ESPR
European Society of Paediatric Radiology

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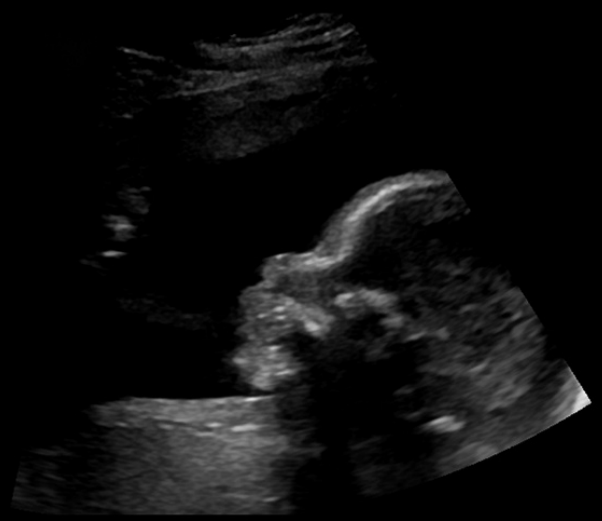
DANA
DANA DWEK Children's Hospital

TEL AVIV SOURASKY MEDICAL CENTER
ICHILOV

The Secret World of Tubulins



Liat Ben Sira
Catherine Garel

NO CONFLICT OF INTEREST

Microtubules

- Tubulins isoforms required for functions during cerebral cortex formation: neurogenesis, neuronal migration and post-migrational organization
- Most common isoforms (alpha- and beta-tubulins) globular subunits co-assemble into large polymers >> microtubules

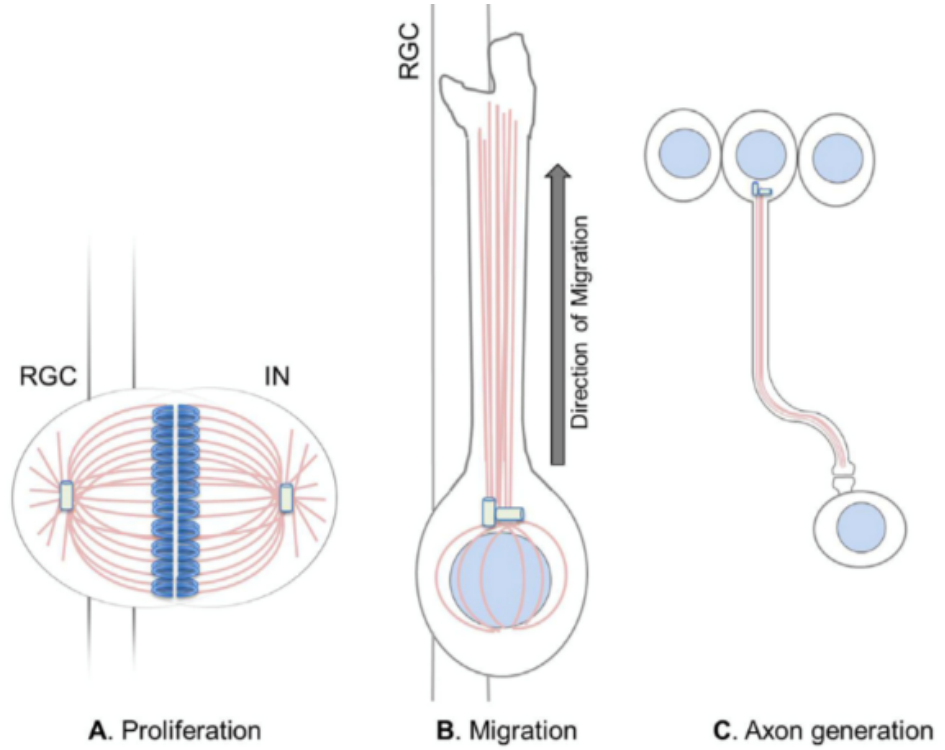


Fig. 2. The role of microtubules in cerebral cortex development.

MT formation affect multiple aspects of brain development

- Microcephaly (impaired mitosis)
- Lissencephaly, band heterotopia (impaired neuronal migration)
- Anomalies of white matter pathways (impaired axonal pathfinding)
- Anomalies of the cranial nerves (impaired axonal pathfinding)
- Malformations of the midbrain and hindbrain (impairment of both neuronal migration and axonal pathfinding)

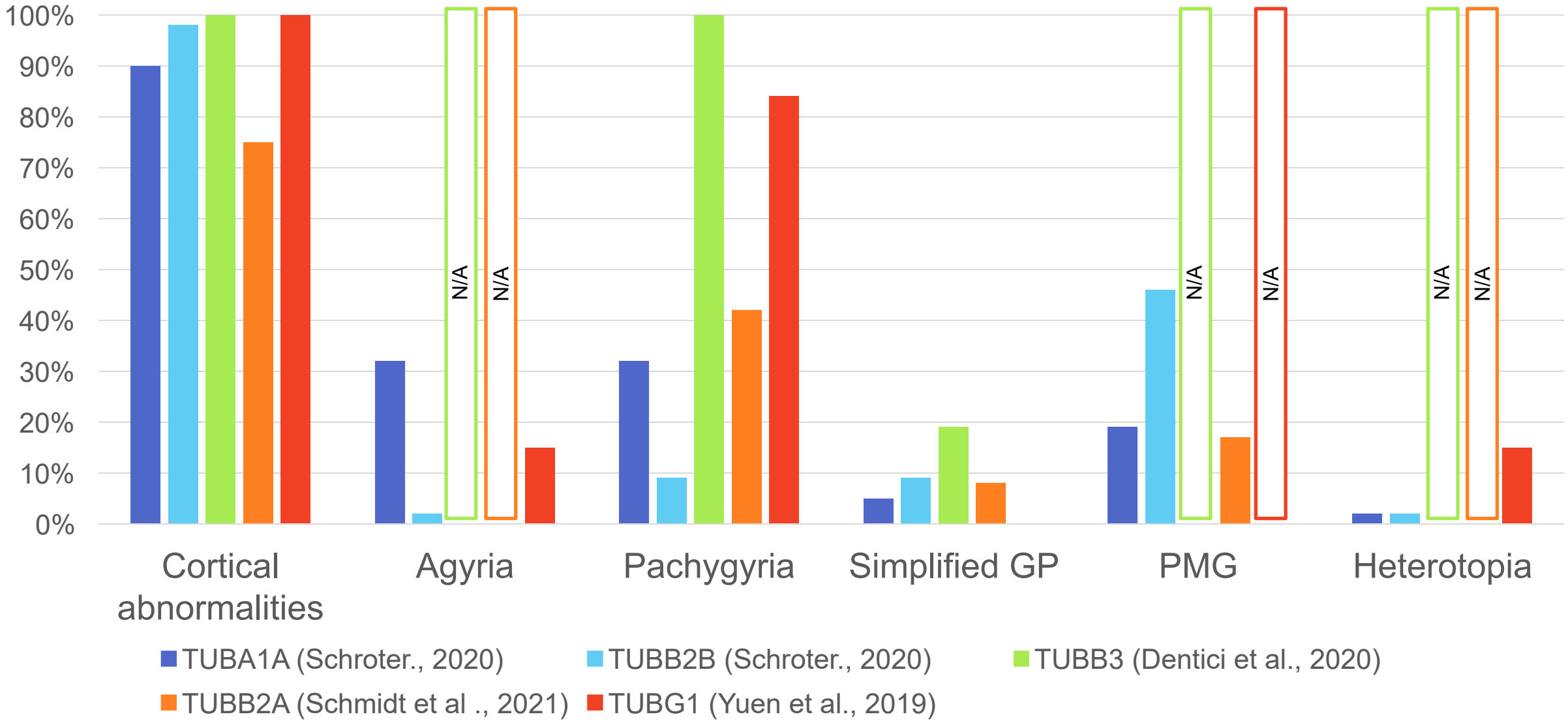
How do mutations of all these genes give nearly the same malformation?

All associated with abnormal protein transport along **microtubules**:

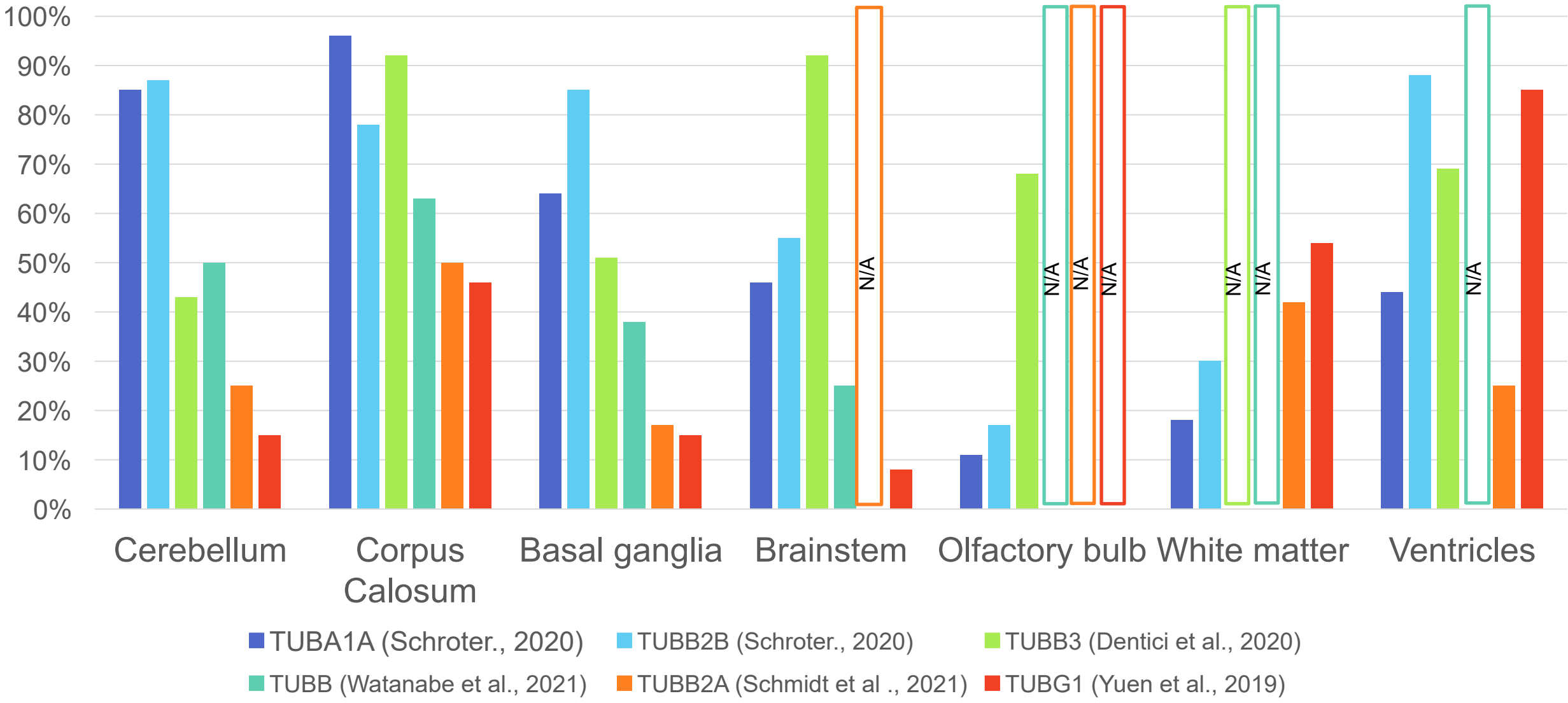
- Mitosis dysfunction > microcephaly
- Neuronal migration > heterotopia, pachygyria
- Axon guidance disturbance > abnormal WM, CTS
- Abnormalities of internal capsule, CC, hypoplasia of brainstem
- Migration/post-migration defects > abnormal cortex and hippocampal lamination, cerebellar dysplasia

Tischfield et al., 2011 ;Cushion et al., 2013 ; Bahi-Buisson et al., 2014 ; Kato, 2015 ; Oegema et al., 2015 ; Breuss et al., 2016;Romaniello et al., 2015/2017

Cortical malformations



Extra cortical abnormalities

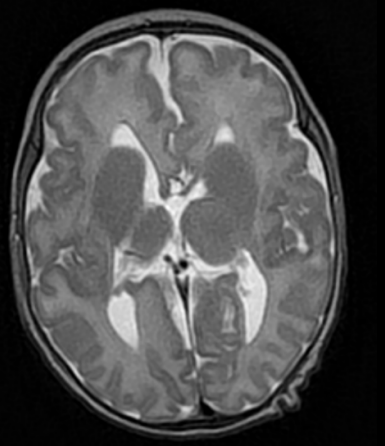


Axonal pathfinding disturbed

- Congenital fibrosis of the extraocular muscles or hypoplastic olfactory nerves
- Hypoplasia or absence of the corpus callosum;
- Small, often asymmetric brain stem
- Abnormal-appearing, fused striatum due to the absence of various parts of the internal capsule (most commonly the anterior limb)
- Diminished overall white matter volume

Characteristic Radiologic Hallmarks

- Dysmorphic basal ganglia (fusion of the caudate nucleus and putamen with absence of the anterior limb of the internal capsule), rounded thalami “hook” ventricle
- Commissural hypoplasia/ ACC
- Cerebellar hypoplasia/dysplasia
- Hypoplasia of the oculomotor /optic nerves
- Dysmorphic hind-brain structures
- Wide spectrum of MCDs



MCD Patterns

Affected genes are associated with predominant cortical phenotypes:
(*Bahi-Buisson et al., 2014)*

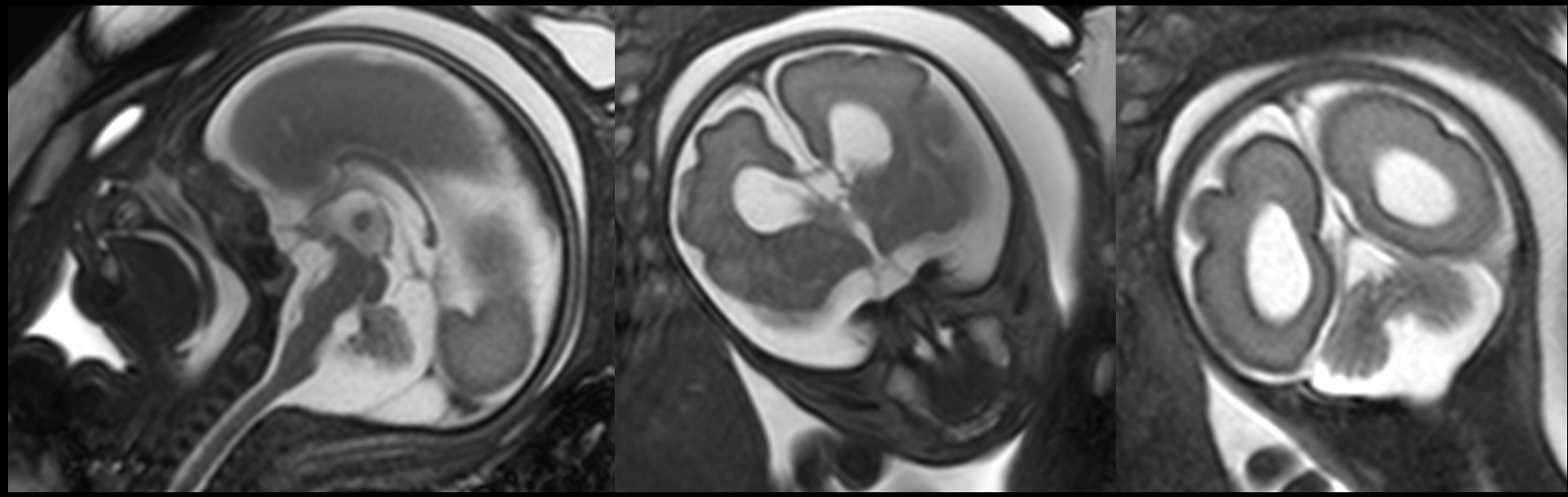
- *TUBA1A* and *TUBG1* - lissencephalic brain surfaces
- *TUBB2B* - polymicrogyria-like
- *TUBB* - microcephalic brains +/- apparent cortical involvement
- *TUBB4A* - seemingly unaffected brain surface but hypomyelination with atrophy of the basal ganglia and cerebellum
- *TUBB2A* - mildly simplified cortical patterning

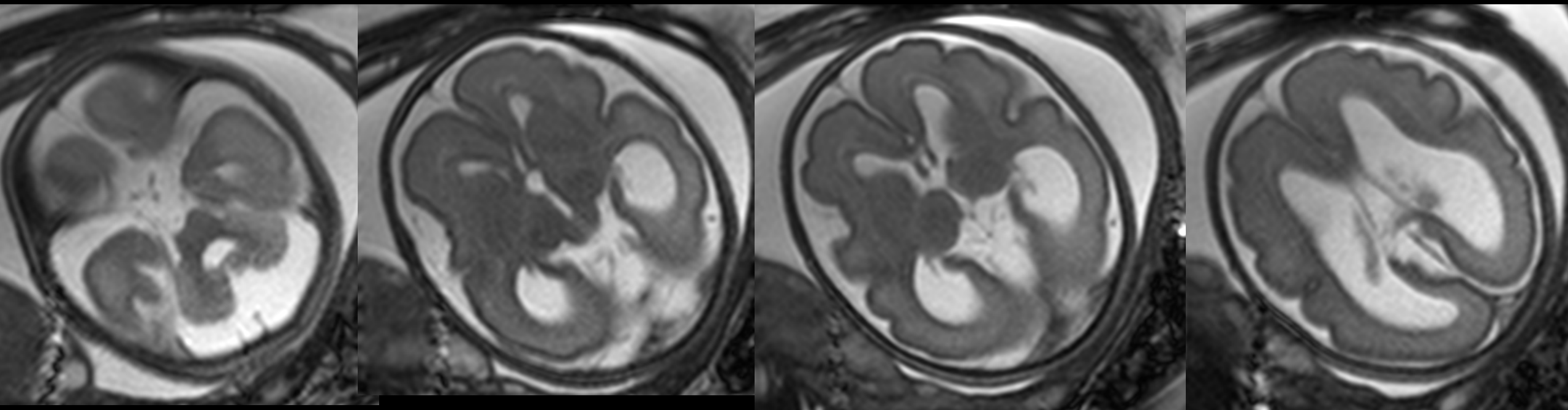
TUBA1A

- 1% of cases of classical lissencephaly
  - P>A pattern (similar to “LIS1”)
- 30% of cases of lissencephaly with cerebellar hypoplasia *(Kumar 2010)*
- Various grades of lissencephaly, ranging from agyria to simplified abnormally thick convolutions (pachygyria) & perisylvian PMG
- Rare: Cerebellar hypoplasia without lissencephaly

TUBA1A

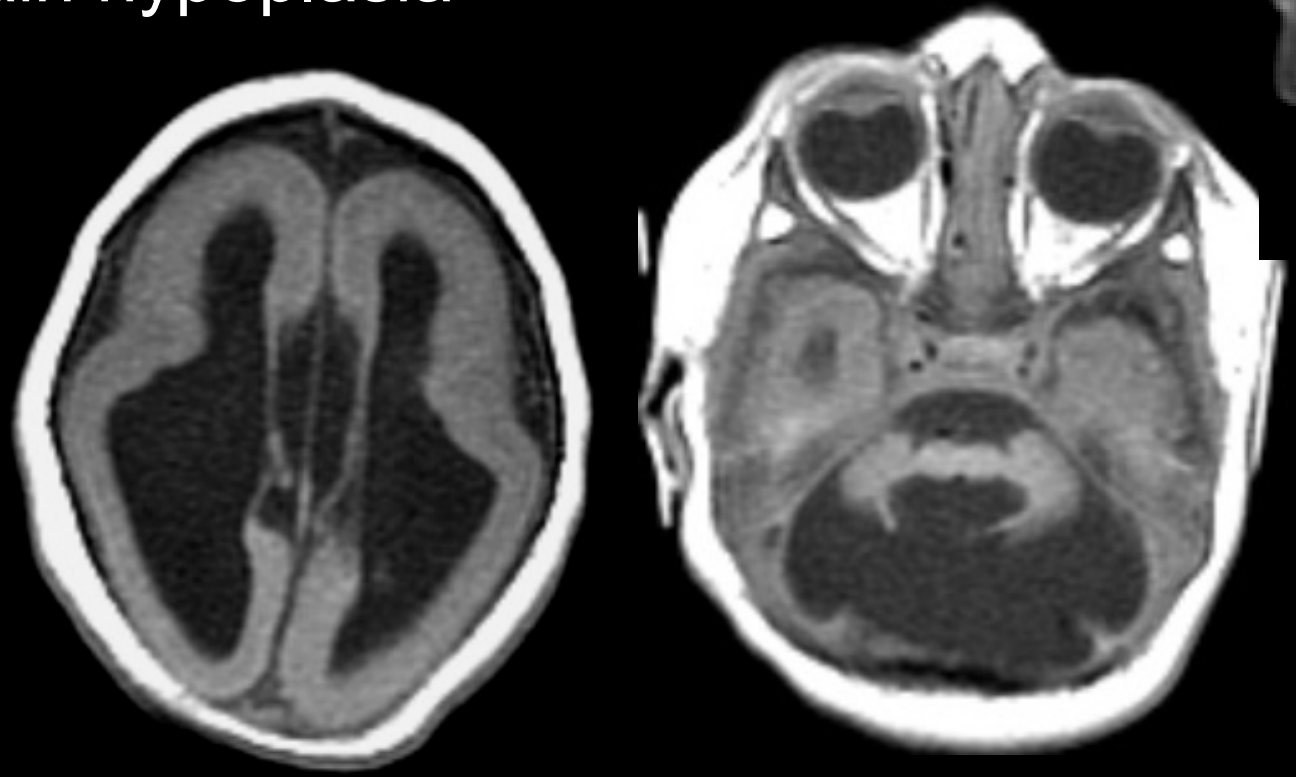
29 GA Fetus

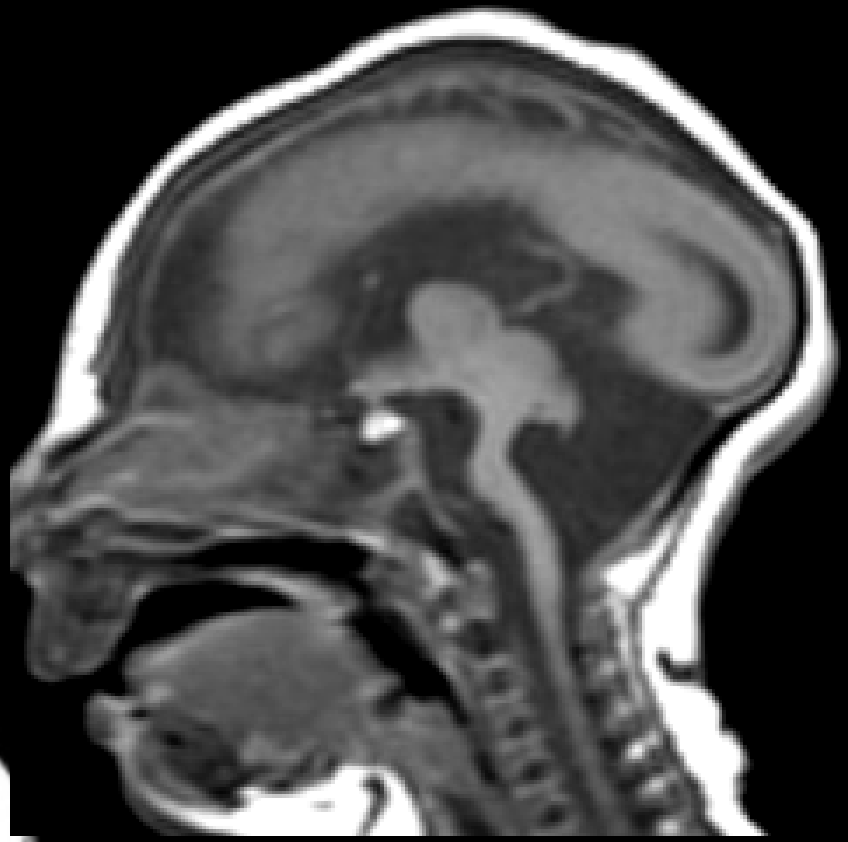




Neonate with profound microcephaly, hypotonia

:*TUBA1A*
Absent CC
Lissencephaly
Mid/hindbrain hypoplasia



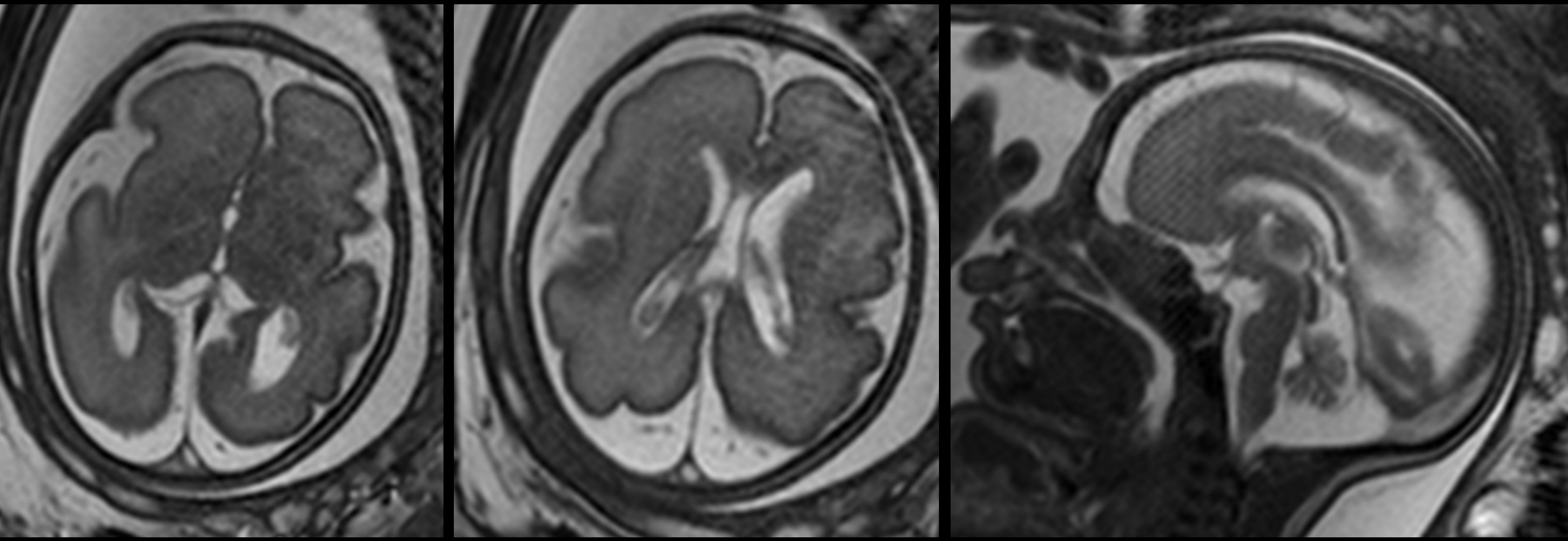


Barkovich

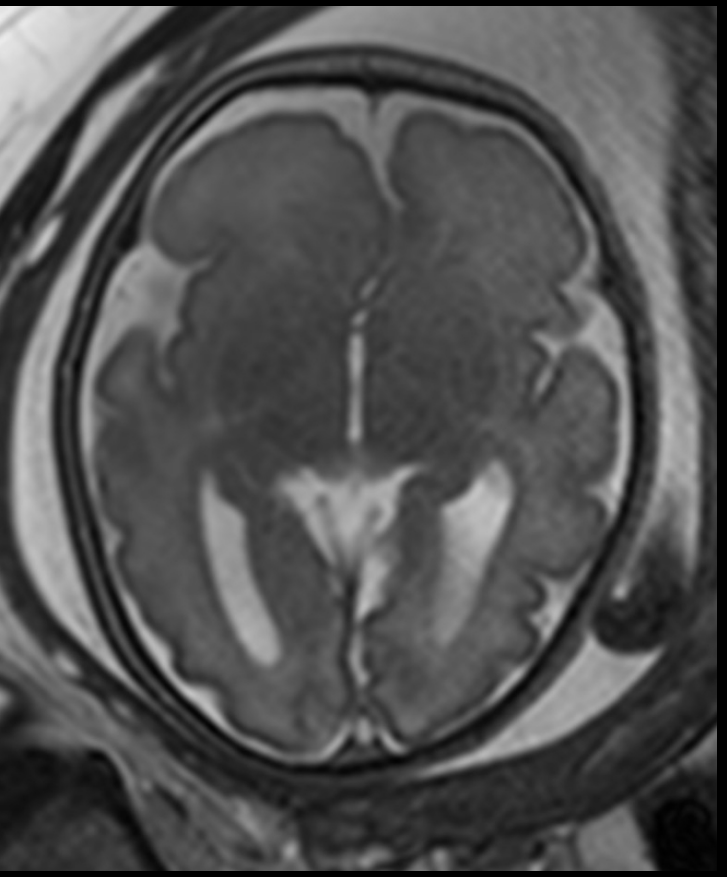
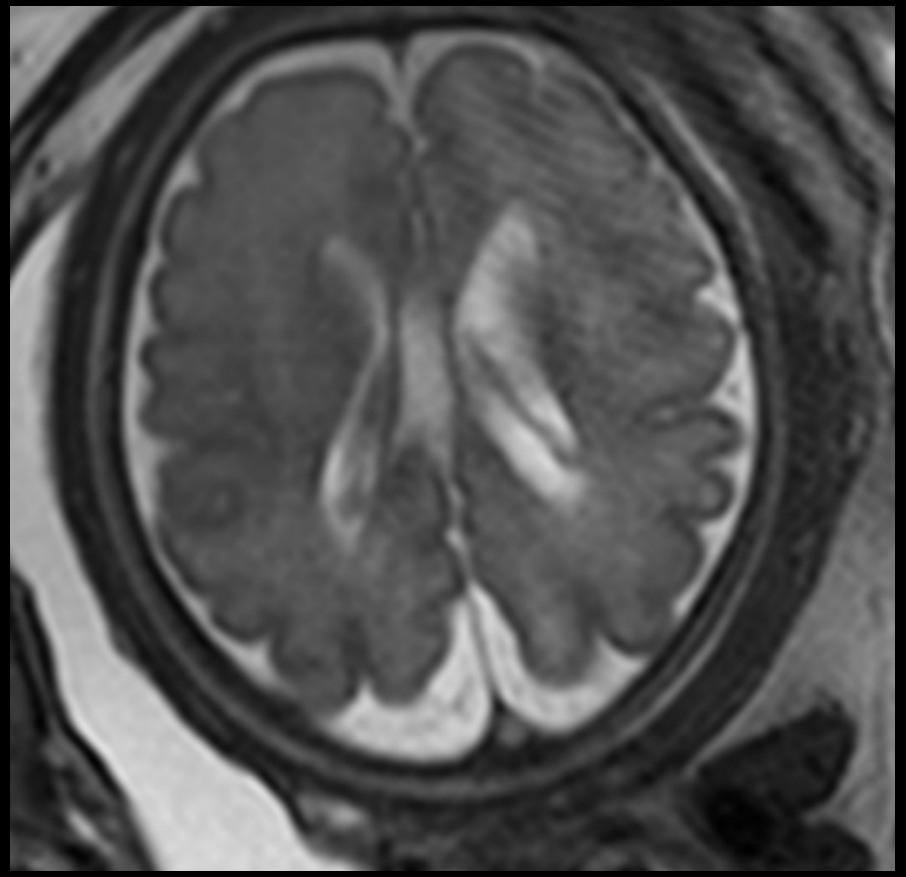
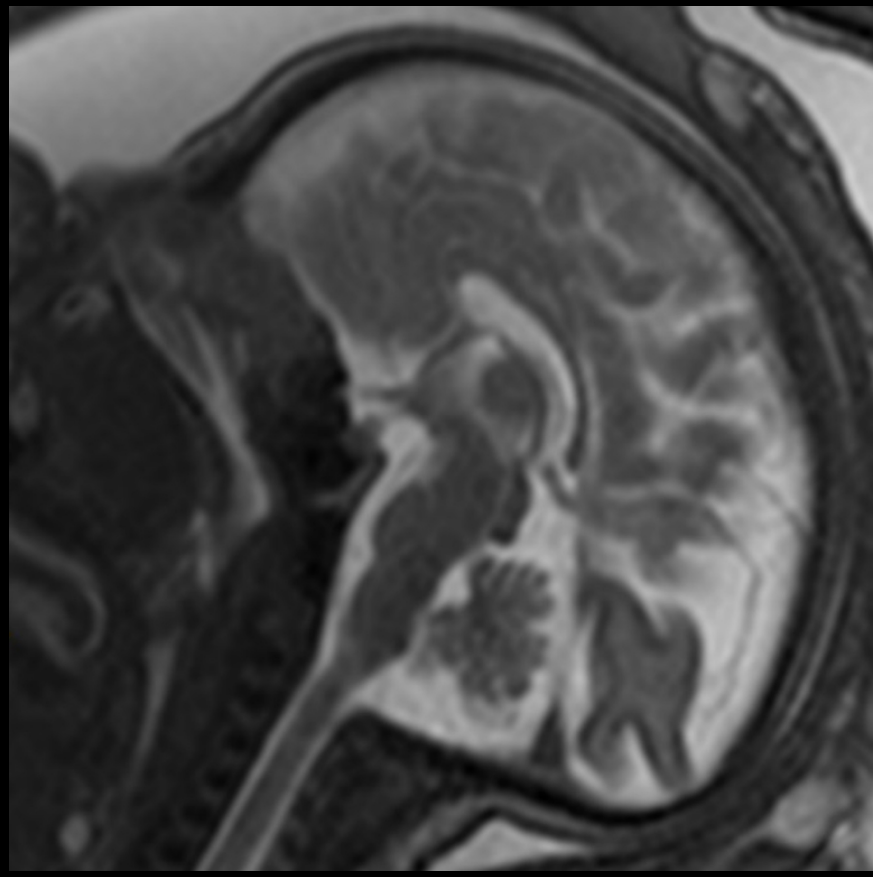
Dysgyria

- Normal cortical thickness
- Abnormal gyral pattern - sulcal depth and orientation, with a smooth cortical surface and radially oriented sulci, or narrow gyri separated by abnormally deep or shallow sulci
- Irregular orientation of sulci
- Not typical for PMG, pachygyria or a simplified gyral pattern
- Dysgyria may be a difficult diagnosis
- Can be subtle

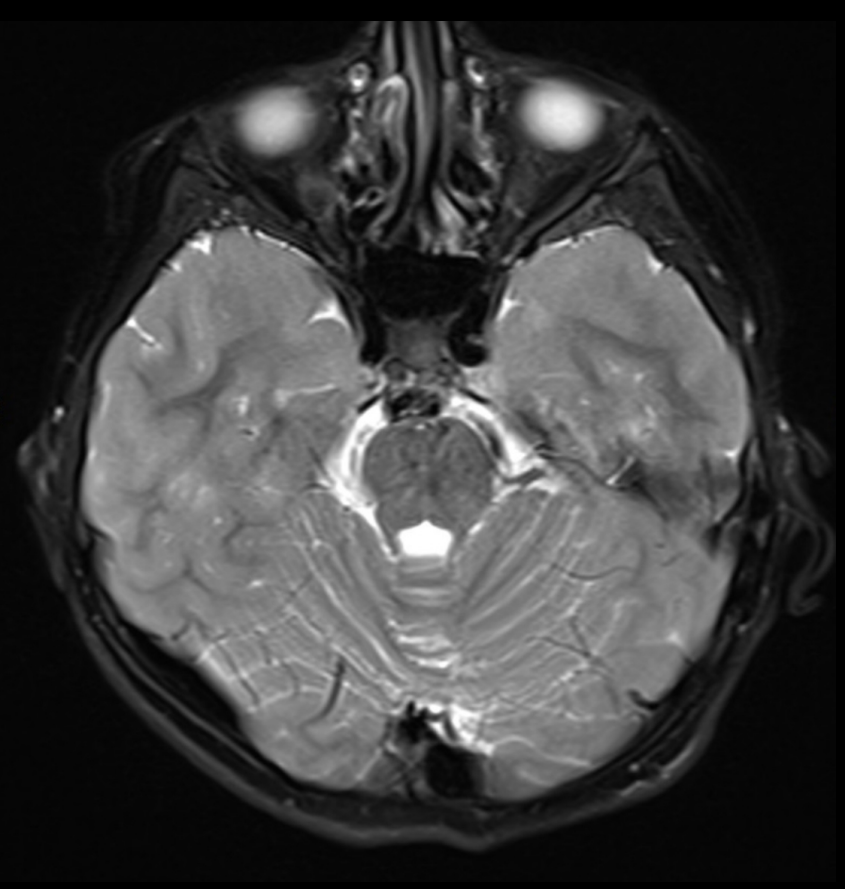
First Pregnancy

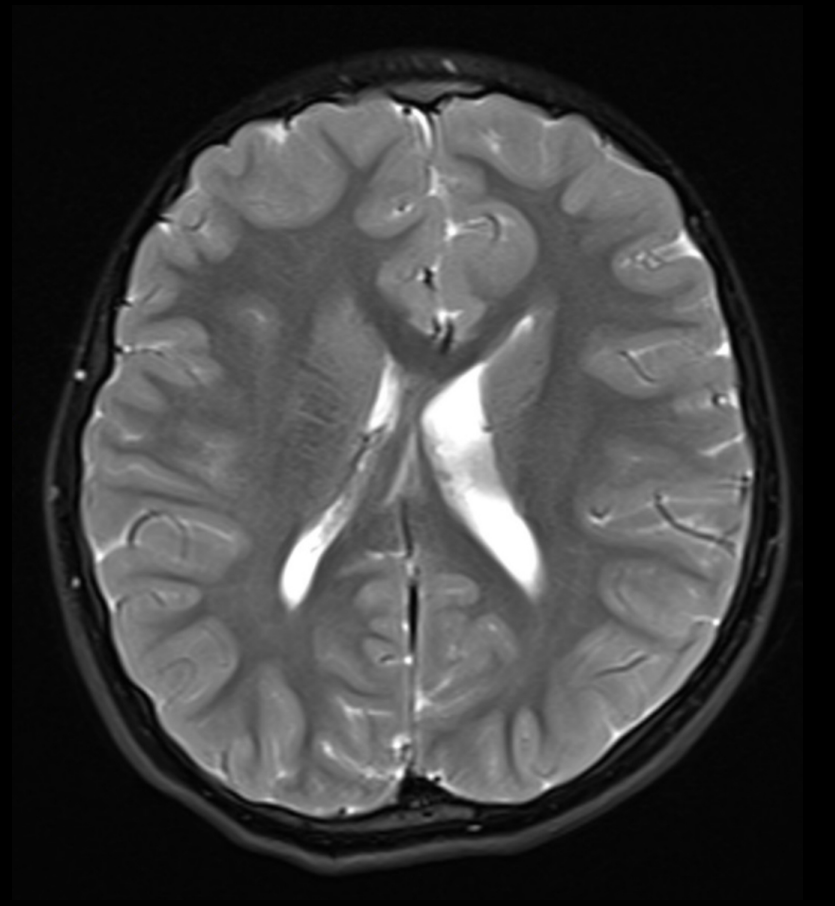


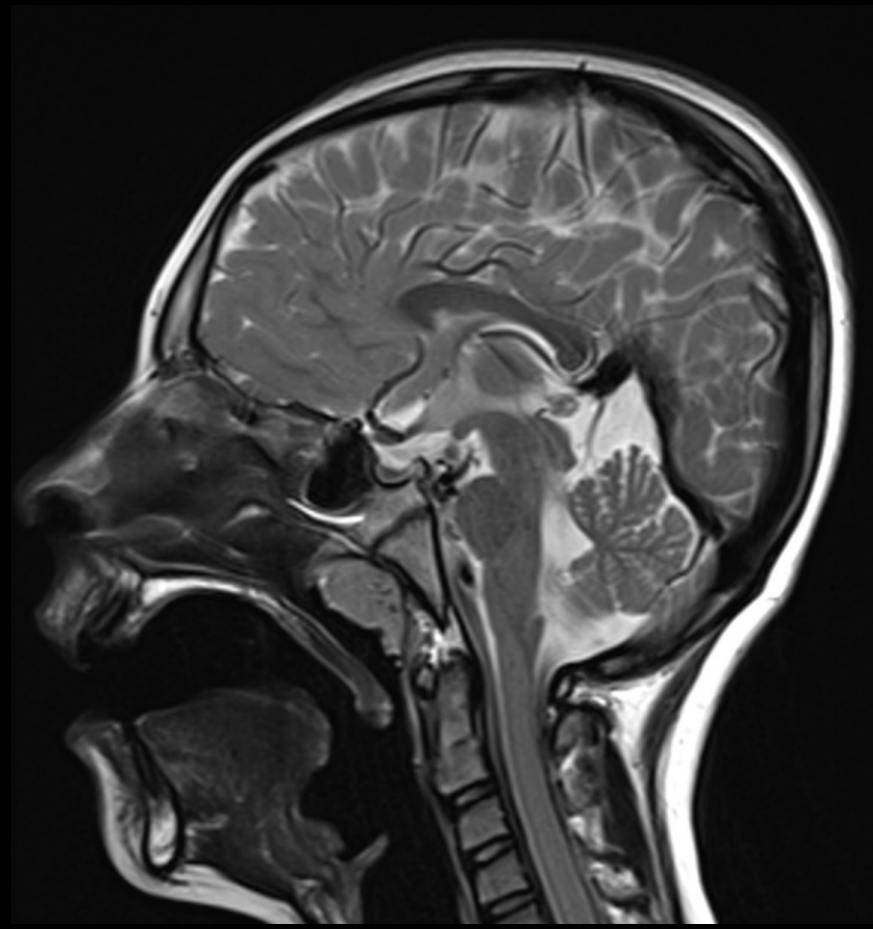
Second Pregnancy

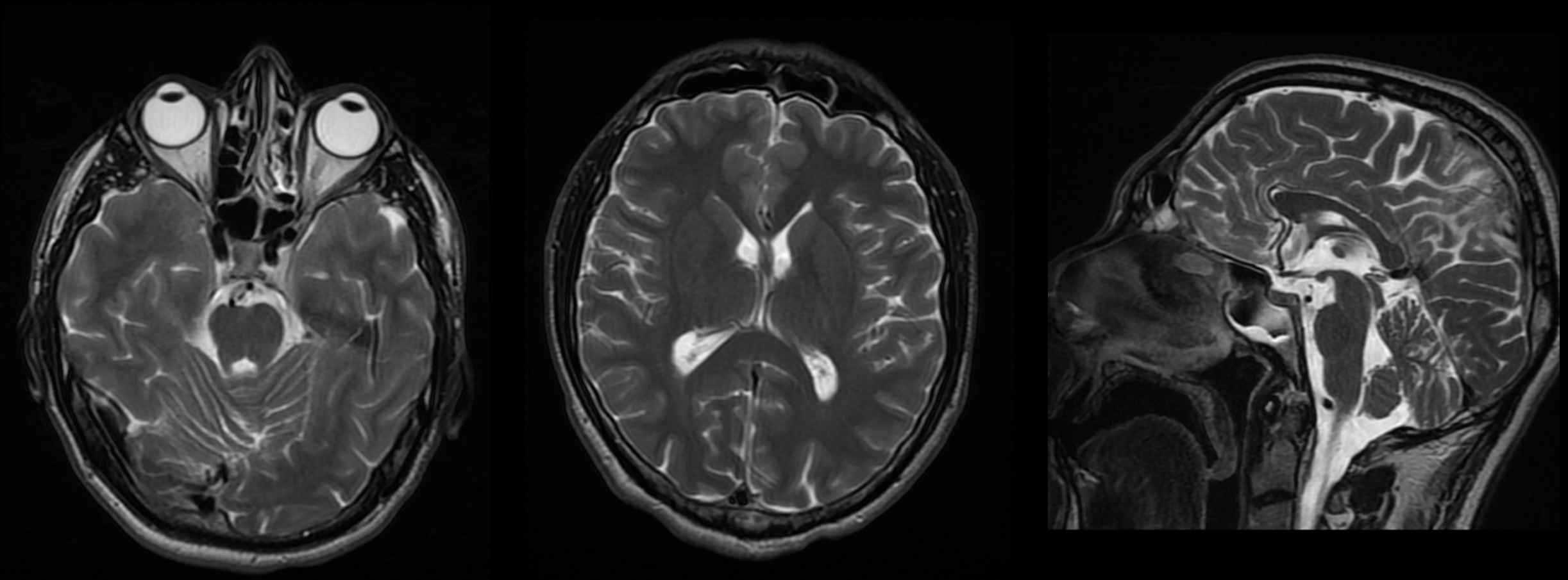
Daughter







Father TUBB



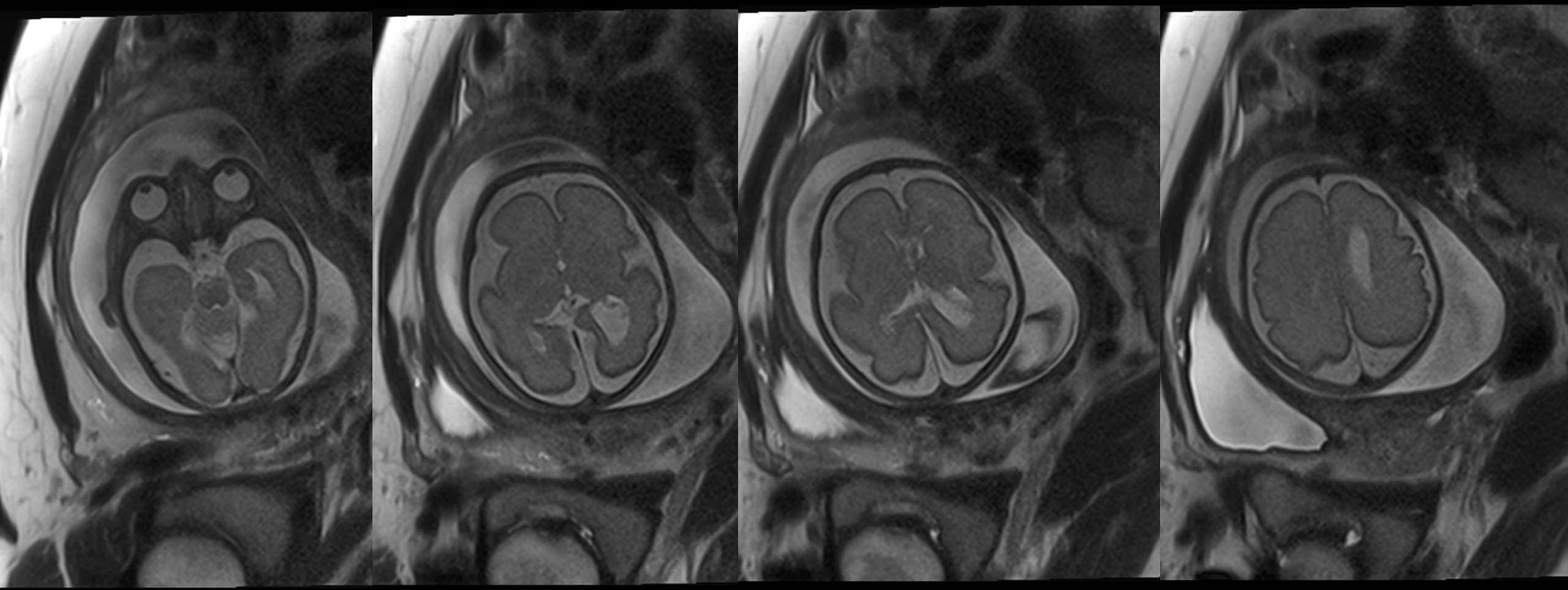
Cohort with a distinct and very similar MRI pattern

TUBB3

- *TUBB3* cortical malformations can be mild
- Hard to differentiate radiologically in utero between PMG and dysgyria.
- Autopsy in fetal TUBB3 related dysgyria are abnormal orientation of sulci and gyri, but normal neuron morphology and layering.
- Clinically can remain only mildly symptomatic

Congenital Mirror Movements Associated With Brain Malformations Child Neurology 2021

Fetal MRI 29 wk TUBB3



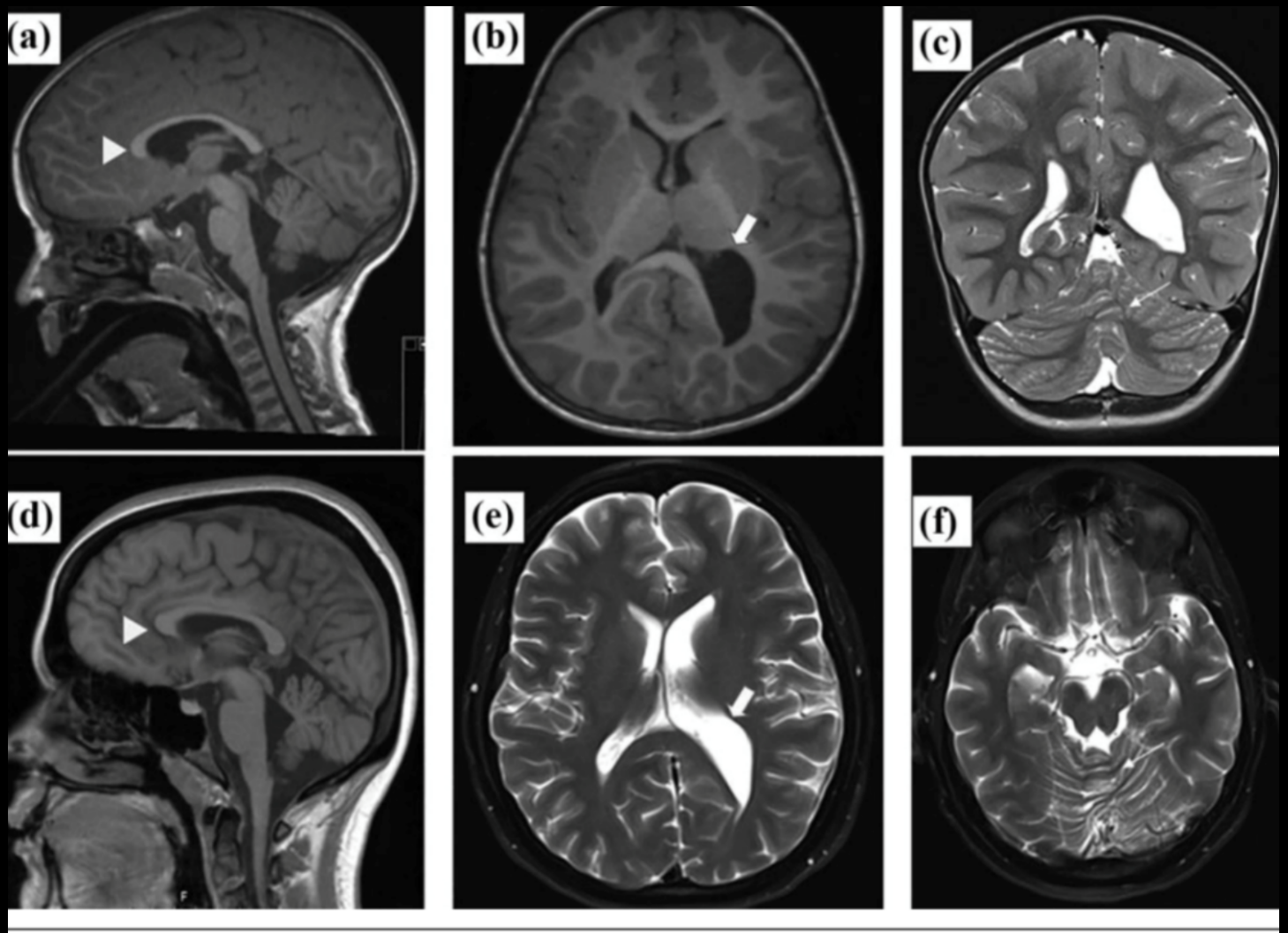
TUBB3

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

Autosomal dominant *TUBB3*-related syndrome: Fetal, radiologic, clinical and morphological features

Lubov Blumkin [a, b, c, *], Zvi Leibovitz [d, e], Karina Krajden-Haratz [c, f], Ayala Arad [g], Keren Yosovich [a, h], Liat Gindes [c, d], Ayelet Zerem [a, b, c], Liat Ben-Sira [c, i], Dorit Lev [a, b, c, j], Andrea Nissenkorn [a, b, c], Dvora Kidron [c, k], William B. Dobyns [l], Gustavo Malinger [c, f], Nadia Bahi-Buisson [m, n], Richard J. Leventer [o], Tally Lerman-Sagie [a, b, c]



maging of family II (cases 3 and 4, TUBB3 mutation). Brain MRI case 3 (age 3.5 years) (2a, 2b, 2c) and case 4 (a
dline T1 imaging depicts hypoplastic corpus callosum with underdeveloped rostrum (2a, d) (arrow head). Axi
l asymmetric enlargement of left lateral ventricle (2b, 2e) (solid arrow). Coronal T2 (2c) and axial T2 (2f)
nian and adjacent cerebellar hemisphere folia (2c, 2f) (arrow) and asymmetric brainstem (2f).

Sanger sequencing revealed the same variant in
(case 7).

ataxic gait and has severe motor dyspraxia. He
eral dystonia in the lower limbs and a positive

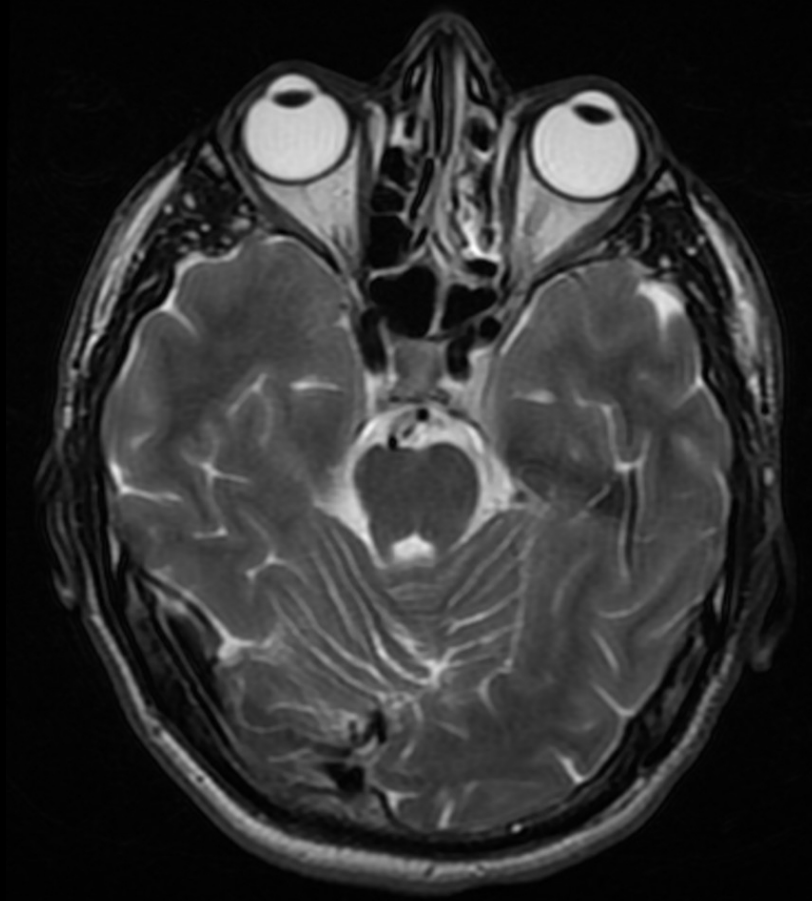
‘Tubulin-related cerebellar dysplasia’

- Cerebellar hemispheres +/- or vermian dysplasia
- Unilateral pattern (right > > left), localized in the postero-superior hemisphere
- Cerebellar cortex with abnormal orientation of the folia

  No cysts, thickening of cerebellar folia or signal abn.
- Frequent focal, unilateral cortical dysplasia refutes tendency to consider a focal cerebellar lesion

  as suggestive of prenatal acquired

  (disruptive)



Tubulin-related cerebellar dysplasia: definition of a distinct pattern of cerebellar malformation. Romaniello 2017

Multicentric study

(Trousseau Hospital in Paris, France, Ichilov Hospital in Tel Aviv and Wolfson Hospital in Holon, Israel)

Drs Benhamou, Malinger, Krajden, Leibovitz

- Retrospective study from 2007 to 2022
- Inclusion criteria:
  - genetically proven cases of tubulinopathies (prenatal diagnosis)
  - at least prenatal US
- Many cases with prenatal MRI
- Retrospective review of US and MR images (biometry and morphology)
  - major criterion (US/MRI) if present in more than 70% of cases
  - minor criterion (US/MRI) if present in more than 50% of cases
- Outcome
- Type of mutation

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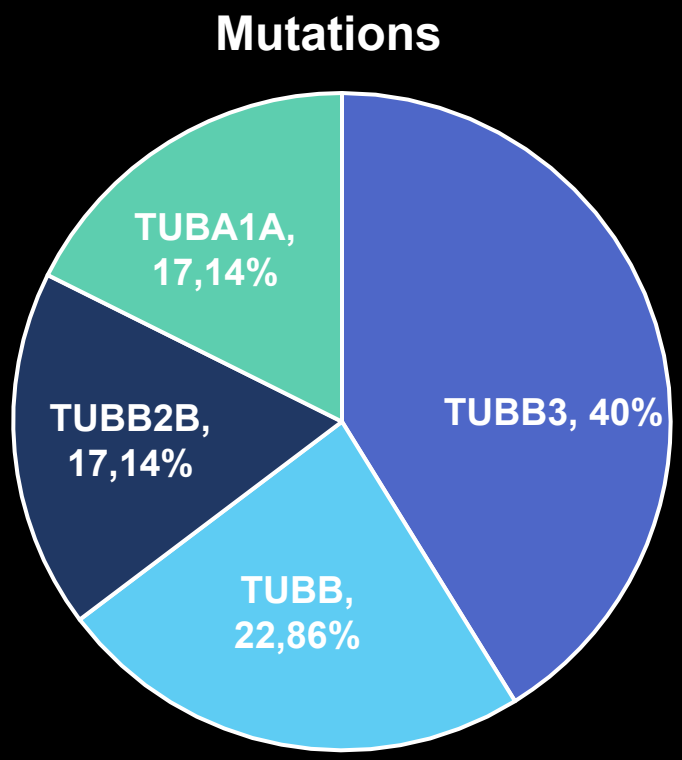
- 35 patients (F= 60%, M =40%) : n=4 < 2016, n= 31 ≥ 2016
- Consanguinity in one case (third-degree cousins)
- Overall 17/35 patients (9 families) with one of the parents (mother n=7, father n=2) showing mutation in a tubulinopathy gene (*TUBB3*, *TUBB* and *TUBB2B*)
- MRI performed in 32 cases



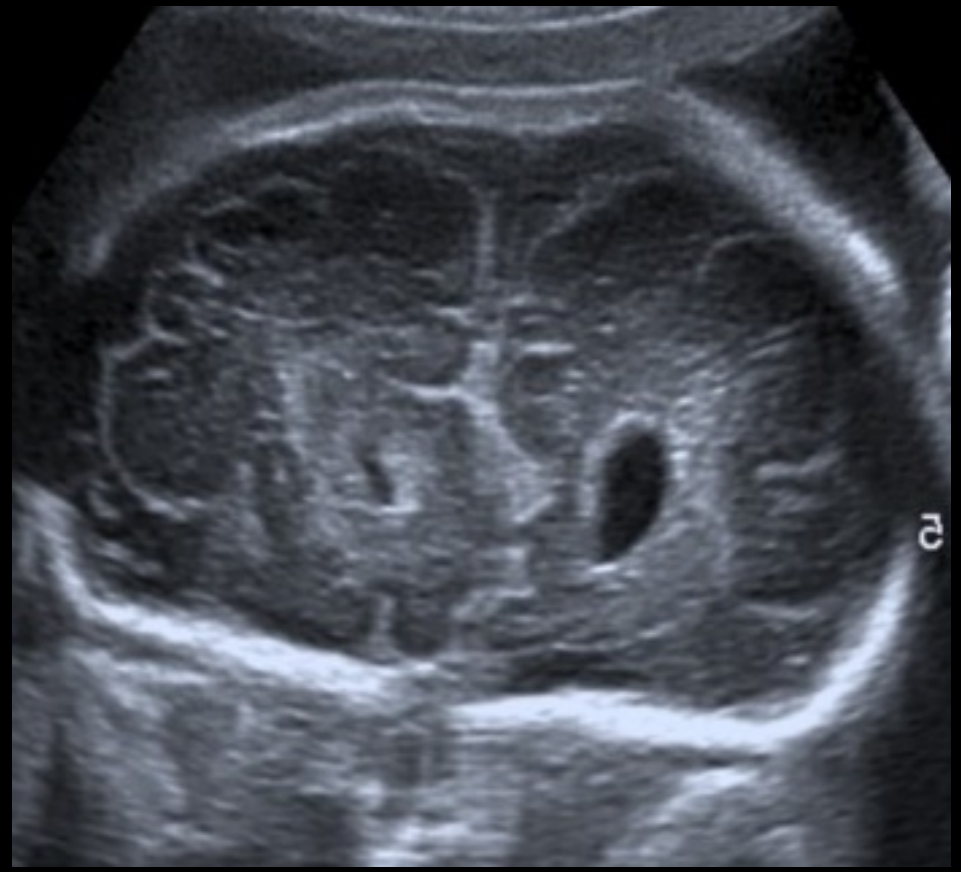
Biometry

- **US**
  - Normal fetal weight n=34
  - Normal HC n= 34, HC= 3rd centile n=1 and = 5th centile n=1)
  - Normal TCD n=32, <3rd centile n=3
  - Normal vermian height n=29
- **MRI:**
  - Normal supratentorial biometry n= 28/32
  - Normal TCD n= 28/32
  - Vermian height <3rd centile in 13/30
  - Anteroposterior diameter of the pons ≤ 5th centile in 20/30 = 66.6%

Morphology: extra CNS findings

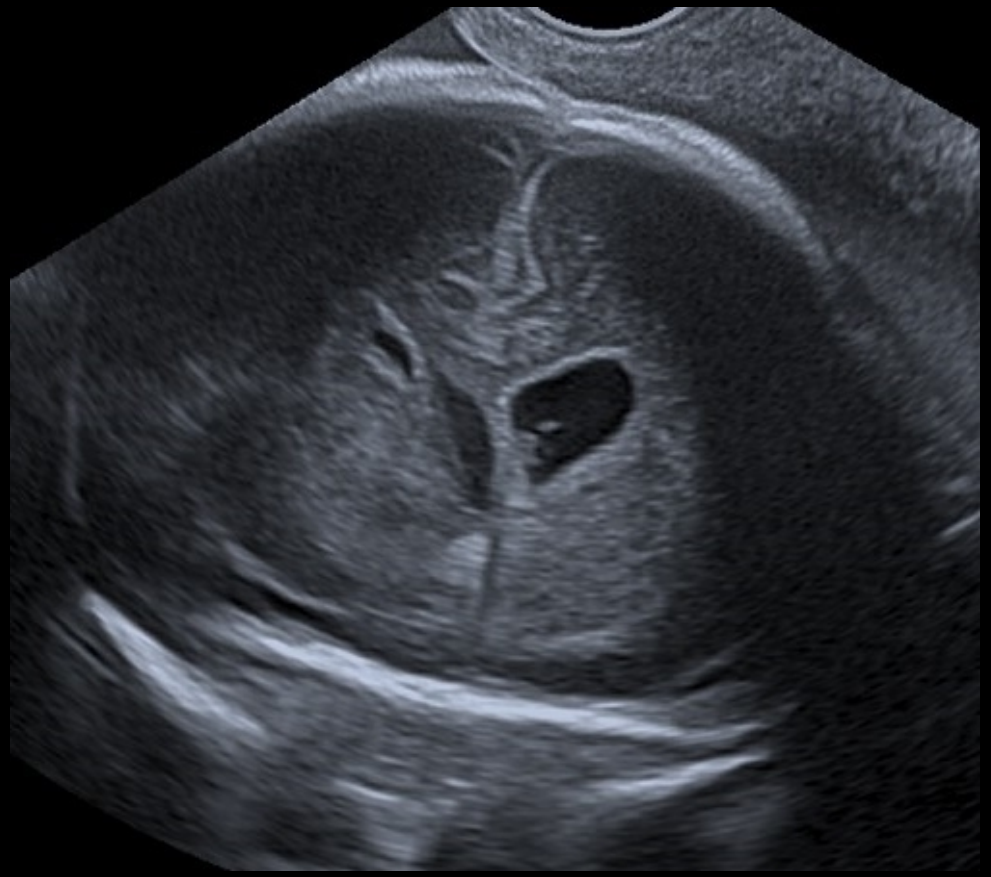
- US
  - Dysplastic kidney n=1
  - Single umbilical artery n=2

Midline



Midline distortion

73.33%

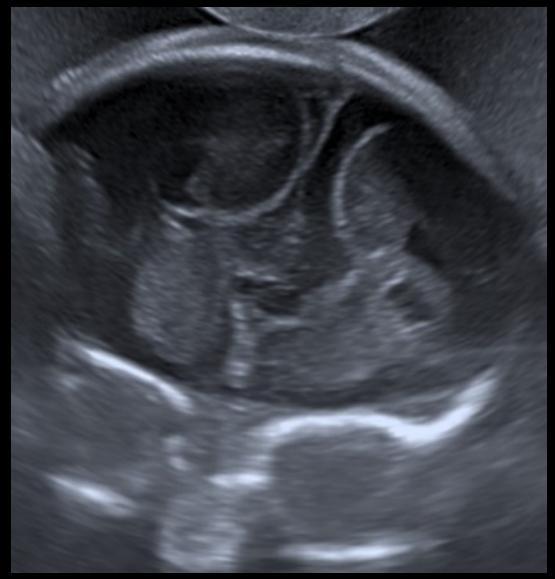


Distortion of the cavum septi pellucidi

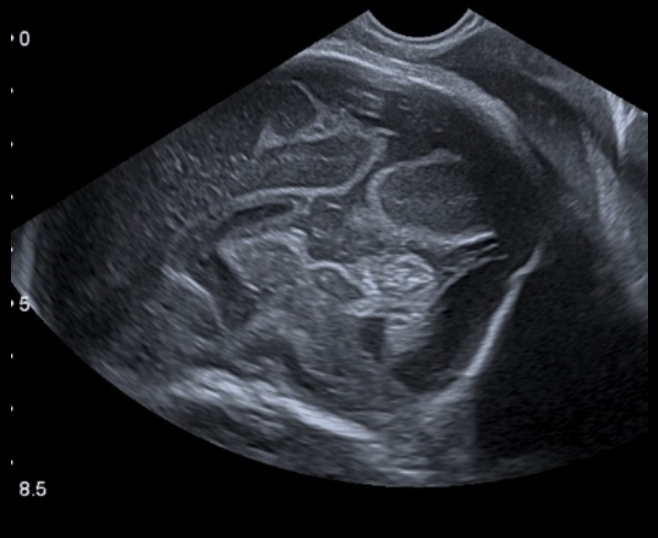
57.69%

Abnormalities of the corpus callosum

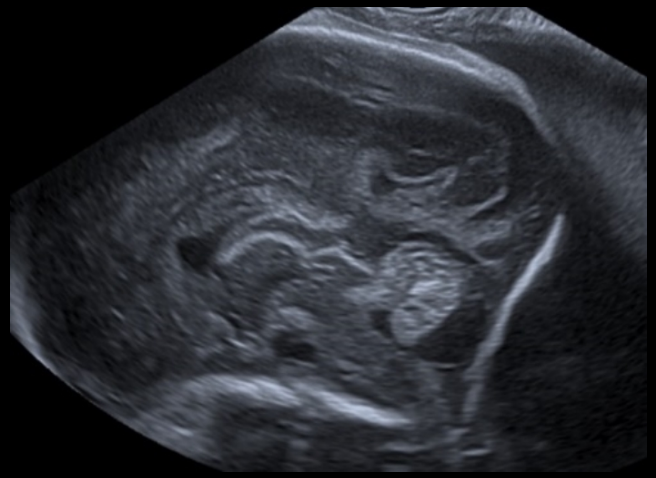
58.82%



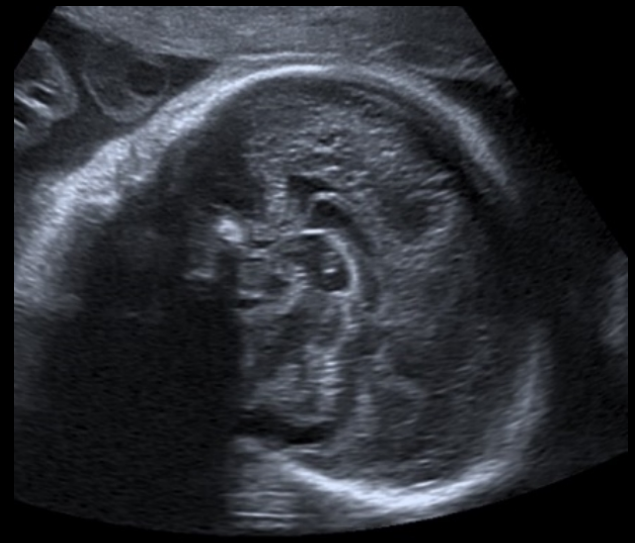
Complete agenesis
10%



Partial agenesis
15%



Short
35%



Dysgenesis
40%

Abnormalities of the lateral ventricles

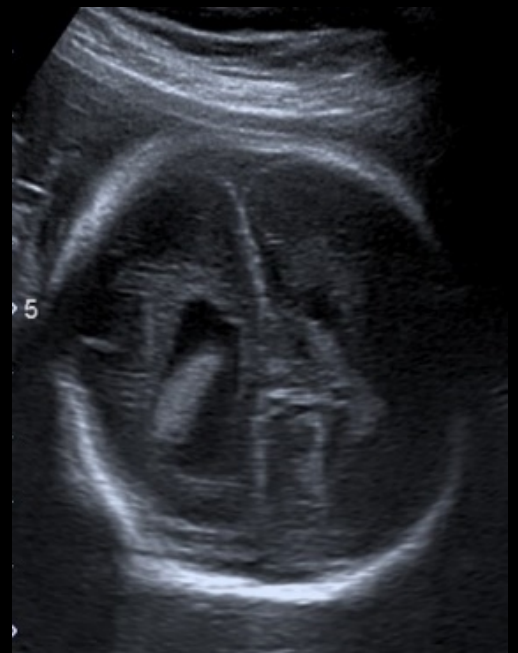
- Ventricular dilatation

61.76%

Unilateral (77 %), bilateral (23%)

- Ventricular asymmetry

87.1%



- Dilated frontal horns

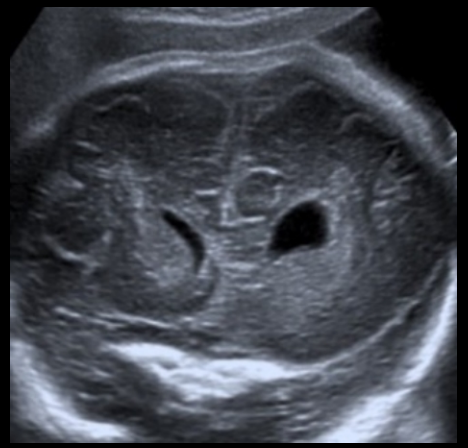
90%

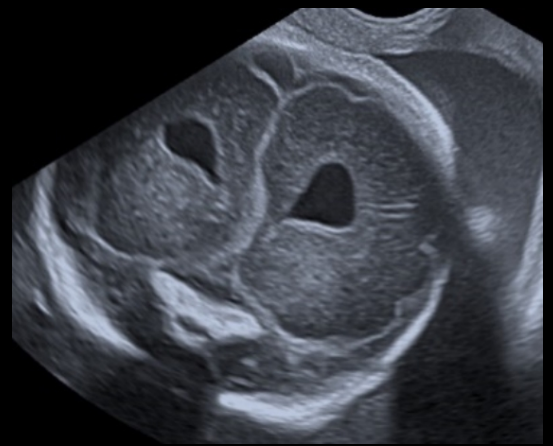
Unilateral (62.96%), bilateral (37.04%)

- Dysmorphic frontal horns

90%

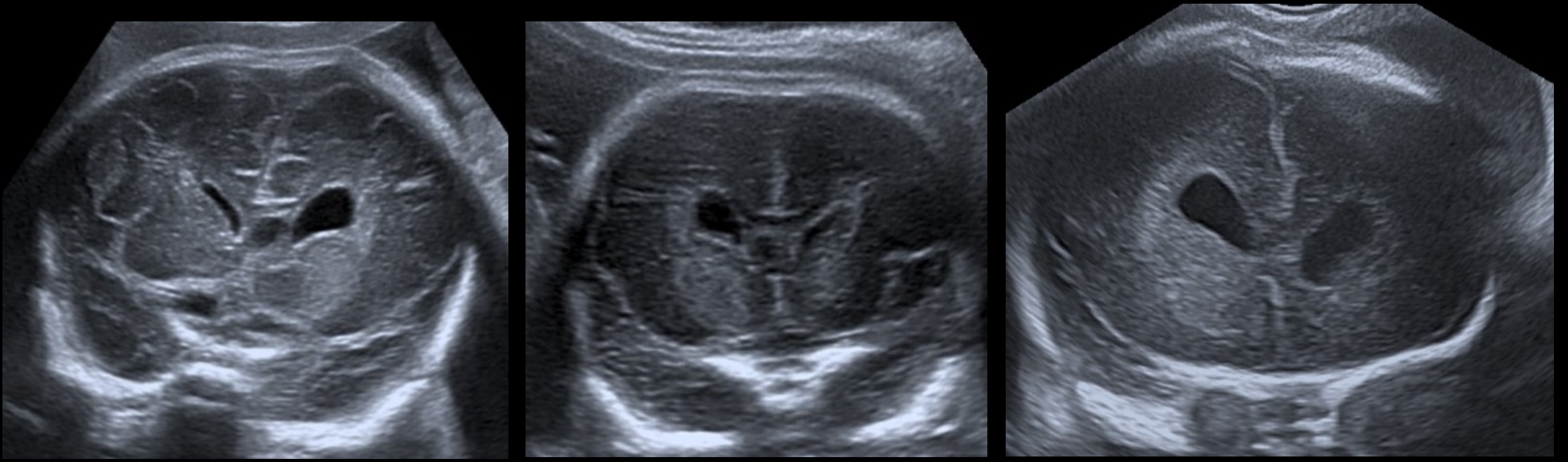
Unilateral (62.96%), bilateral (37.04%)





Hypertrophic basal ganglia

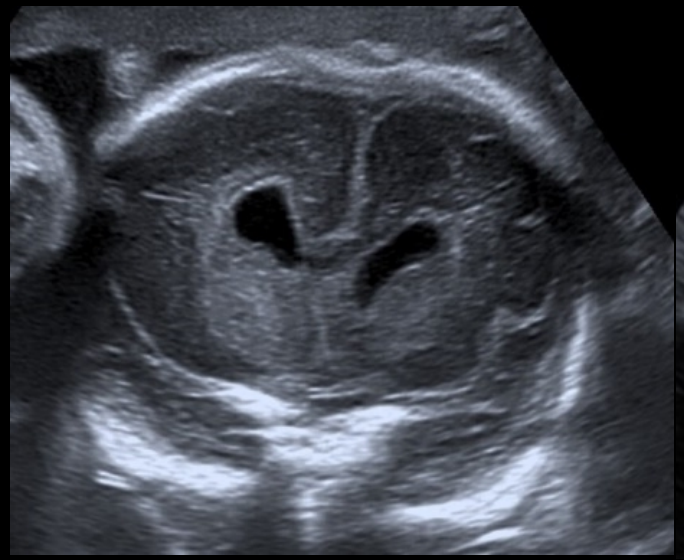
61.29%

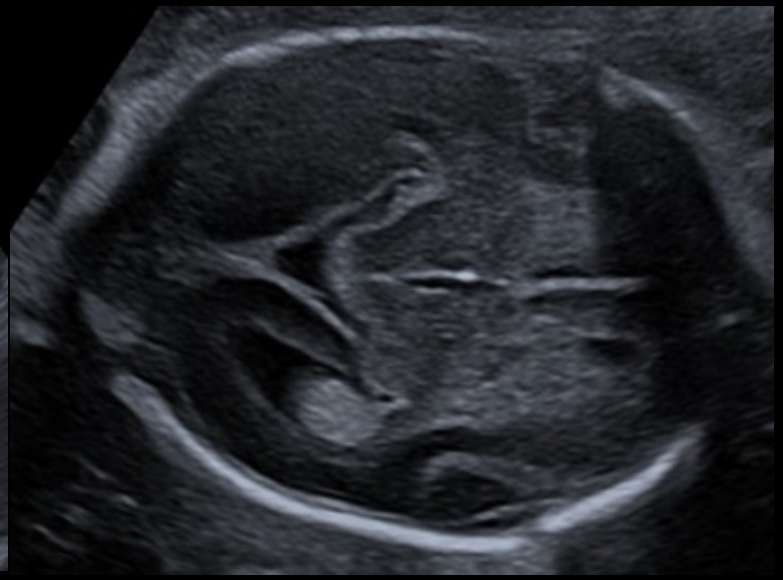


Gyration abnormalities

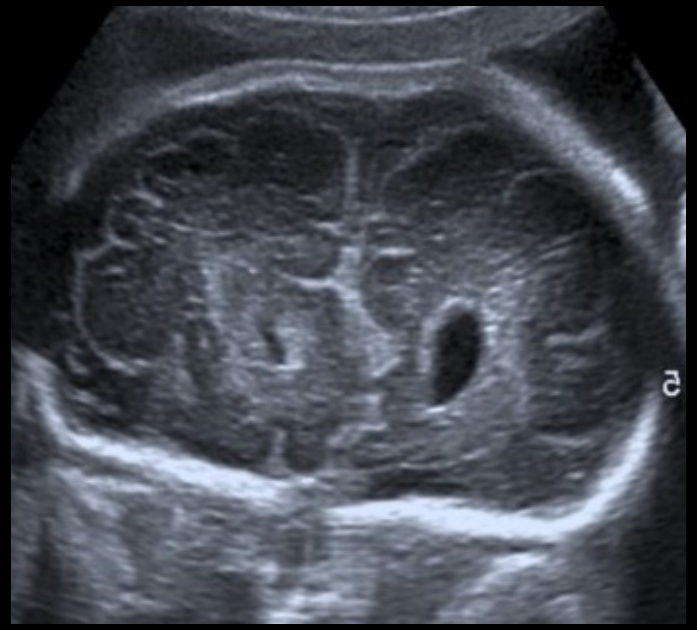
70.97%

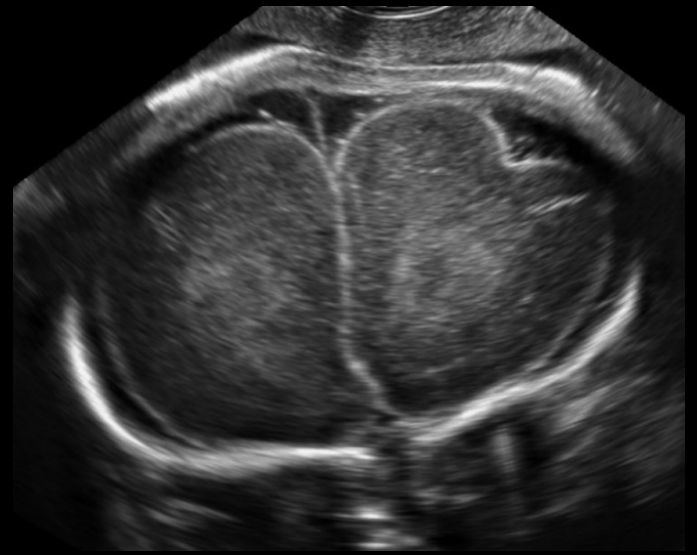
Asymmetrical Sylvian fissures 84%





Dysgyria (19%)





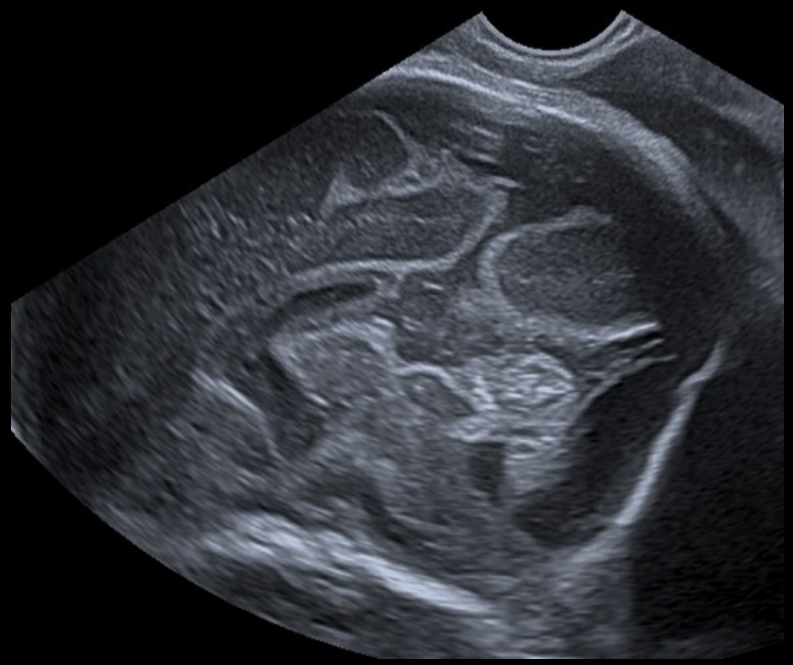
Posterior fossa

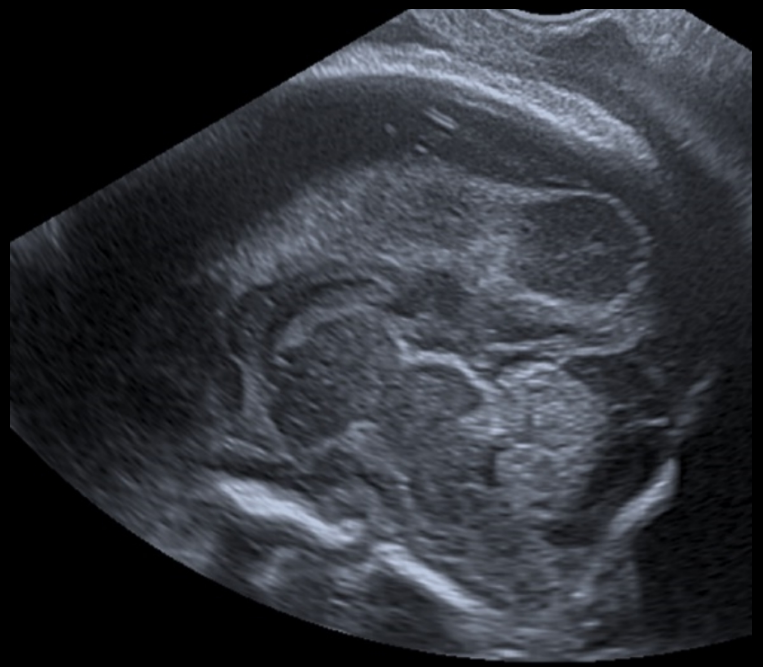
Abnormal brainstem

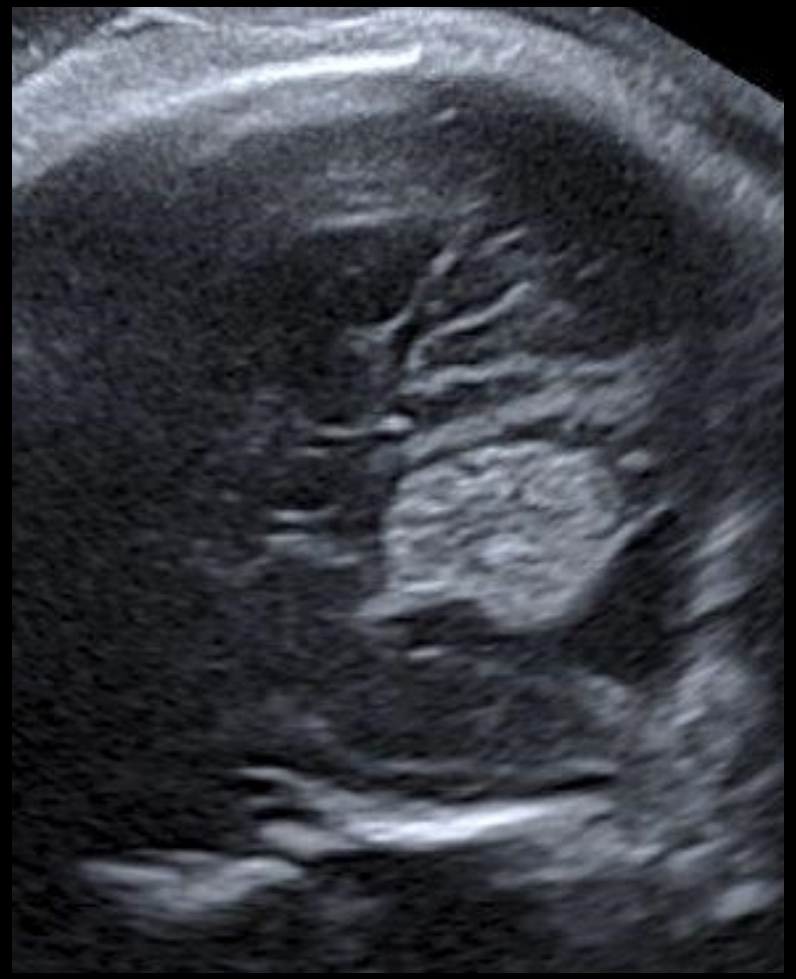
48.28%

Abnormal vermis

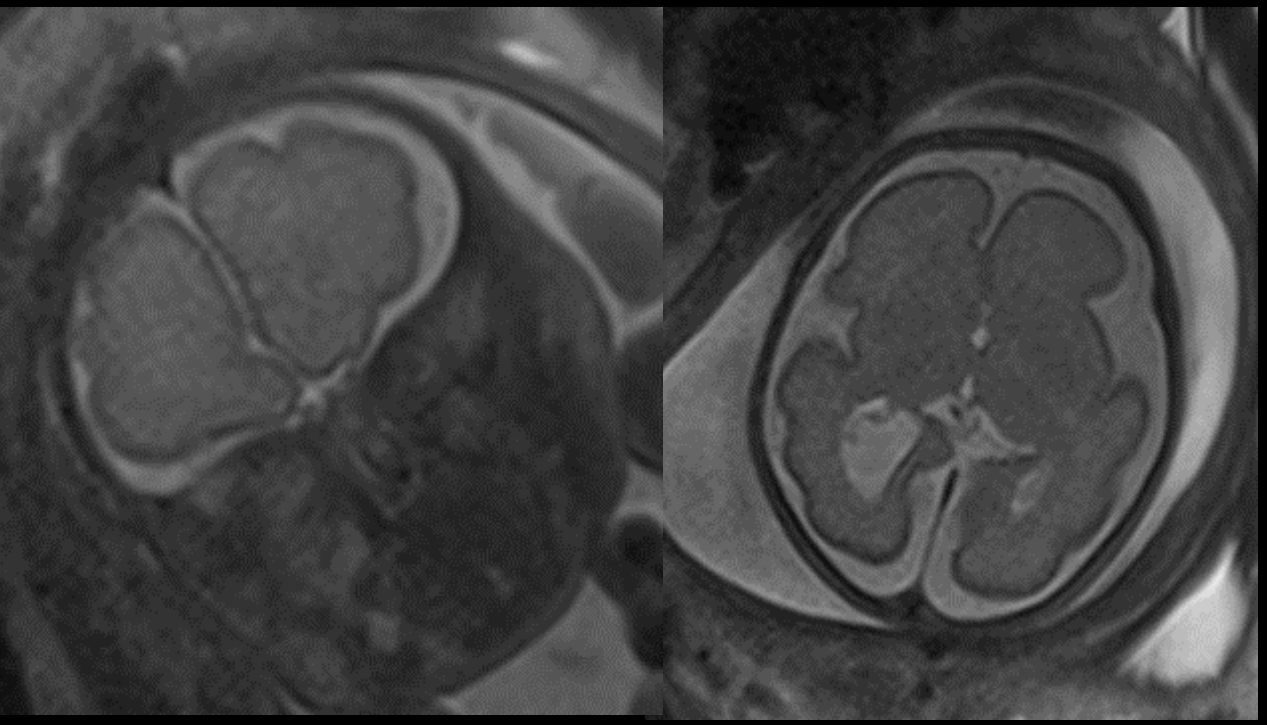
35.48%





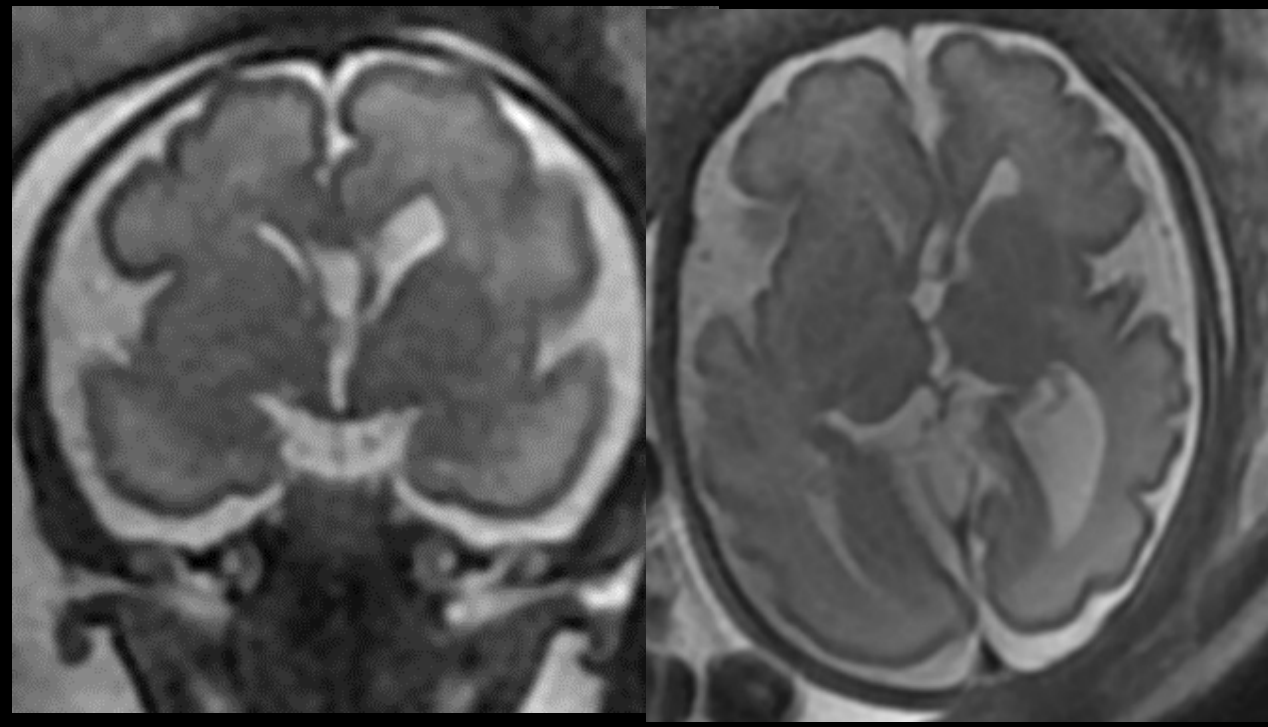


Midline



Midline distortion

87.10%

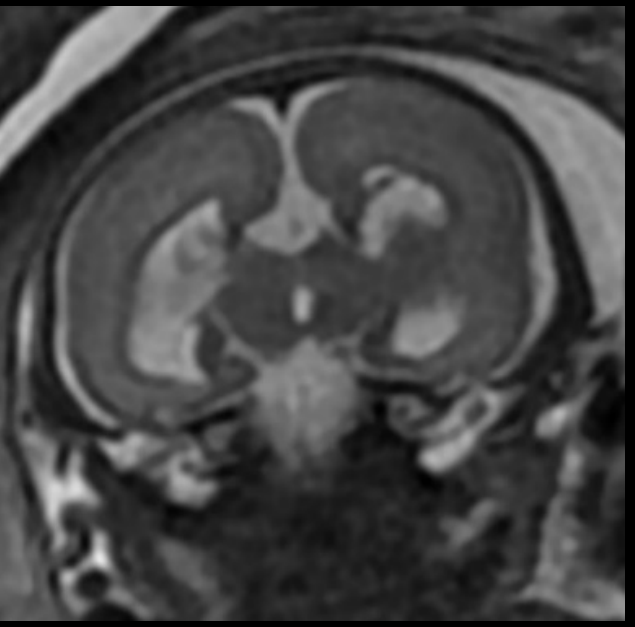


Distortion of the cavum septi pellucidi

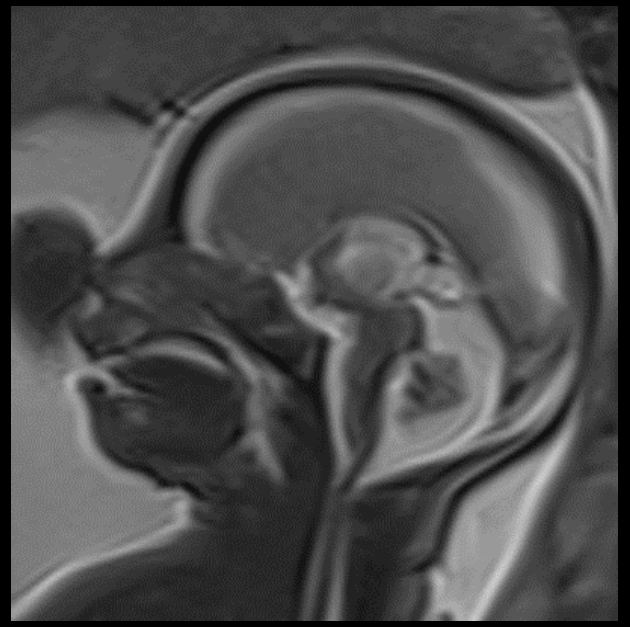
85.19%

Abnormalities of the corpus callosum

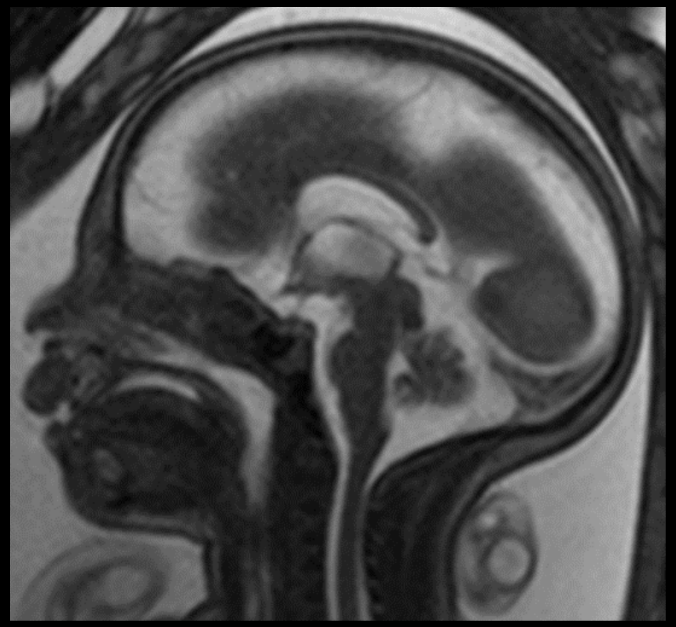
38.71%



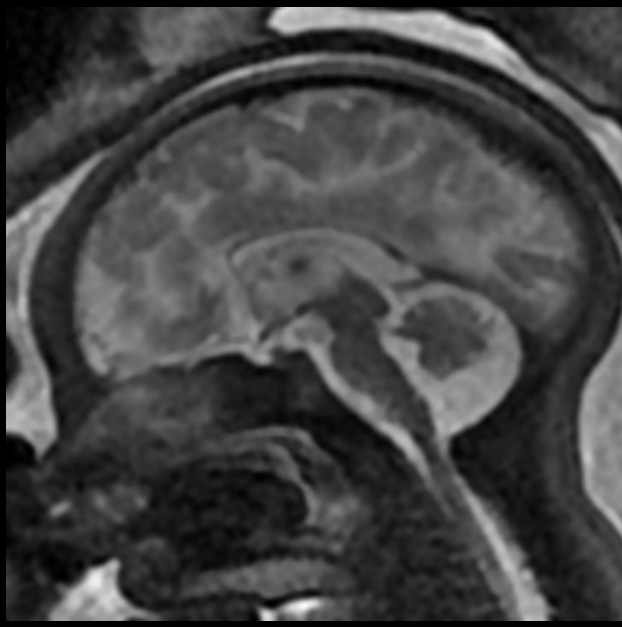
Complete agenesis
8.3%



Partial agenesis
50%



Short
16.67%



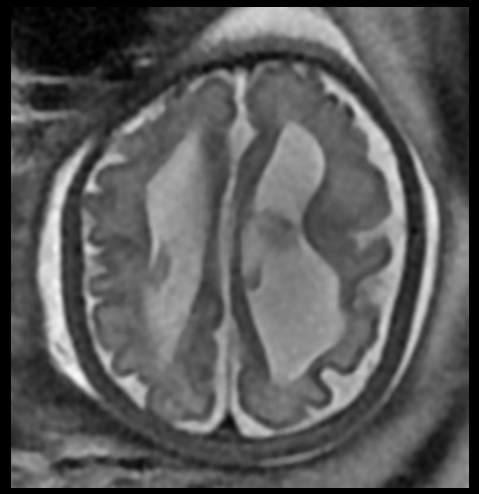
Dysgenesis
25%

Abnormalities of the lateral ventricles

- Ventricular dilatation

78.13%

Unilateral (84 %), bilateral (16%)

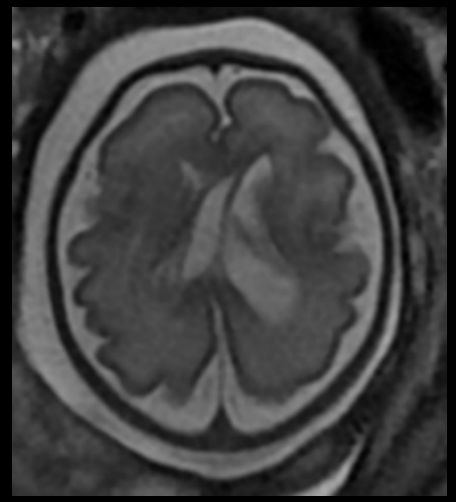


- Ventricular asymmetry

96.77%

- Ventricular distortion

90%



- Dilated frontal horns

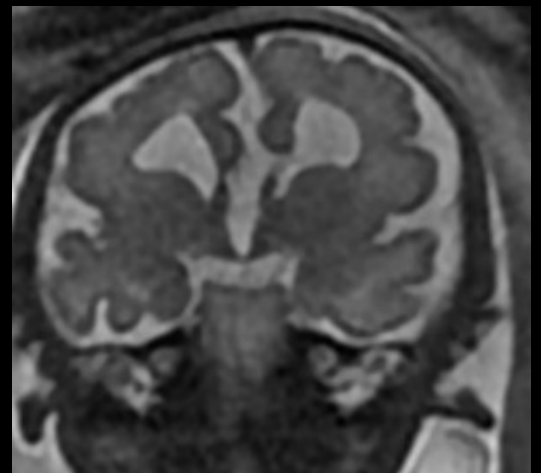
89.66%

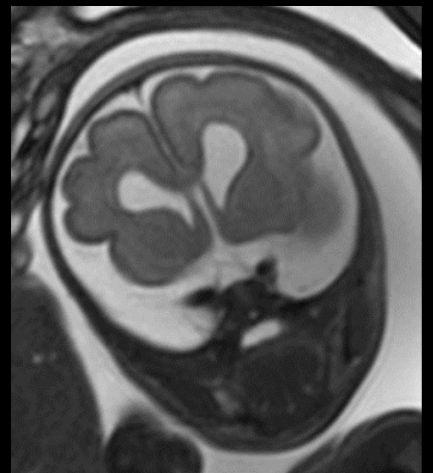
Unilateral (70%), bilateral (30%)

- Dysmorphic frontal horns

80%

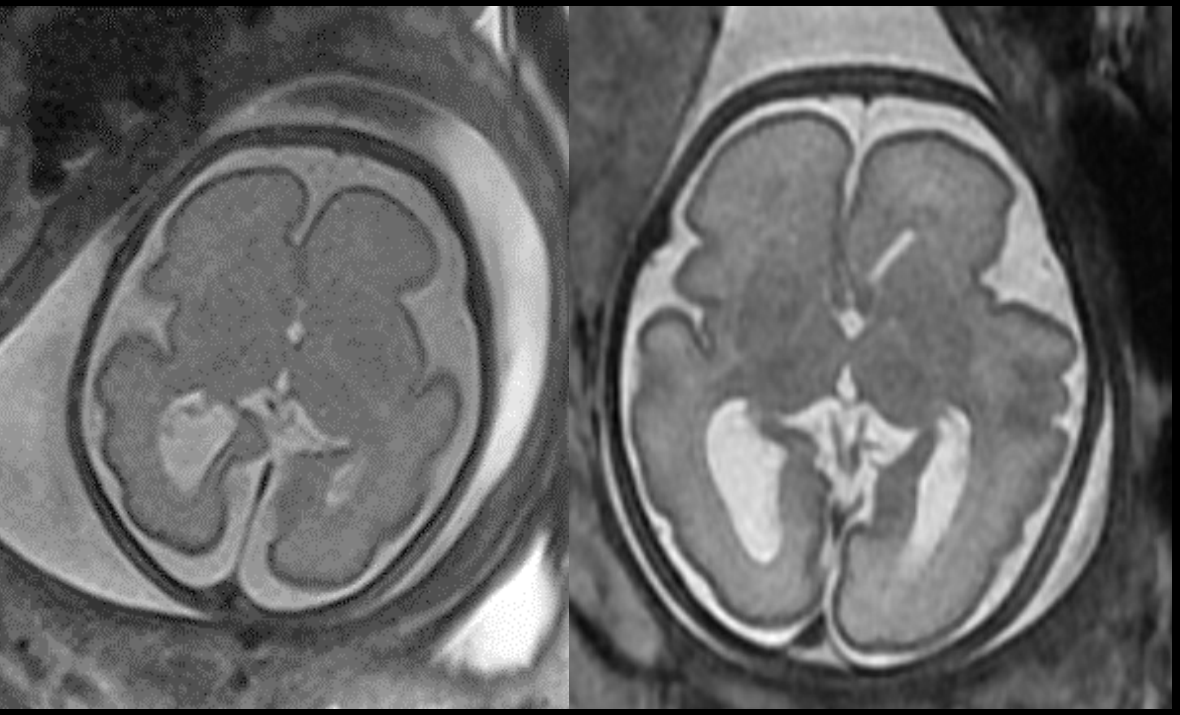
Unilateral (58.33%), bilateral (41.67%)





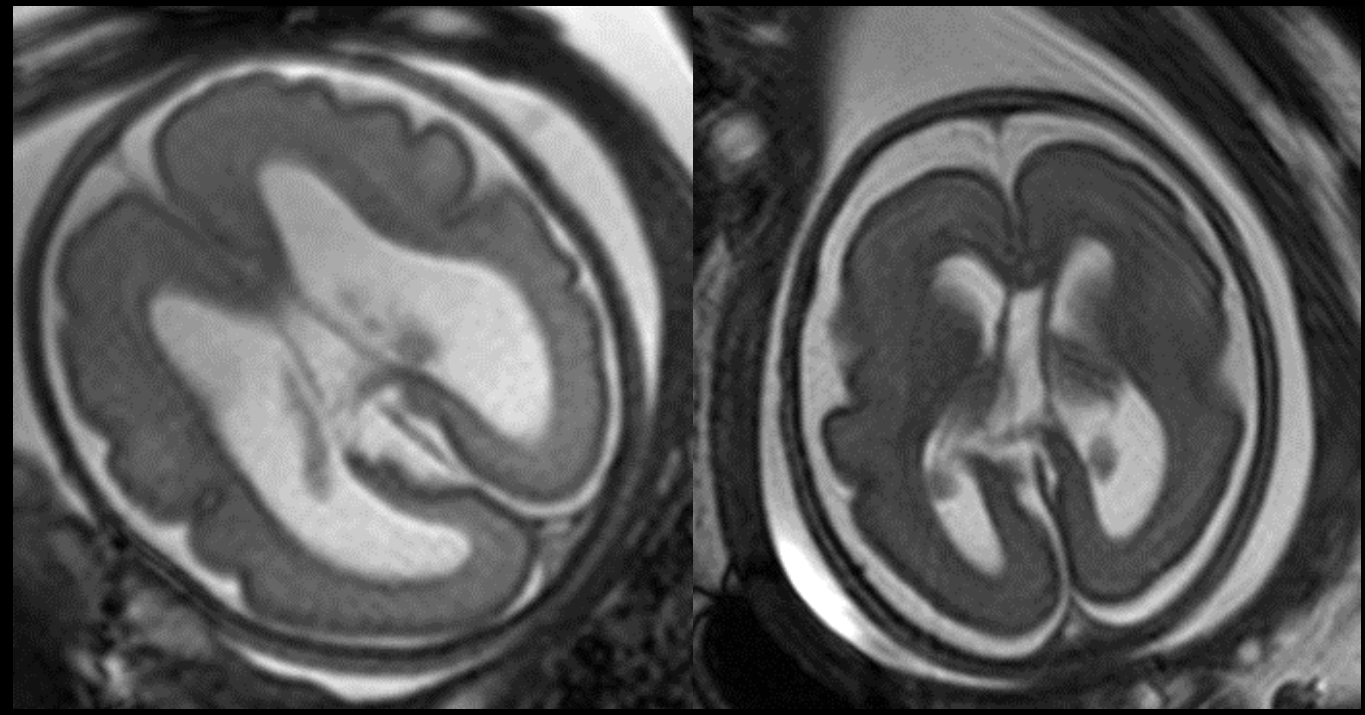
Gyration abnormalities

100%



Asymmetrical Sylvian fissures
+/- delayed gyration

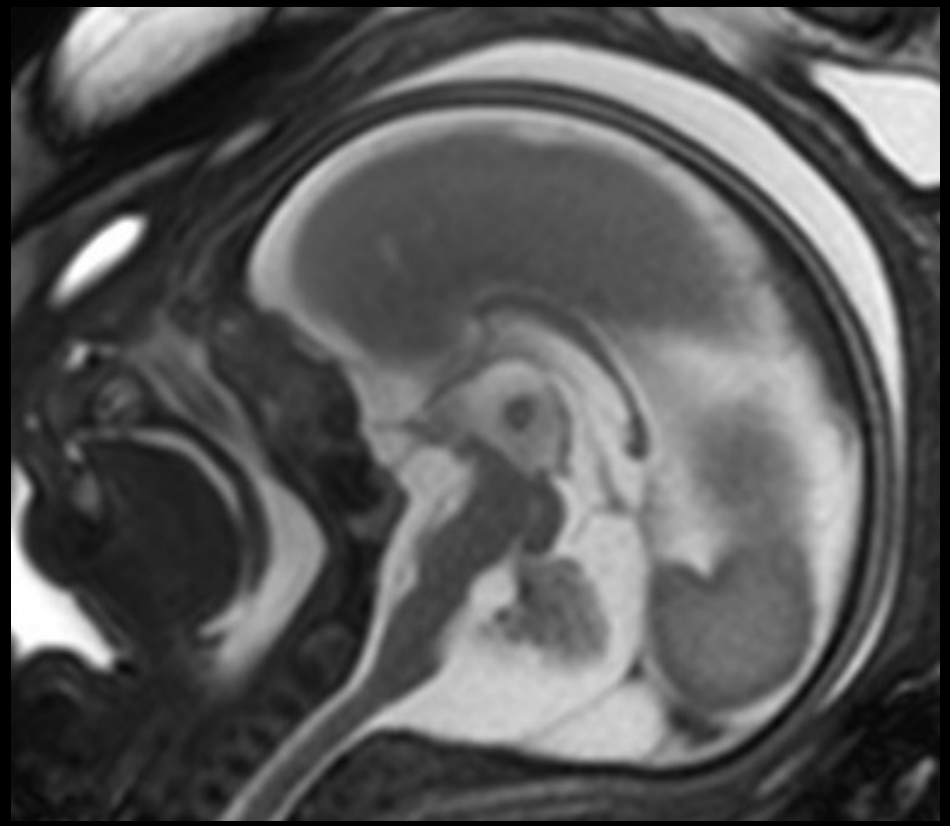
23.33%



Dysgyria +
asymmetrical Sylvian fissures

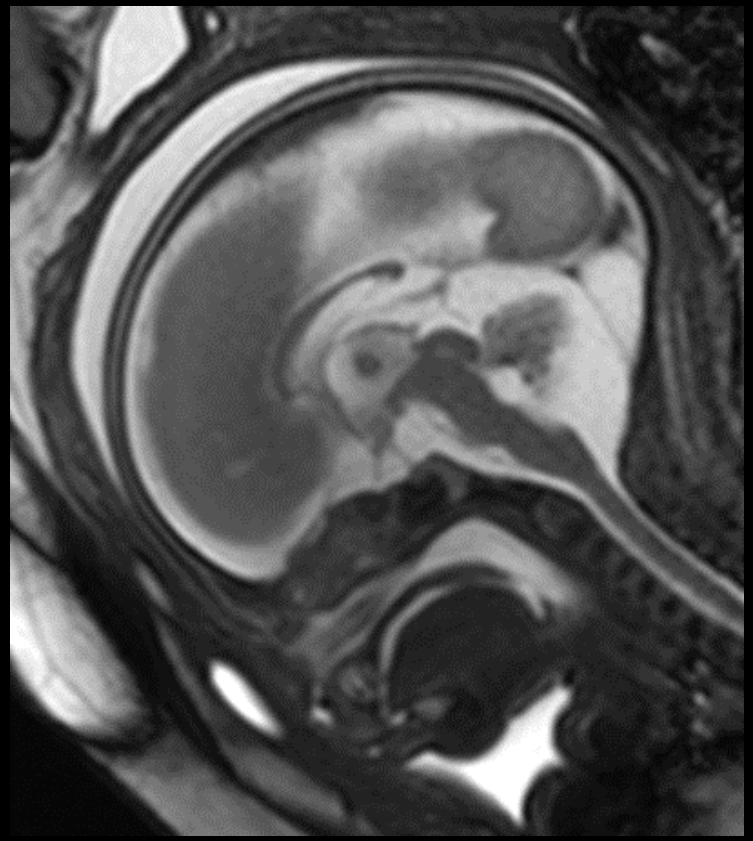
76.67%

Posterior fossa



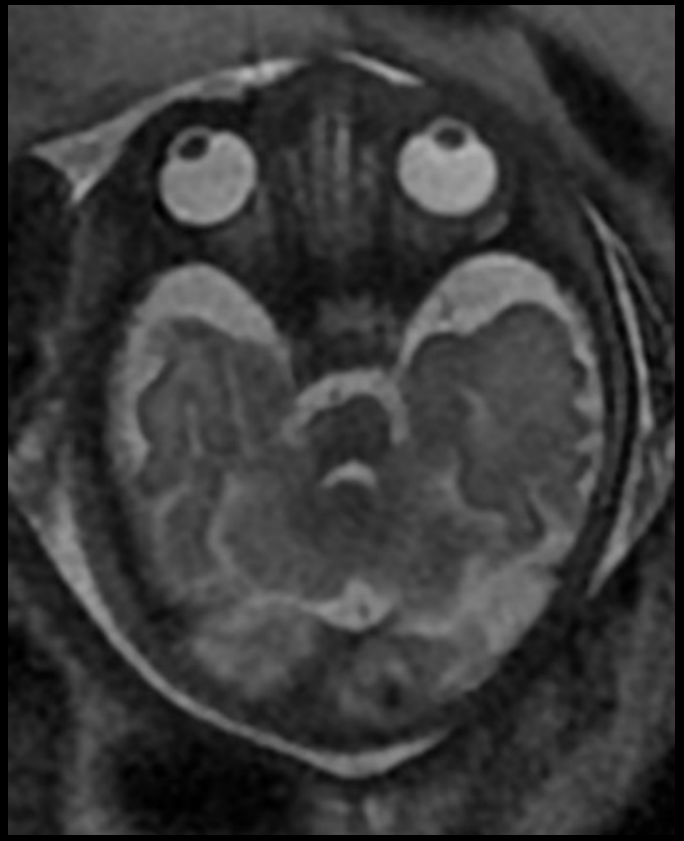
Abnormal vermis

30%



Abnormal brainstem

70%



Brainstem asymmetry

70%

Major findings

US

- Midline distortion
- Ventricular asymmetry
- Dysmorphic frontal horns
- Dilated frontal horns
- Abnormal gyration

Minor findings

US

- Distortion of the CSP
- Anomalies of the corpus callosum
- Ventricular dilatation
- Hypertrophic basal ganglia

MRI

- Midline distortion
- Distortion of the CSP
- Ventricular dilatation
- Ventricular asymmetry
- Ventricular distortion
- Dysmorphic frontal horns
- Dilated frontal horns
- Abnormal gyration
- Abnormal bulge of the pons
- Brainstem asymmetry

MRI

- None

Outcome

Termination of pregnancy in 22/35 cases at a mean gestational age of 26 weeks (25-34)

Conclusion

- Many underdiagnosed cases of tubulinopathies before 2016
- Disease probably affecting much more fetuses than previously thought
- In half patients, disease inherited from one parent (mother++), may be asymptomatic
- Diagnosis achieved by US only
- US> MRI: morphology of the CC, basal ganglia
- MRI> US: dysgyria, brainstem (bulge of the pons, asymmetry), ventricular distortion

BRAINSHOP TEL-AVIV