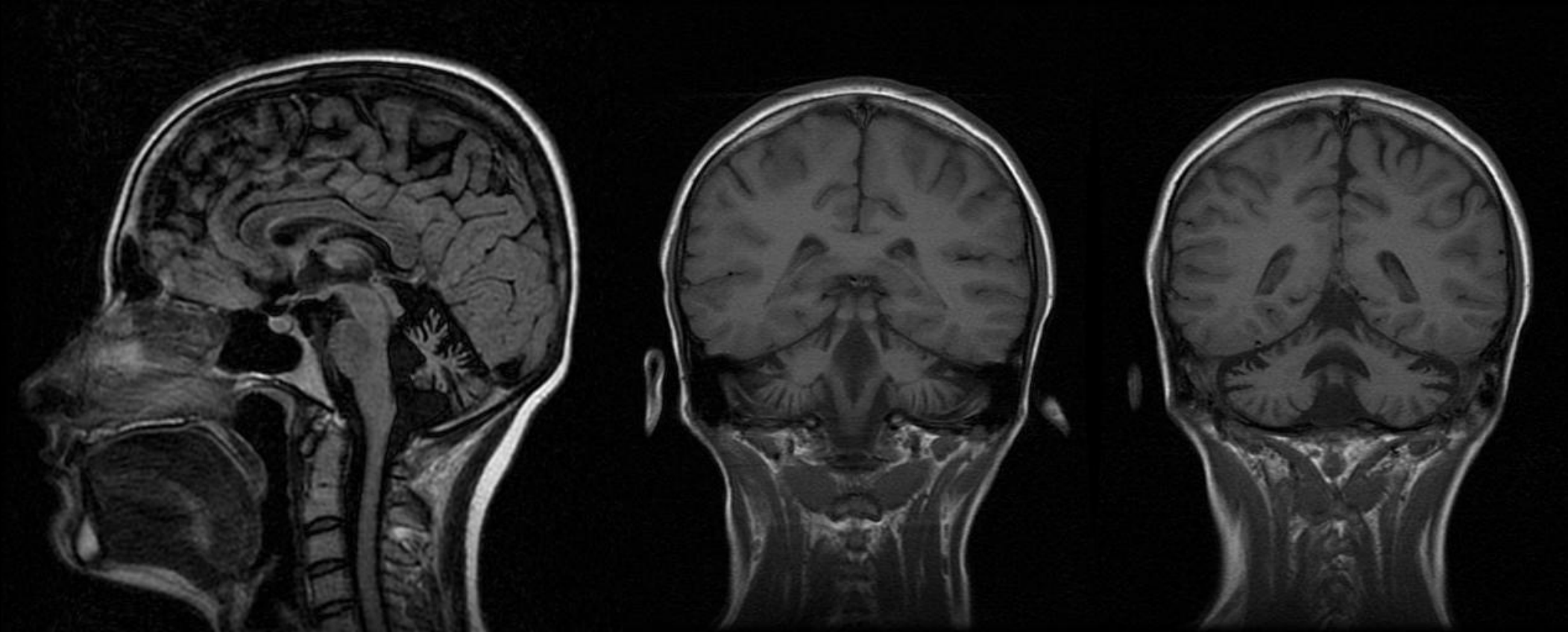


Ear of the lynx sign
AR SPG 11 and SPG15



AJNR Am J Neuroradiol. 2019 Jan; 40(1): 199–203

Cerebellar atrophy



APTX, ATM, ATP1A3, ATXN1-3, ATXN7-8, C10orf2, CANCA1A, CYP27A1, FXN, ITPR1, KCNJ10, PEX7, PHYH, PNKP, POLG, POLR3A, POLR3B, SACS, SETX, SIL1, STUB1, SYNE1, TTPA, WFS1

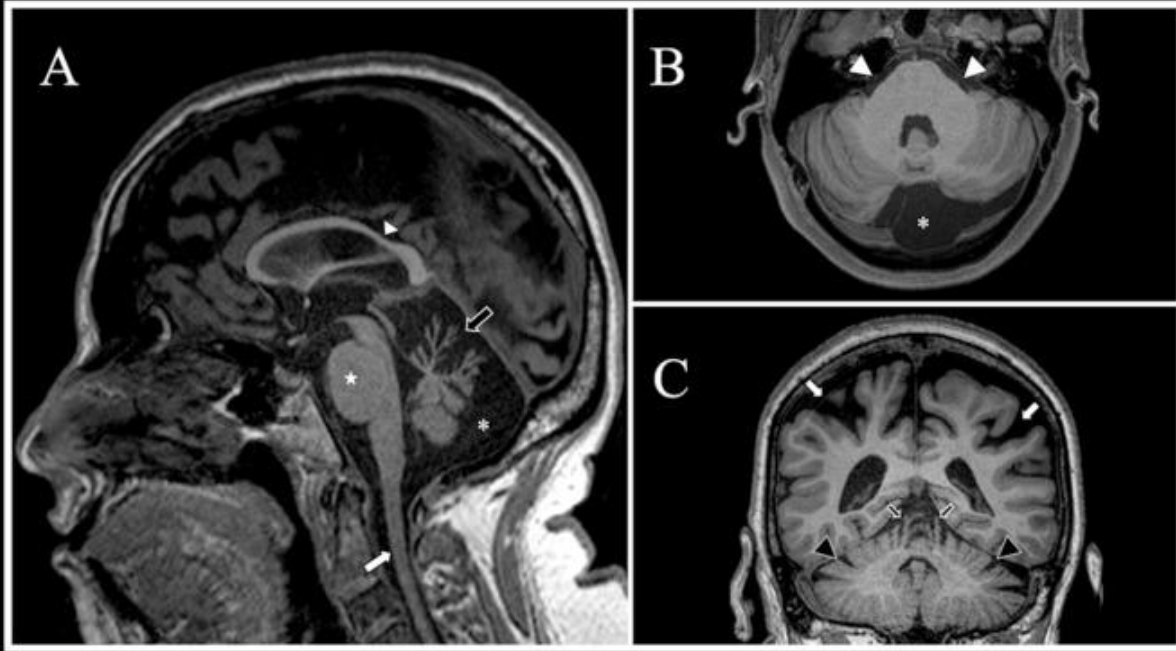
Ataxic cerebral palsy?

- 13-year-old boy
 - Uneventful delivery at term
 - Delay in motor milestones
 - Ataxic CP diagnosed at 3 years
- Admitted with suspected raised ICP
- Review of previous MRIs
- Clinical diagnosis of ARSACS
- R61.4 HSP panel requested
 - Biallelic SACS variants
 - c.1052_1053insC p.(Leu352SerfsTer7)
 - 1.4Mb loss at 13q12.12 including the entire SACS gene

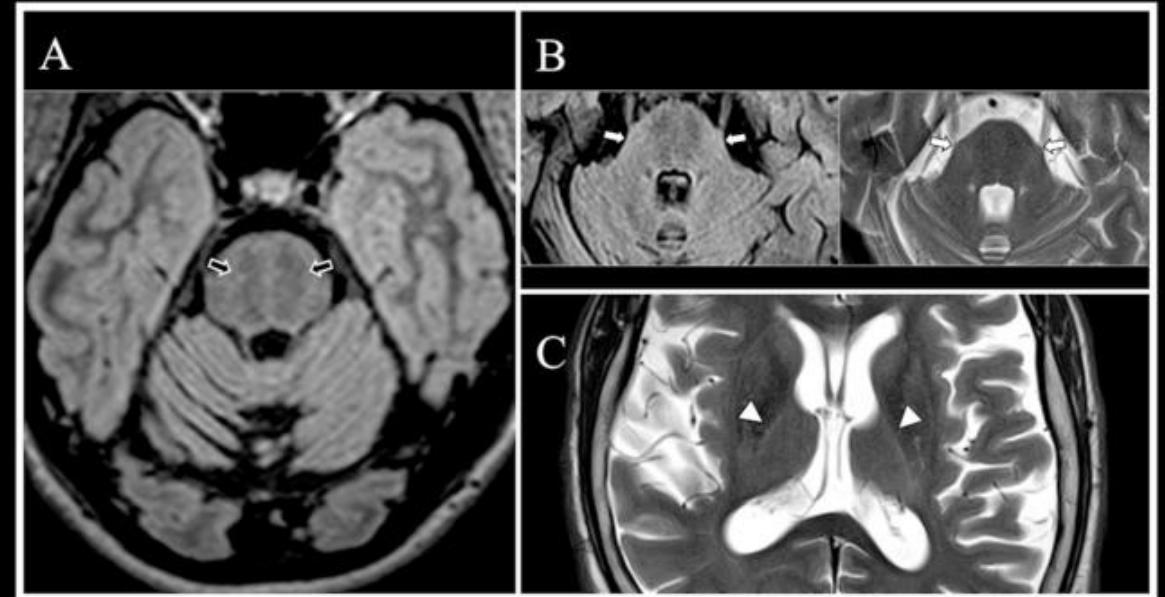
Autosomal recessive spastic ataxia of
Charlevoix-Saguenay (ARSACS)



ARSACS imaging



- Thinning of mid-posterior CC
- Superior vermis atrophy
- Bulky pons
- Mild upper cervical cord atrophy
- Thickened middle cerebellar peduncles
- Superior vermis atrophy
- Biparietal cerebral atrophy



- **Pontine stripes**
- Hyperintensity in lateral pons
- **Thalamic rim** sign

Pontocerebellar hypoplasia



dragonfly sign

Pontocerebellar hypoplasia

PCH type 1

EXOSC3

EXOSC8

PCH type 2 and 4

TSEN54

TSEN2

TSEN34

TSEN15

SEPSECS

MICPCH

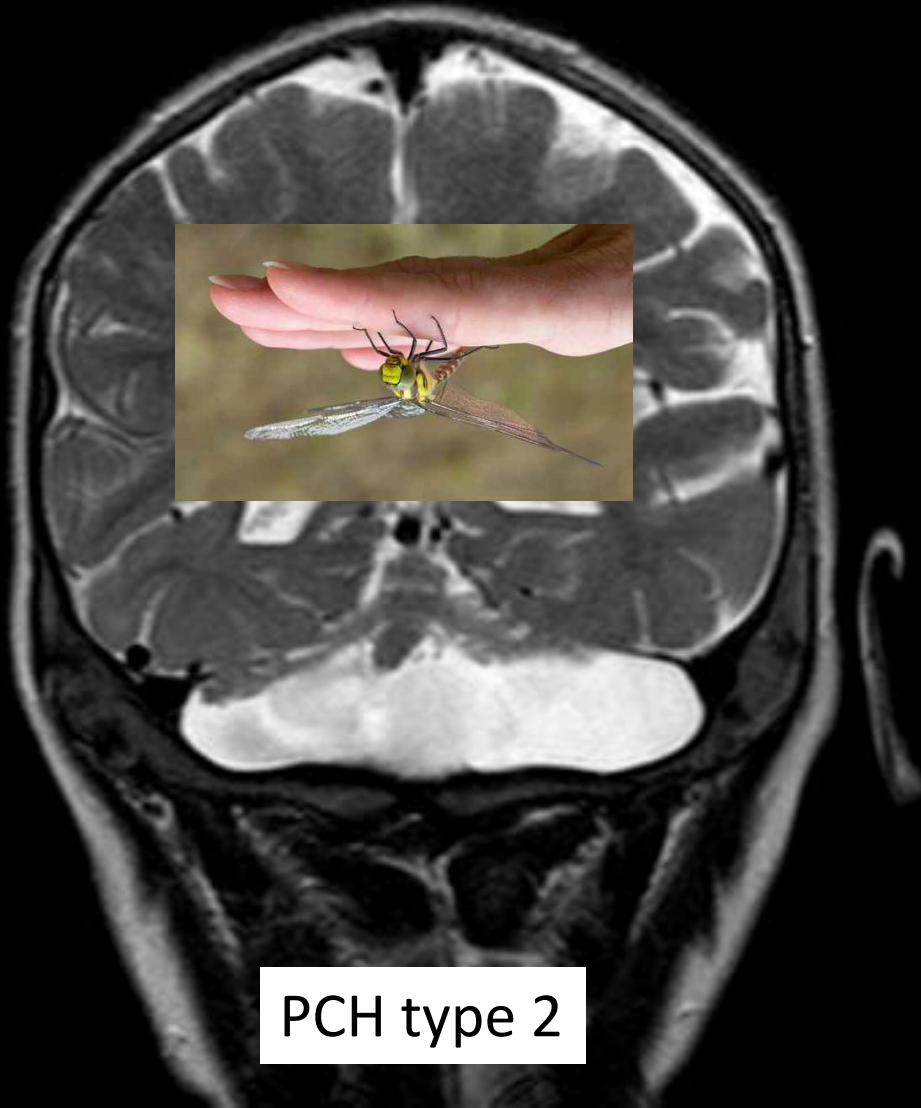
CASK

CHMP1A

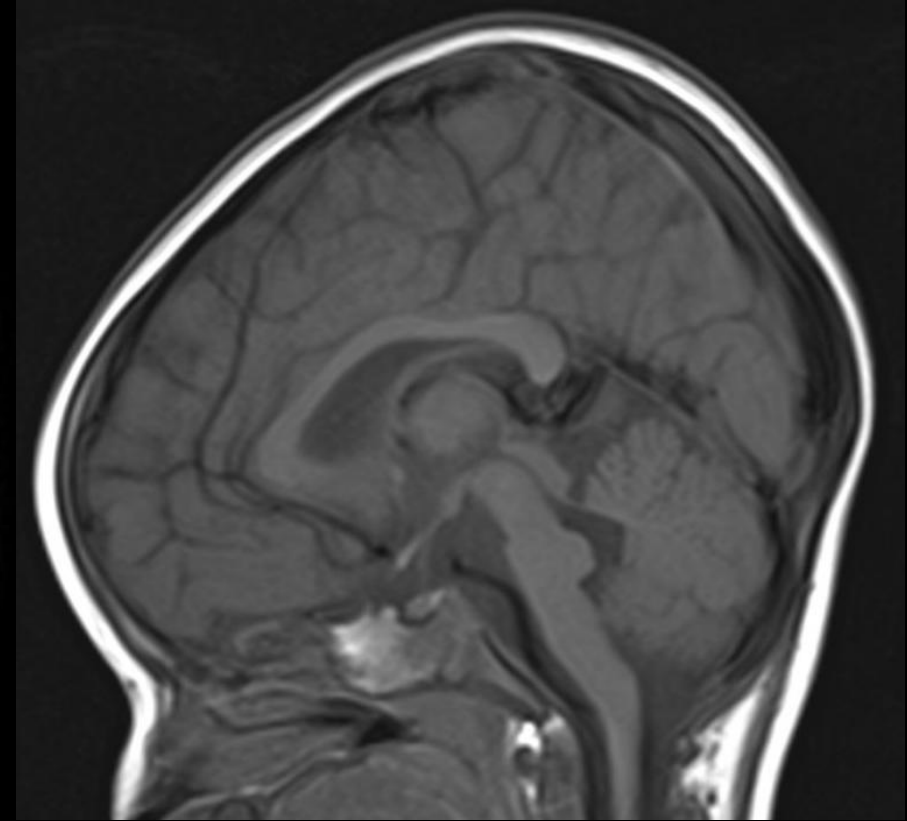
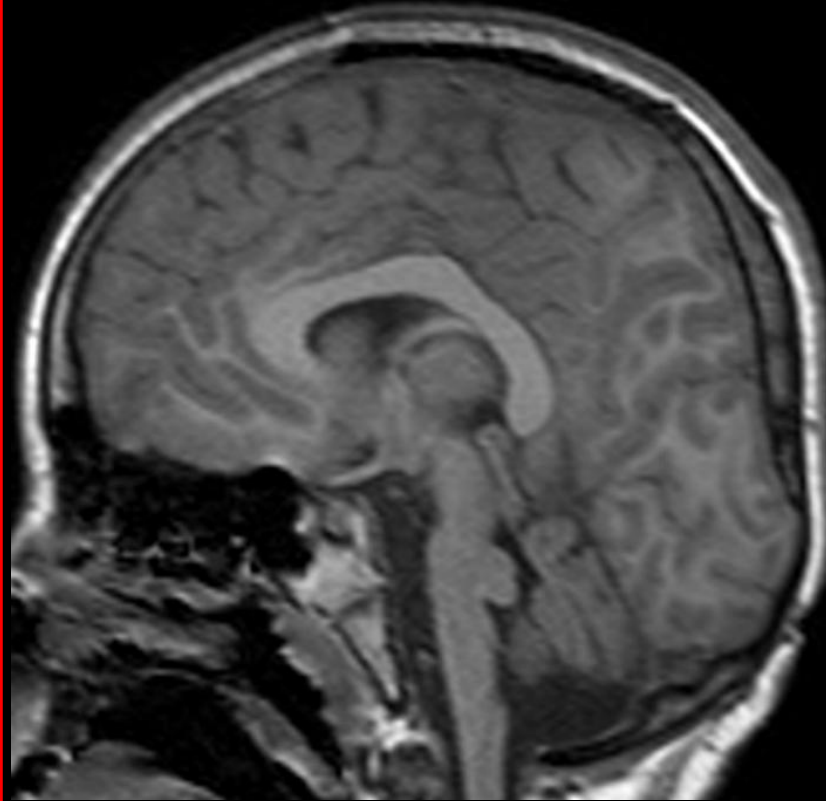
RELN

VLDLR

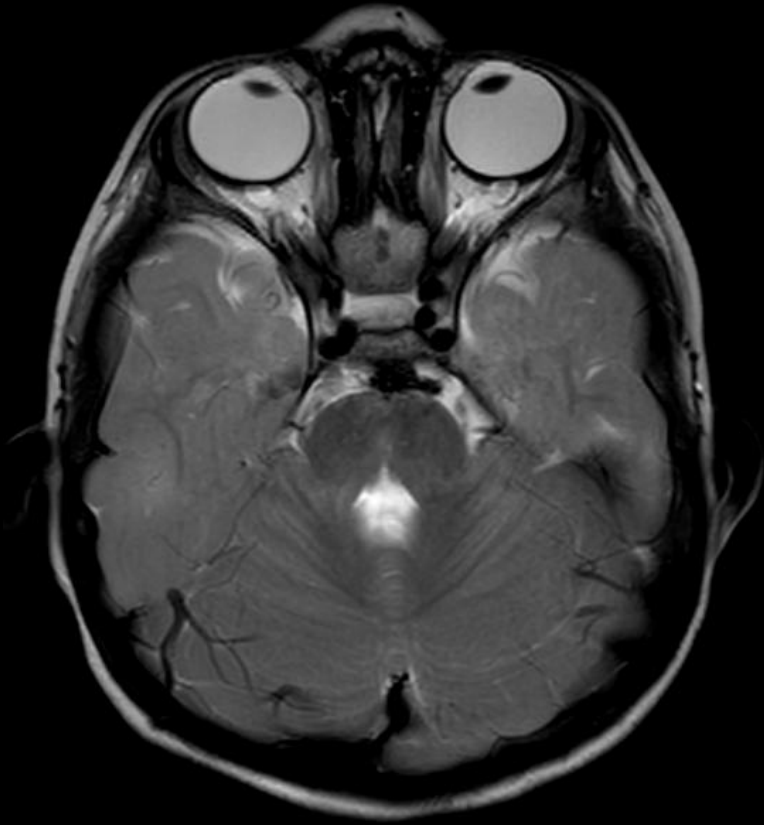
PCH type 2



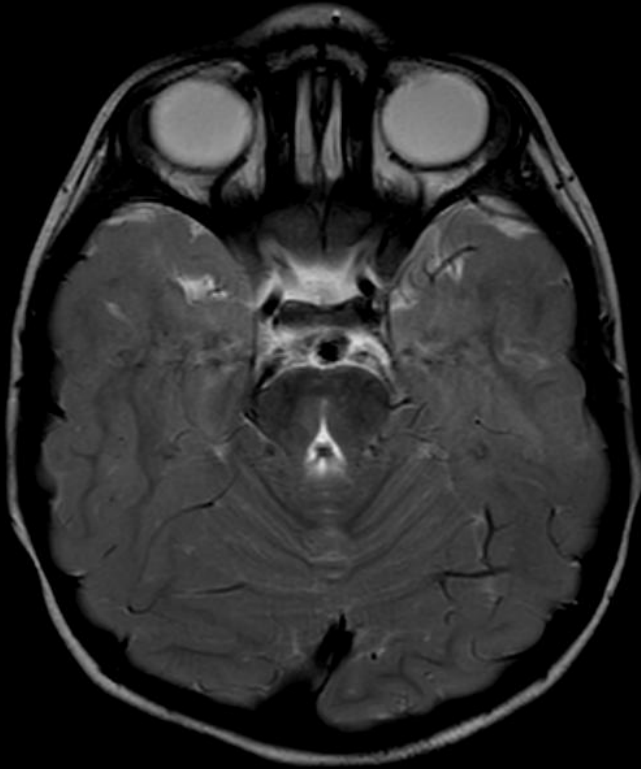
Pontine Tegmental Cap Dysplasia



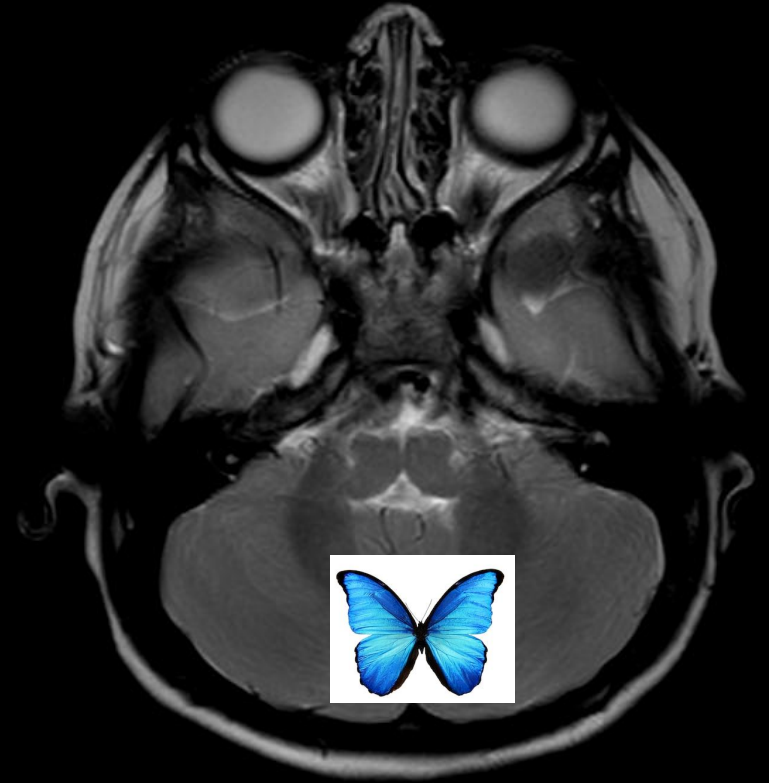
Abnormal posterior contour of the brainstem, hypoplasia of middle cerebellar peduncles,
bilateral V, VII and **VIII nerve** aplasia/hypoplasia
Genetic basis unknown; sporadic



Horizontal gaze palsy
Dorsal pontine cleft



Dorsal pontine cleft



Medullary cleft

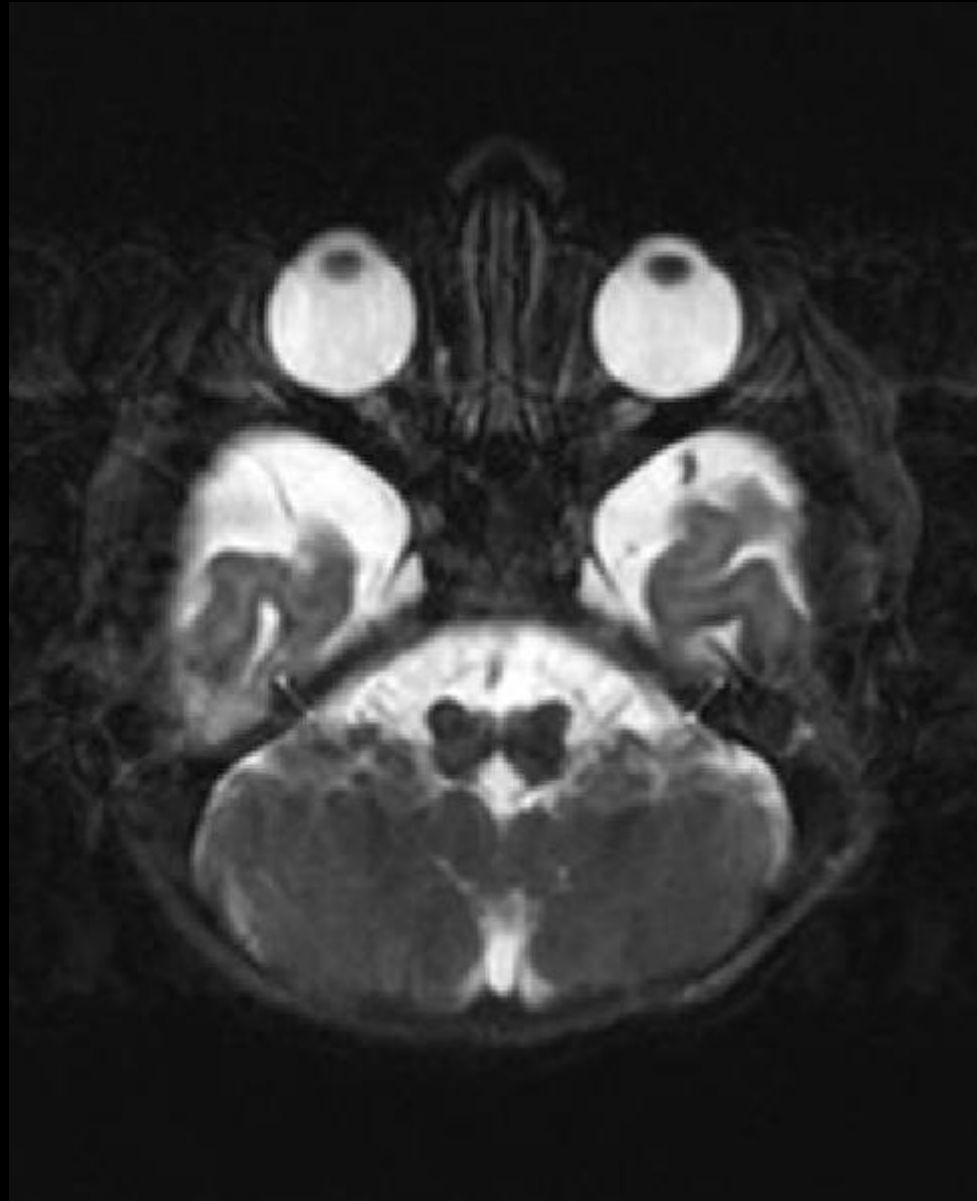
Horizontal gaze palsy with progressive scoliosis

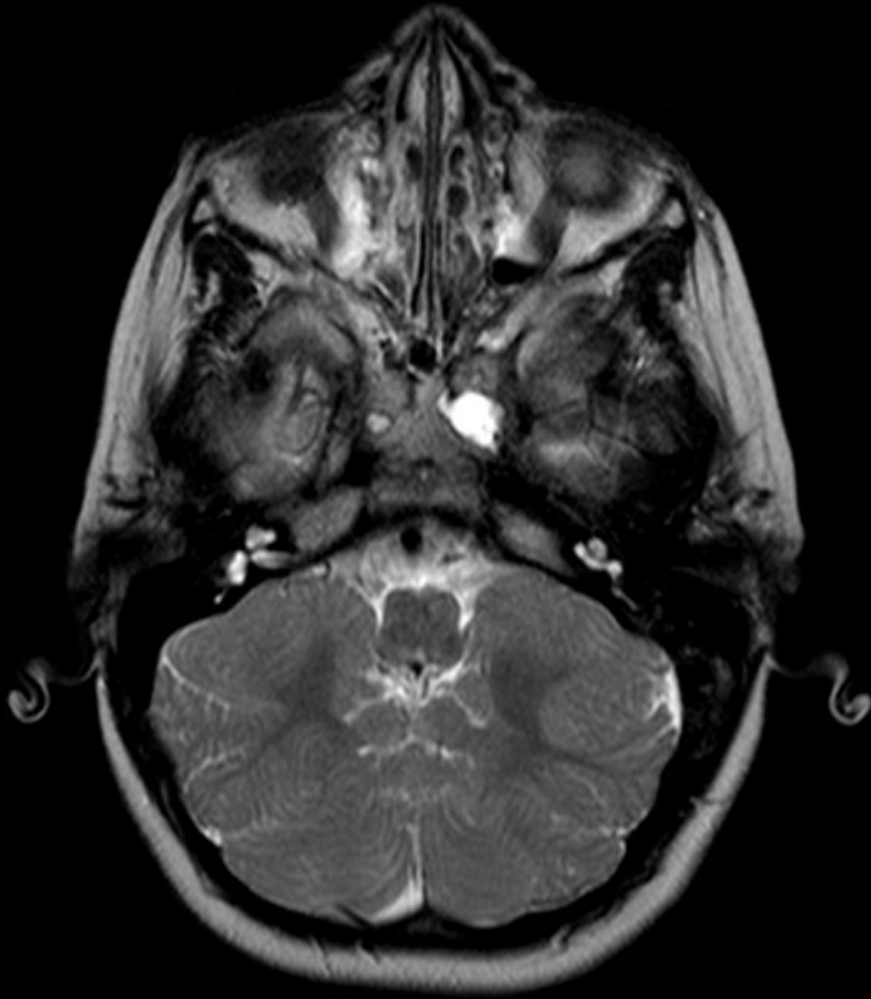
AR – biallelic *ROBO3* variants

4-month-old boy with horizontal gaze palsy

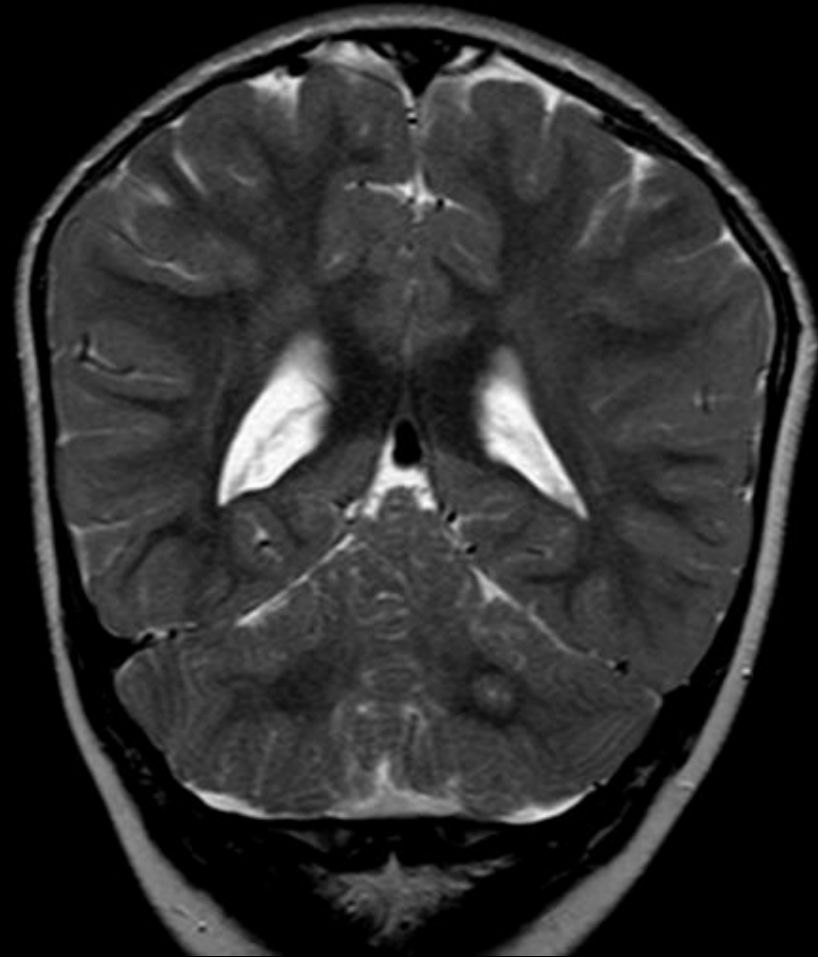


butterfly sign

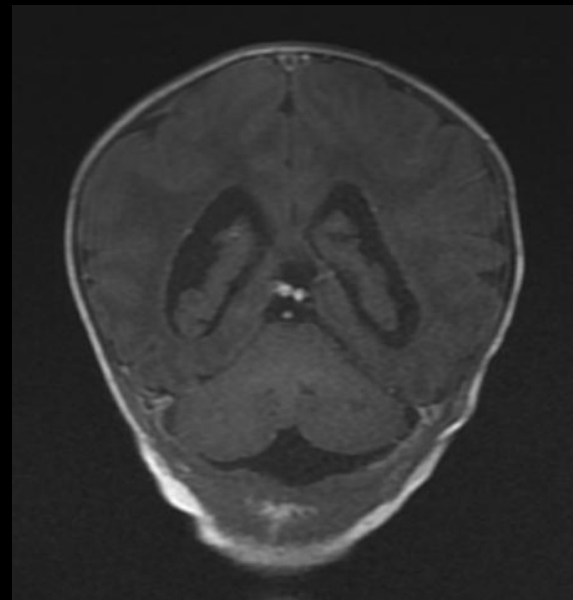
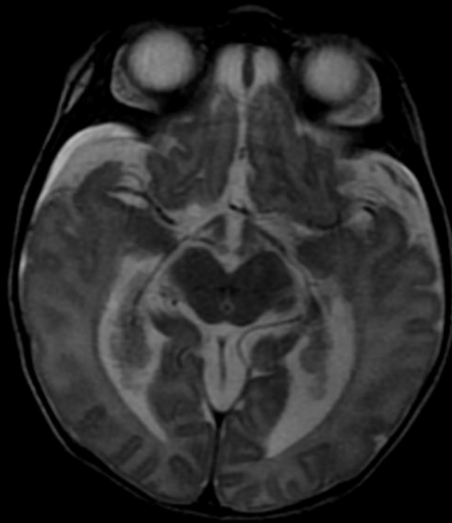
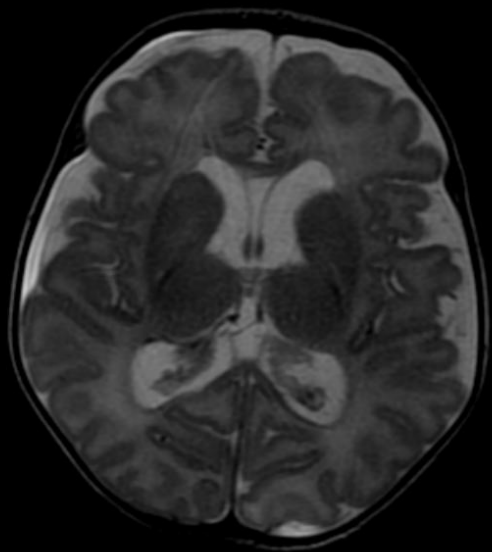




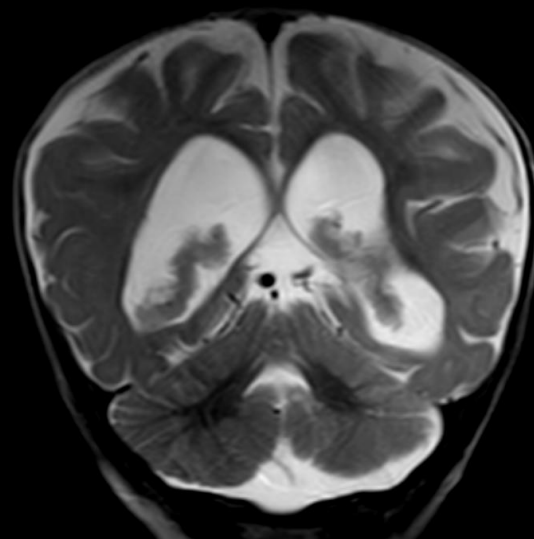
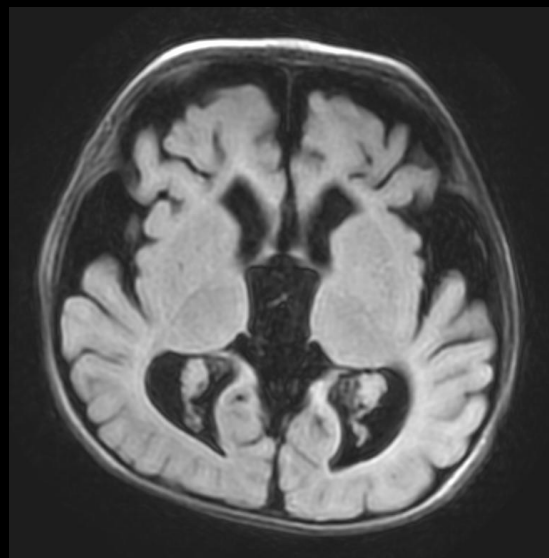
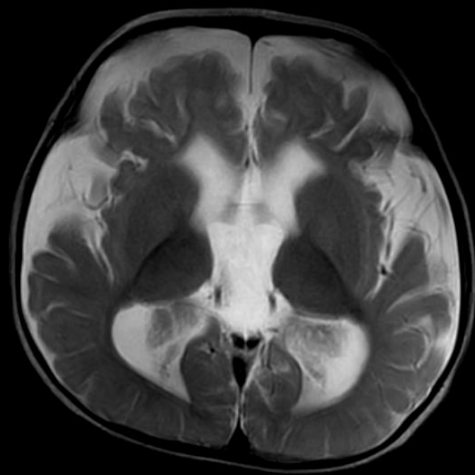
10-year-old boy, consanguineous parents
Devp delay and intellectual disability, oculomotor apraxia



Homozygous *LAMA1* c.5497-2A>G
Poretti-Boltshauser syndrome



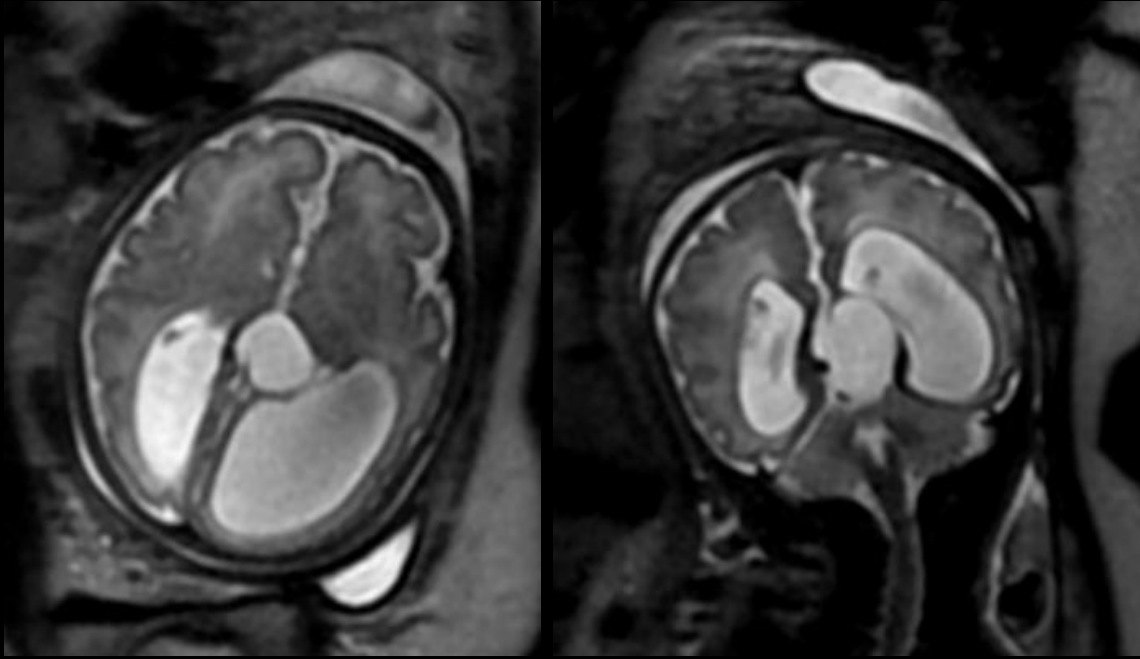
2.5-year-old boy
Neonatal urosepsis and meningitis
Bilateral VUR; neuropathic bladder
Hydrocephalus
Severe devp delay
Cortical visual impairment



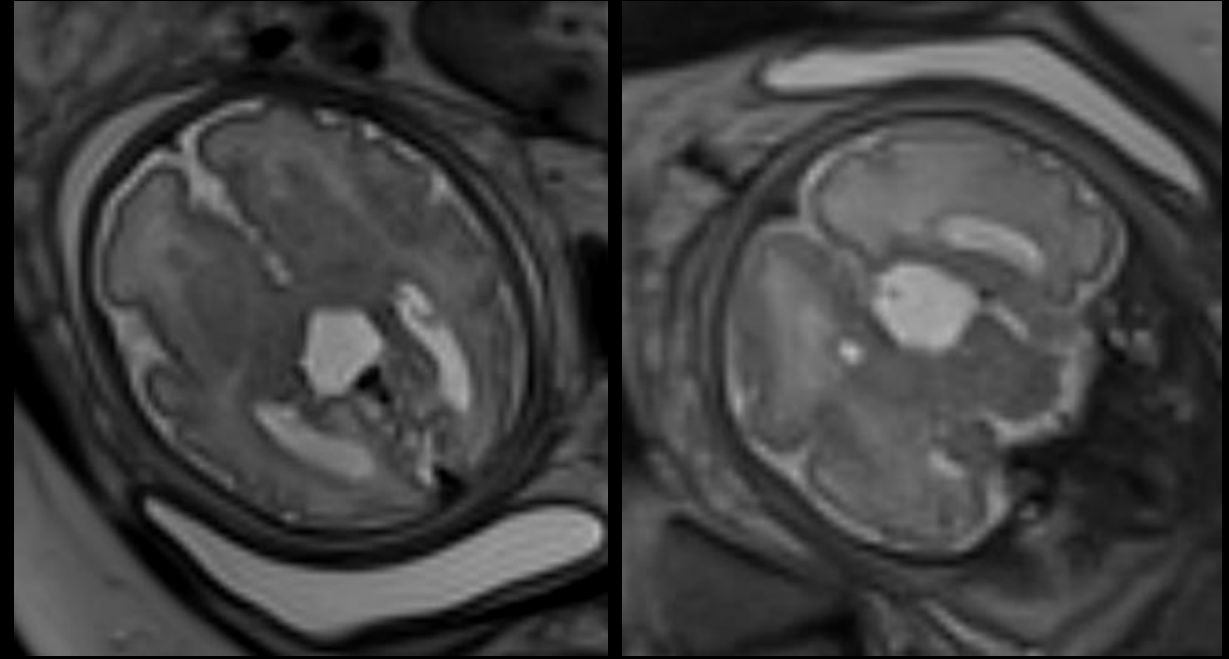
Episignature-specific phenotype
SMARCB1 p.Arg37His and others

Choroid plexus hyperplasia
CSF overproduction
Hydrocephalus

2022 – fetal MRI @ 34 weeks



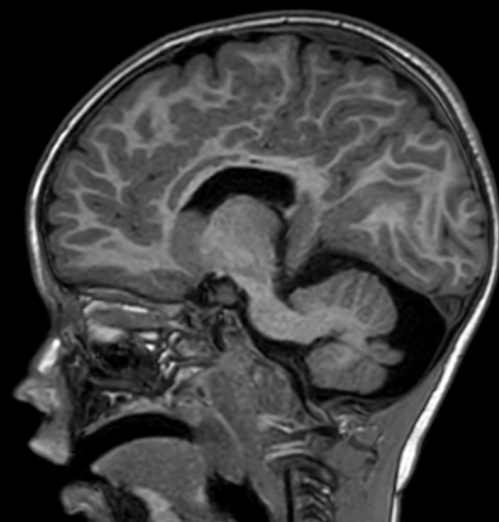
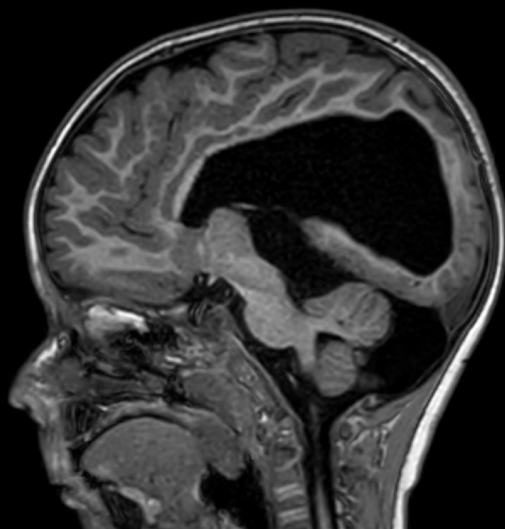
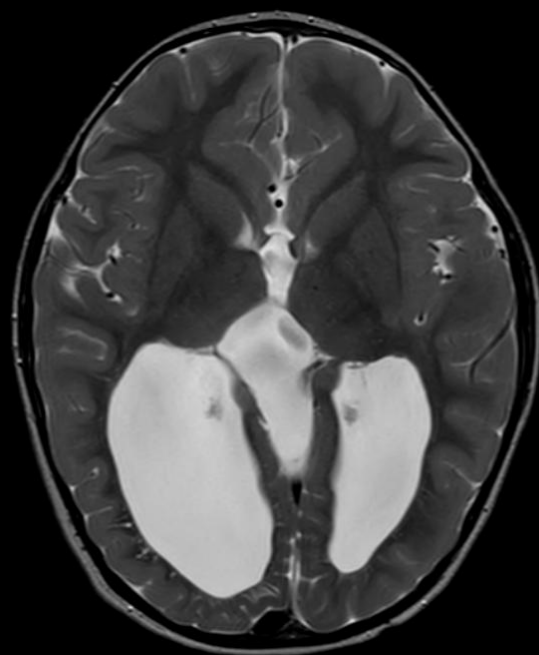
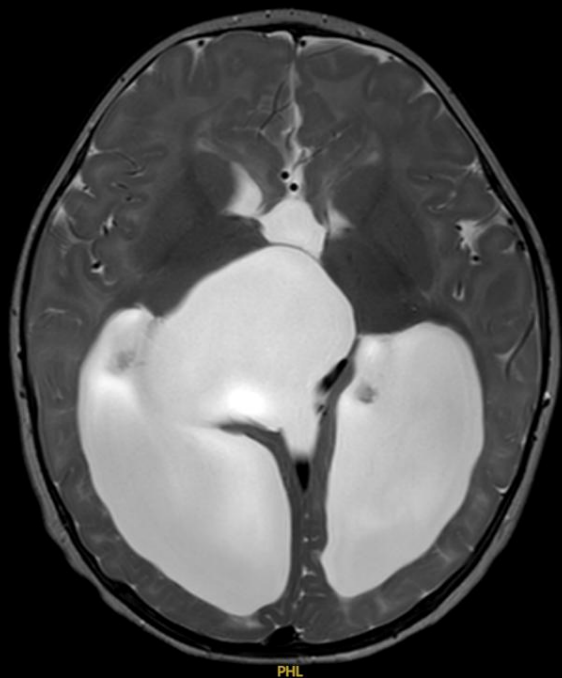
2025 – fetal MRI @ 34⁺⁵ weeks



- Consanguineous couple
- Corpus callosum dysgenesis and interhemispheric arachnoid cyst on antenatal scan
- in two successive pregnancies
- 3-year-old child has profound SNHL; awaiting cochlear implants

8m

34m



Chudley-McCullough syndrome

- **Imaging hallmarks**

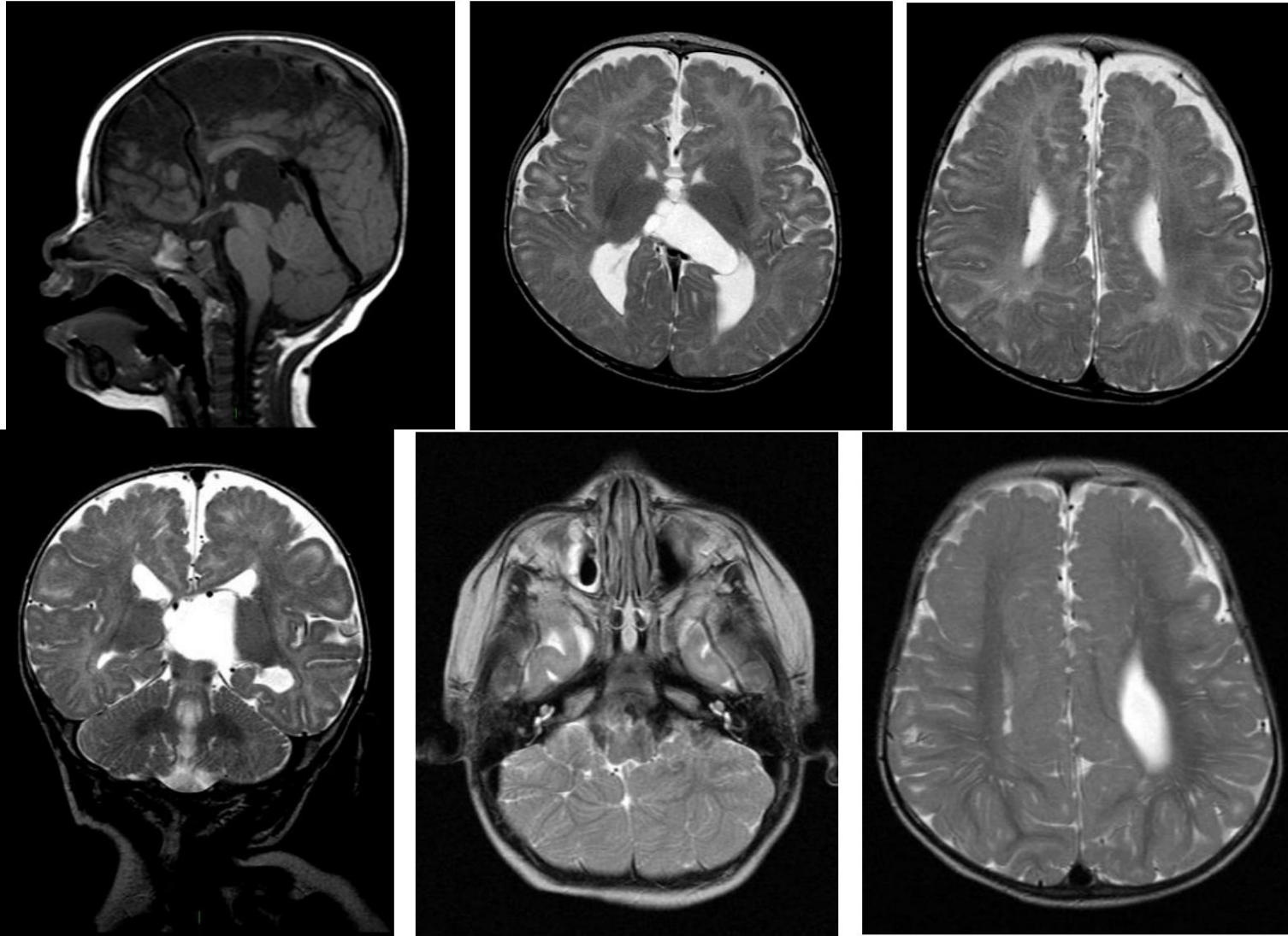
- ✓ Posterior CC dysgenesis
- ✓ Interhemispheric arachnoid cyst
- Frontal and ✓ parasagittal polymicrogyria
- Subcortical heterotopia
- ✓ Cerebellar dysplasia

- **Clinical**

- ✓ Macrocephaly
- Severe-profound sensorineural hearing loss

Genetic test result:

Homozygous *GPSM2* c.1600+3A>C



Posterior agenesis of CC
Ventriculomegaly
Arachnoid cyst (interhemispheric)
Frontal polymicrogyria
Parasagittal polymicrogyria
Frontal subcortical heterotopia
Cerebellar dysplasia

Macrocephaly
Hearing loss

Diagnosis on MRI brain

- Four broad categories

- **'Spot' diagnosis**

- No other Ix required

Chudley-McCullough syndrome

- **Main clue to diagnosis**

- No need to see face

Dysmorphic basal ganglia – TUBx gene

- **Narrows down the ballpark diagnosis**

- Makes accurate diagnosis easier/cheaper

Hypomyelination

- **Supportive features**

- Other clues are more important

Abnormal corpus callosum

Take-home messages

- Look at MRI scans of your patients; attend neuroradiology MDTs, if available
 - Clinical geneticists can use a **‘facial dysmorphology’ approach** to MRI analysis
 - It is possible for clinicians to make a **gestalt diagnosis** on MRI brain
- Learn to analyse MRI brain systematically, to make a ‘ballpark’ diagnosis
- Recognition of neuroimaging phenotypes can:
 - help with selection of correct genetic test
 - help in analysis of results – ‘reverse phenotyping’
 - make a non-genetic diagnosis
- You might still have to ask the radiologist to identify ‘normal’ variation

