ESPR
European Society of Paediatric Radiology
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42nd Post Graduate Course

The fetal brain: migration and gyration anomalies – Pre and postnatal correlations

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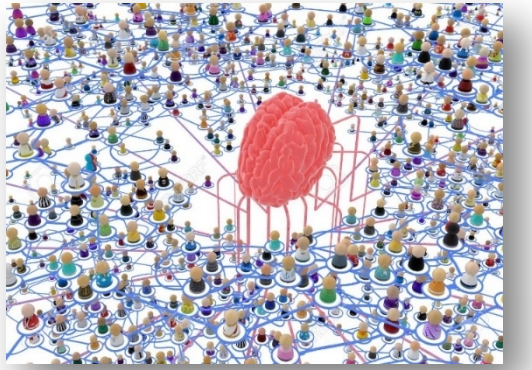
- No disclosures

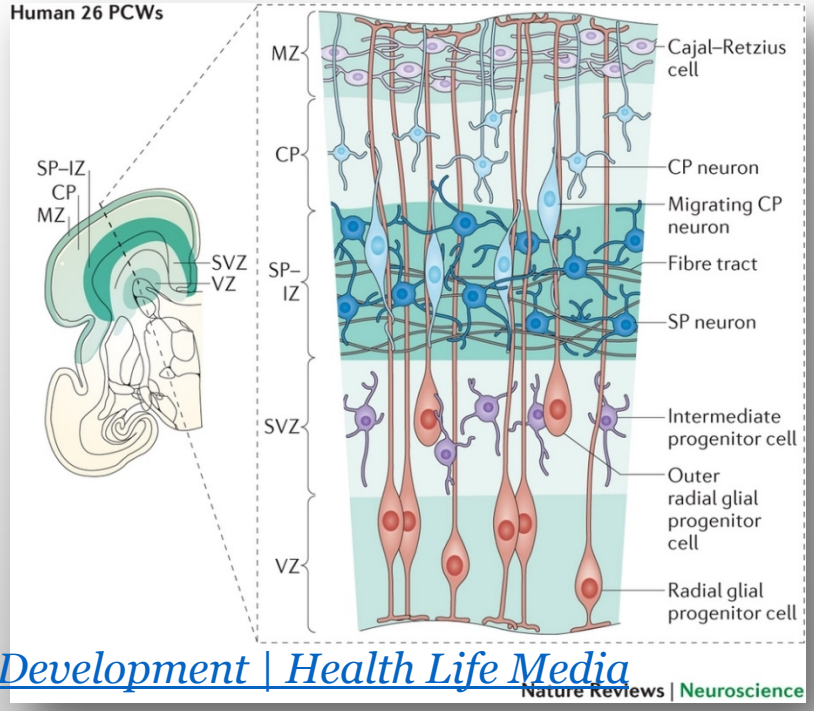
Learning objectives

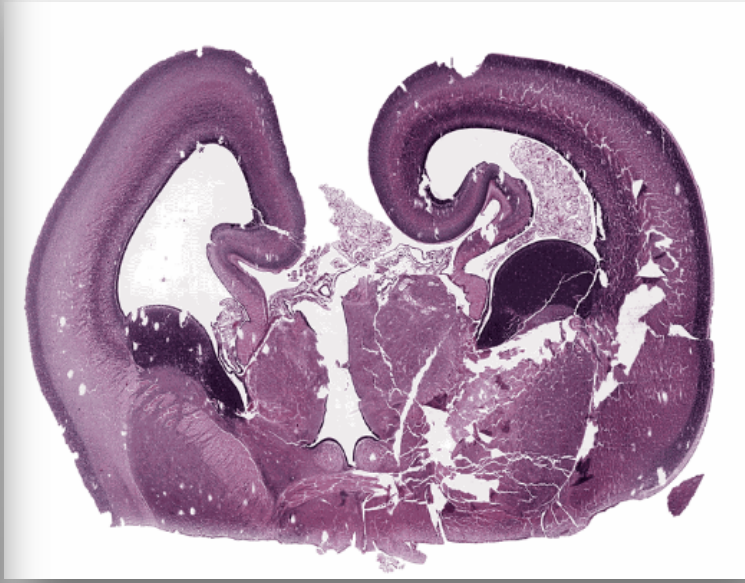
- Focus on those cortical malformations (MCD) detected with antenatal imaging, mainly fetal MRI
- Present the main antenatal MR findings to raise the suspicion for MCD and guide genetic testing
- Present those MCD that may be missed with antenatal imaging
- Describe correlation between fetal and postnatal MRI findings
- ~~Mention the role of important signaling pathways and of some groups of genes~~

Cerebral cortex – embryology



- Laminar structure of precisely spatially organized neurons in horizontal layers and vertical columns
- Development is a result of tightly regulated and coordinated procedures:
  - Neurogenesis
  - Neuronal migration
  - Neuronal wiring

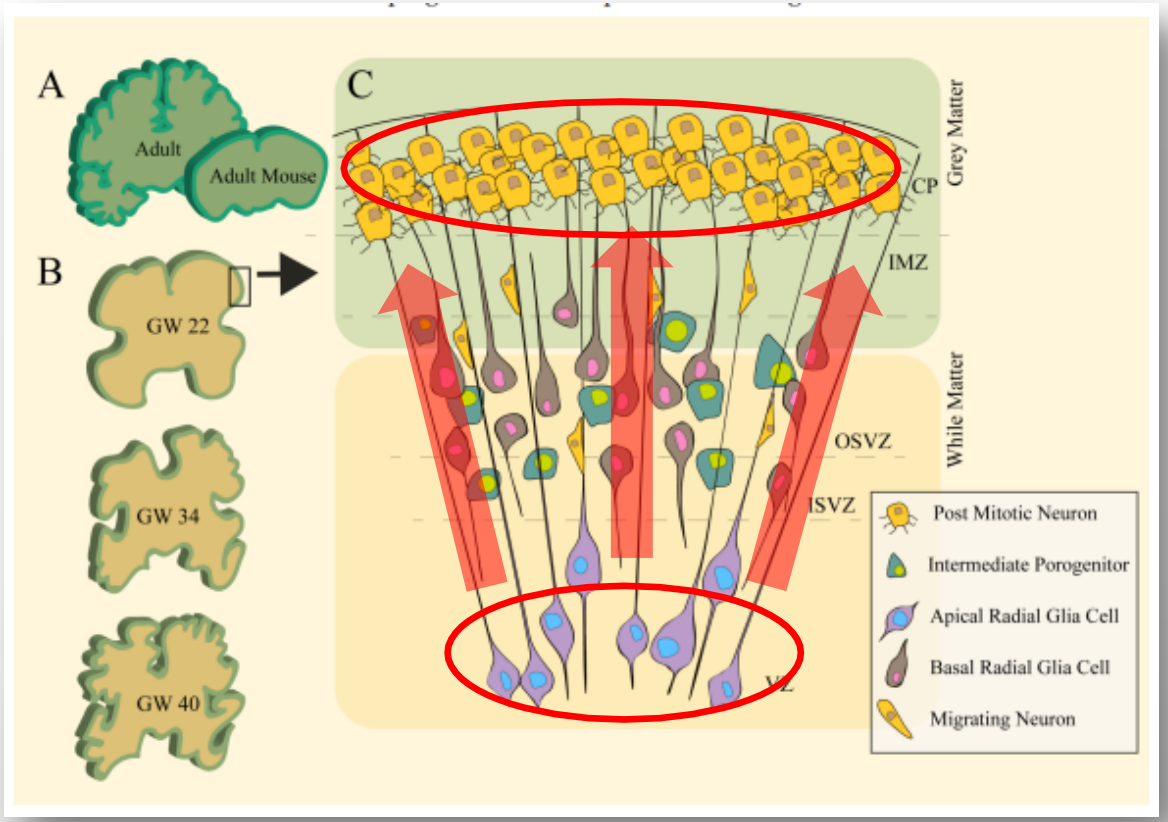




[Cerebral Cortex: Development | Health Life Media]

Cortical development

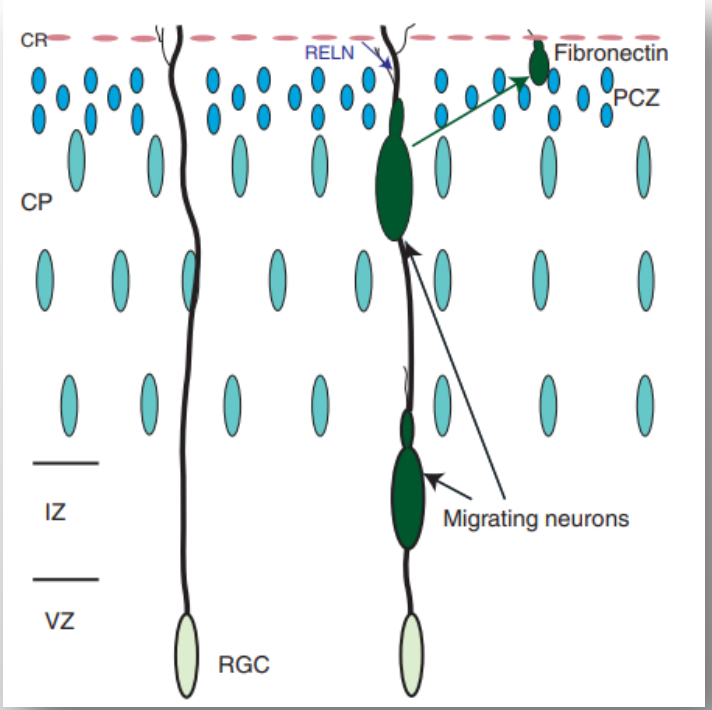
- Ventricular zone
  - neuronal precursor **proliferation**
  - neuroblast departure
- Neuroblast **migration** tangentially and radially
  - microtubule transport and stabilization
  - centrosomal positioning
  - vesicle trafficking and fusion
  - neuroependymal integrity
- Migration arrest
- Neuronal **organization**



Karlinski M. Opera Med Physiol 2018

Abnormal corticogenesis

- Developmental disorders of migration and gyration – malformations of cortical development (MCD)
- Pathogenesis is multifactorial
  - genetic mutations
  - in utero insults, such as infection or ischemia
- Timing
  - either in utero at different stages of brain development
  - during the perinatal period after corticogenesis
- According to the stage affected
  - abnormal head size
  - abnormal brain surface
  - abnormal cortical layering



Classification systems of MCD

- Recent systems are based on the stage of the disrupted development, the underlying genes, the pathological pathways that have been disrupted and the imaging features
- Result in a large spectrum of disorders with variable
  - cortical morphologies
  - clinical manifestations
    - epilepsy, developmental delay, intellectual disability, autism, and schizophrenia
- Introduction of
  - new syndromes
  - tubulinopathies

- *Barkovich AJ, Dobyns WB, Guerrini R (2015) Malformations of cortical development and epilepsy. Cold Spring Harb Perspect Med 5:a022392*

Ossola Ch.
Roots of the malformations of cortical development in the cell biology of neural progenitor cells. Front Neurosci 2021

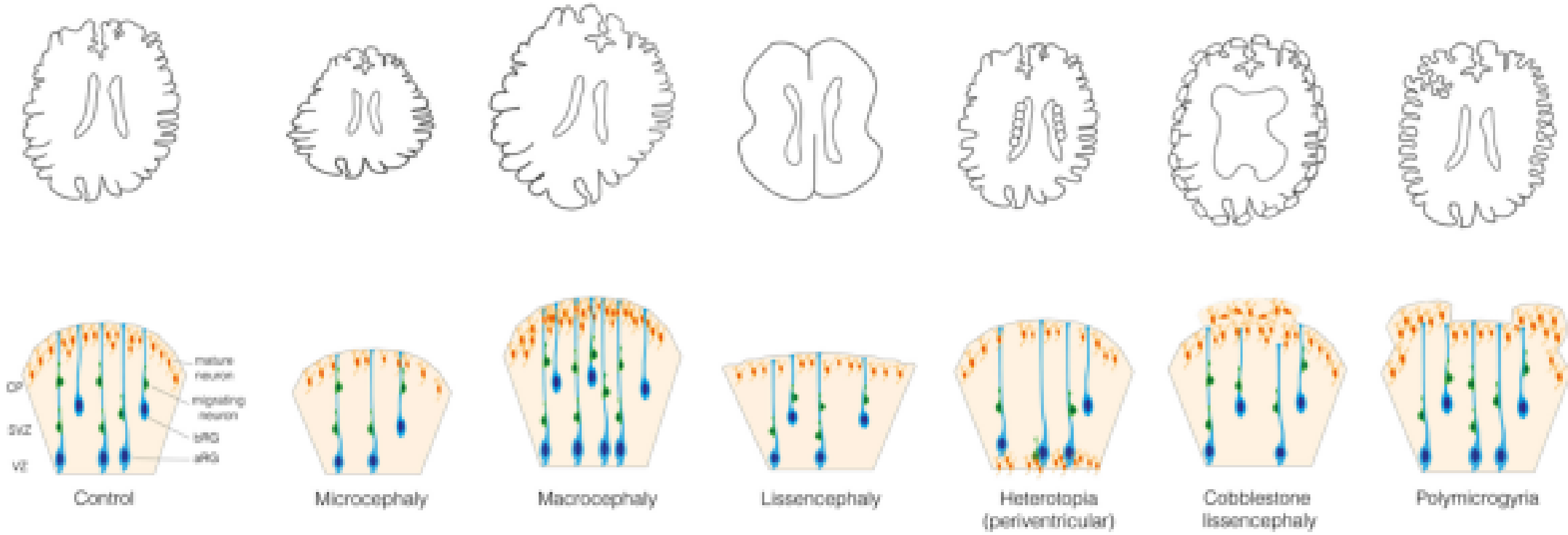
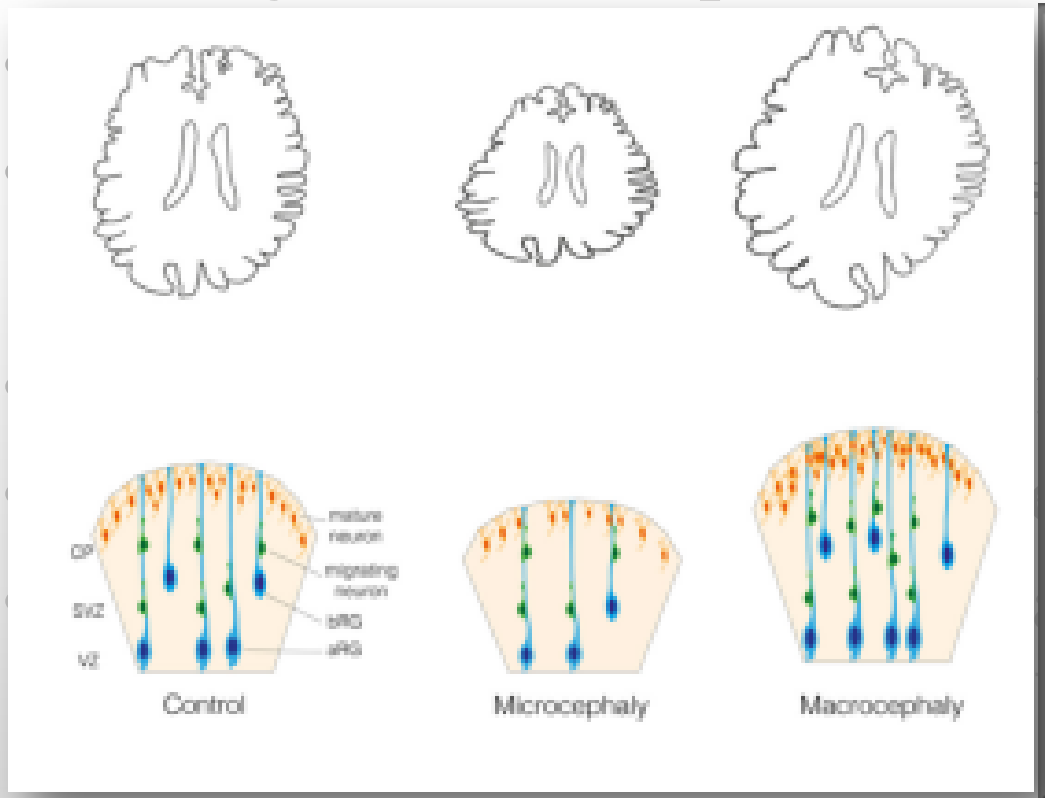


FIGURE 1 | Malformations of the cortical development. **(Upper)** Schematic representations of the control brain and brains affected by the following MCDs: microcephaly, macrocephaly, lissencephaly, periventricular nodular heterotopia, cobblestone lissencephaly and polymicrogyria. **(Lower)** Schematic representation of the mechanisms underlying these MCDs. In Control: VZ, ventricular zone; SVZ, subventricular zone; CP, cortical plate; aRG, apical radial glia; bRG, basal radial glia; migrating and mature neurons.

Classification according to stage of disruption

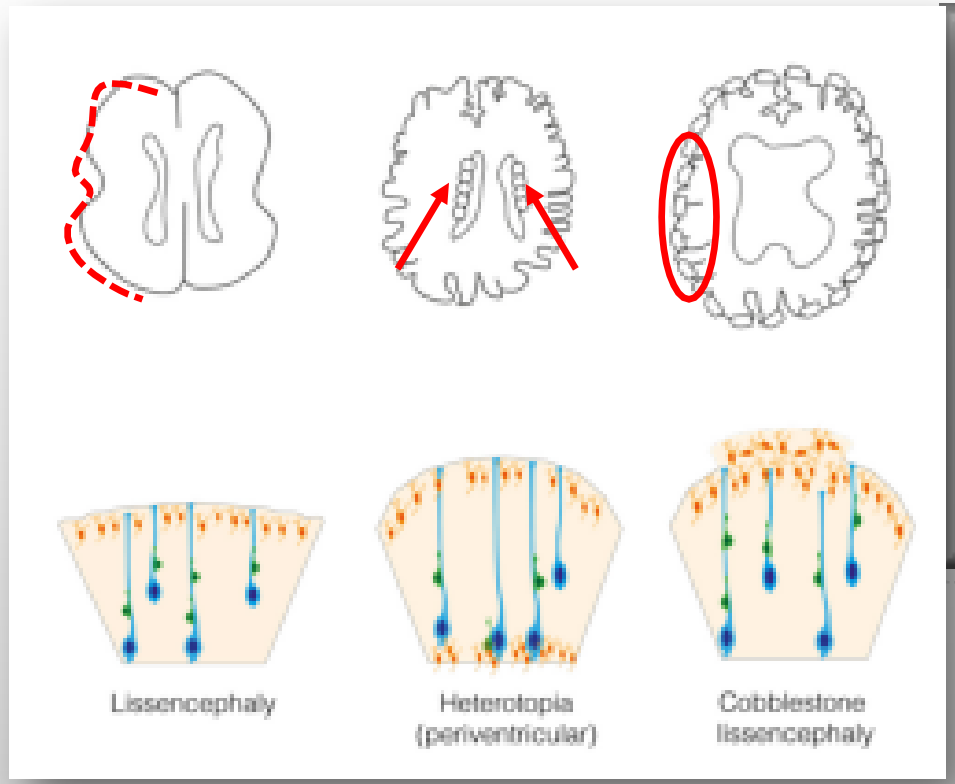
- Neurogenesis / cell proliferation or apoptosis



- microcephaly
- macrocephaly
  - TSC
- hemimegalencephaly
- tumors with dysplastic features
- FCD II

Classification according to stage of disruption

- Neurogenesis / cell proliferation or apoptosis
- Neuroblast migration

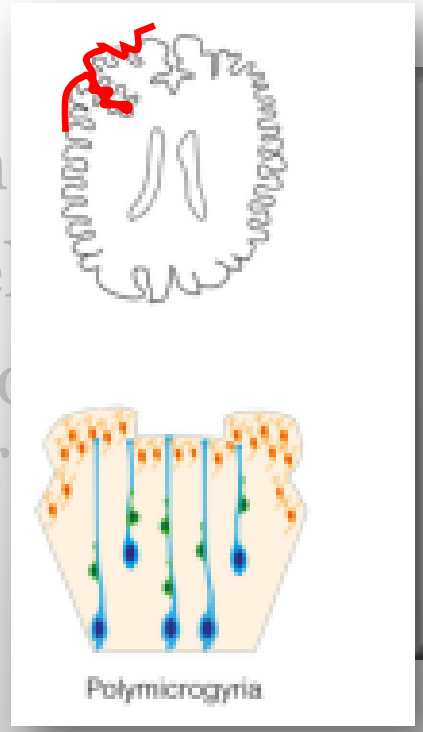


- Early: periventricular heterotopia
- Late: lissencephaly or subcortical band heterotopia

- Abnormal neuronal migration arrest: cobblestone lissencephaly

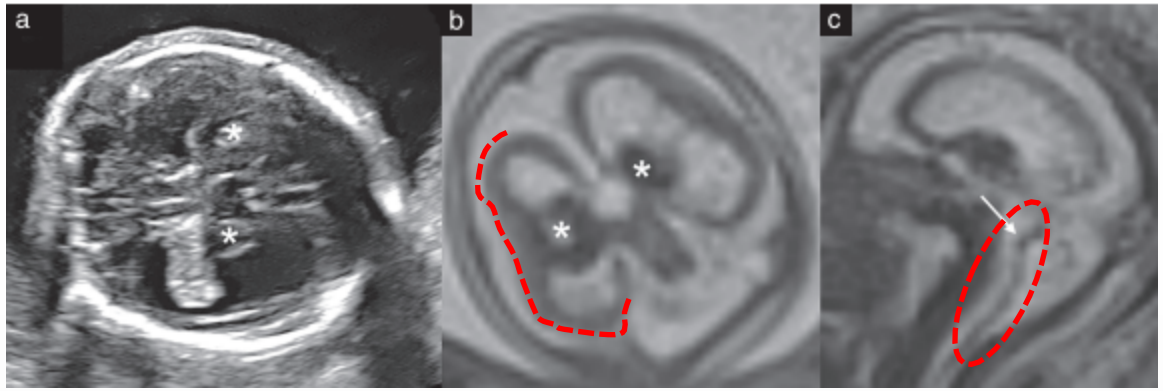
Classification according to stage of disruption

- Neurogenesis / cell proliferation or apoptosis
- Neuroblast migration
- Neuronal post-migrational organization and connectivity



- polymicrogyria
- Schizencephaly
  - type I – closed lip
  - type II – open lip

Tubulinopathies



- Complex and heterogeneous group of genetic diseases resulting in complex cerebral malformations
- Several tubulin genes tha
  or microtubule-associate
- Wide spectrum of clinica
- Different phenotypes, se

- microcephaly
- neuronal migration abnormalities
  - gray matter heterotopia
  - cortical dysgenesis – lissencephaly
- anomalies in the axonal path finding
  - white matter volume loss
  - corpus callosum dysgenesis
- hypoplasia of the cerebellum
- malformations of the brain stem

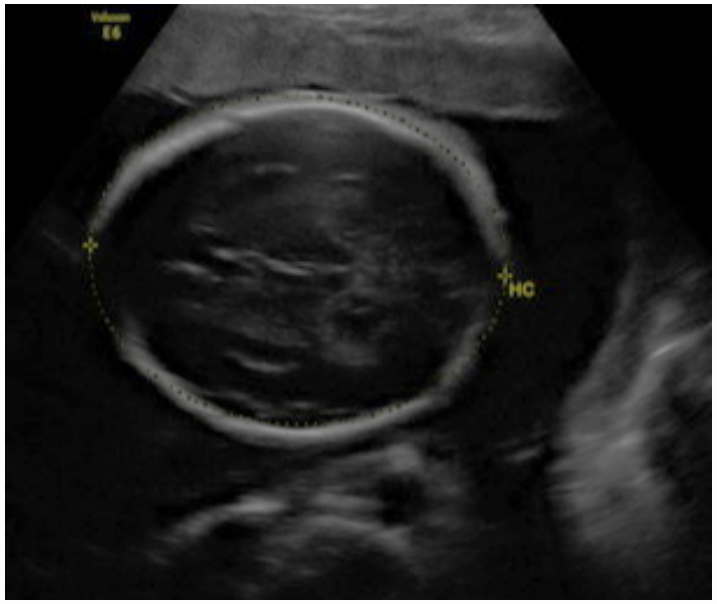
MCD – basic genetic approach

- The majority are caused by **genetic mutations**
  - interruption of the encoded proteins and associated molecular pathways involved in different stages of cerebral cortex development, i.e. the mTOR signaling pathway

- Together with **environmental insults**, occurring in utero or during the perinatal phase, such as infection or ischemia
  - timing of insult is important
  - later phase events cause more severe network disruptions

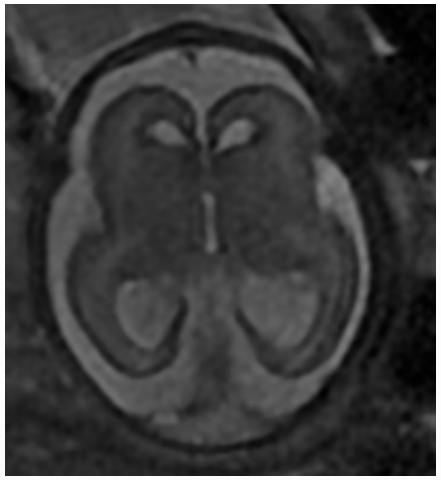
- *Juric-Sekhar G. Annu Rev Pathol 2019*

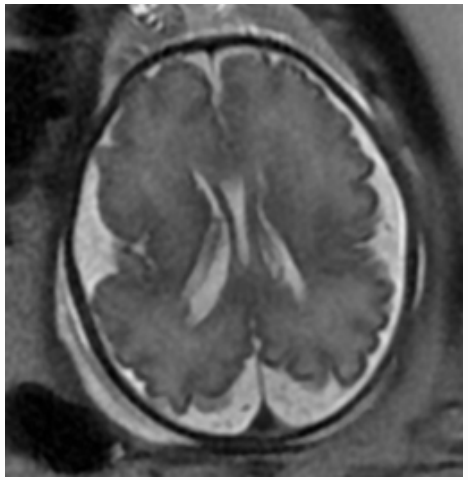
Prenatal US in MCD
Biometric findings



- Microcephaly
  - head circumference < 3rd centile for GA
  - micrencephaly not measurable on US
- Macrocephaly
  - head circumference > 97th centile for GA
    - mTOR-related syndromes: if early in pregnancy with associated anomalies
  - Megalencephaly
    - unilateral (hemimegalencephaly)
    - malformed cortex
      - mild polymicrogyria to more diffuse dysplastic cortex (pachygyria or polymicrogyria)
    - coronal images are mandatory

Fetal MRI in MCD
Biometric findings





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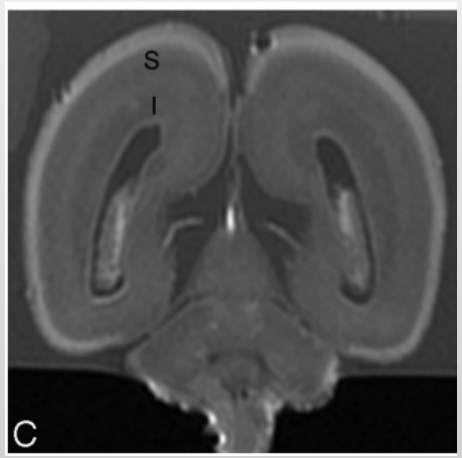
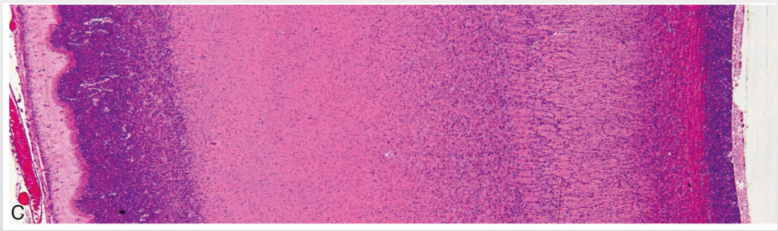
Fetal MRI

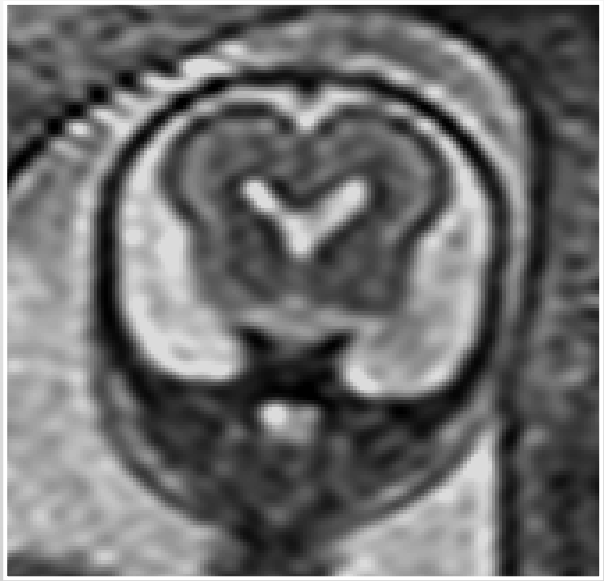
Advantages

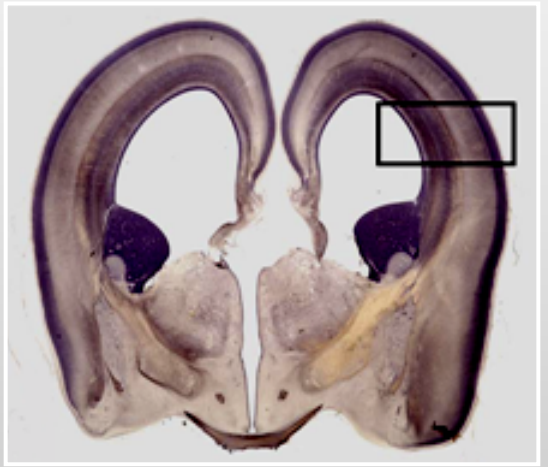
- Superb contrast resolution
- Visualization of cortical ribbon in all stages, particularly late in gestation
- Depiction of layered structure of brain parenchyma, typical for fetuses up to 27th week of GA, that matches gross histologic appearance





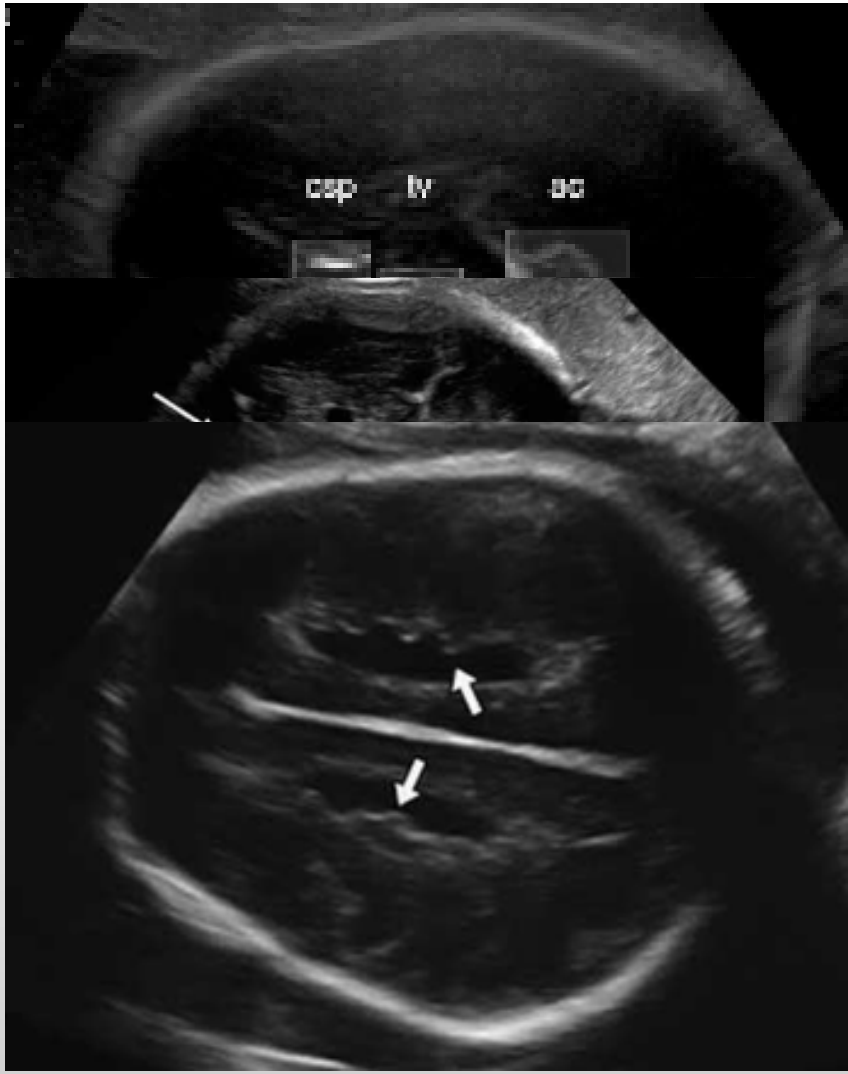
- *E. Widjaja, et al. AJNR 2010*





Prenatal US in MCD
Morphological findings that can be detected

- Sylvian fissure development and operculization – *cortical dysplasia*
  - *Quarello E, Ultrasound Obstet Gynecol 2008*
- Overfolding of cortical ribbon – *polymicrogyria*
- Irregularities of ventricular wall – *subependymal nodular heterotopia*
  - Squared-shaped frontal horns with irregular borders on coronal images



Prenatal US in MCD
Morphological findings that may be missed

- Sometimes
  - *Lissencephaly type I* in early gestation
  - Cortical tubers and white matter abnormalities – *tuberous sclerosis complex* in unfavorable conditions

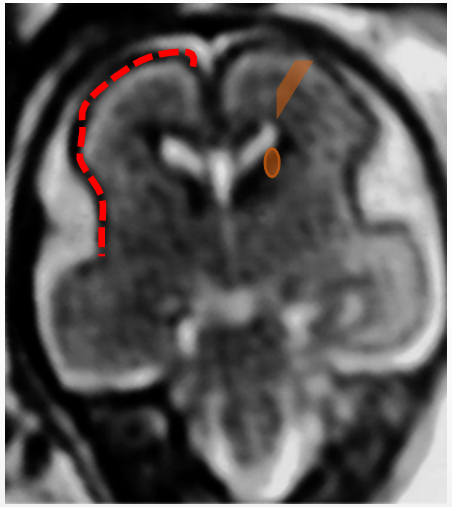
- Usually
  - *Subcortical heterotopia*
  - *Closed-lip schizencephaly*

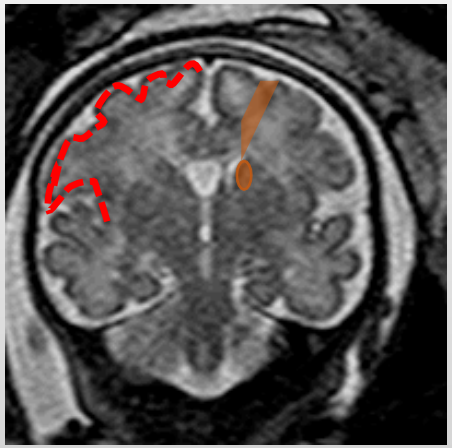
What are we looking for on fetal MRI?

- Distortion of the profile of cortical plate
  - T2-weighted hypointense rim delineating the brain surface
- Thinning / blurring of subplate and intermediate zone

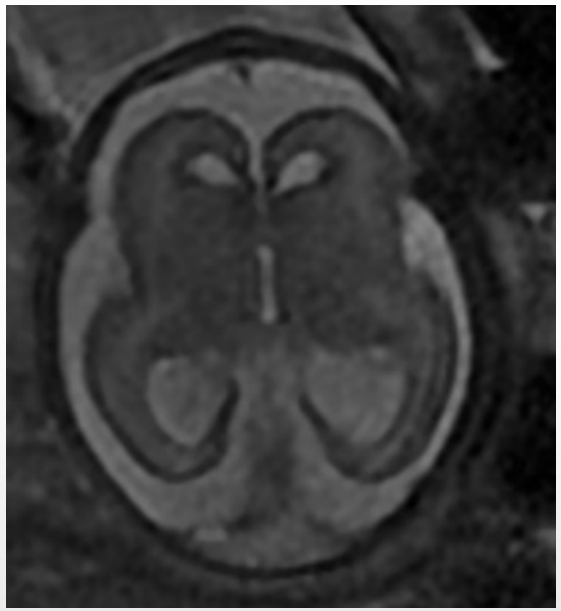
- Heterotopic grey matter
  - T2-weighted hypointense periventricular nodule
  - transmantle stripe
  - subcortical focal area

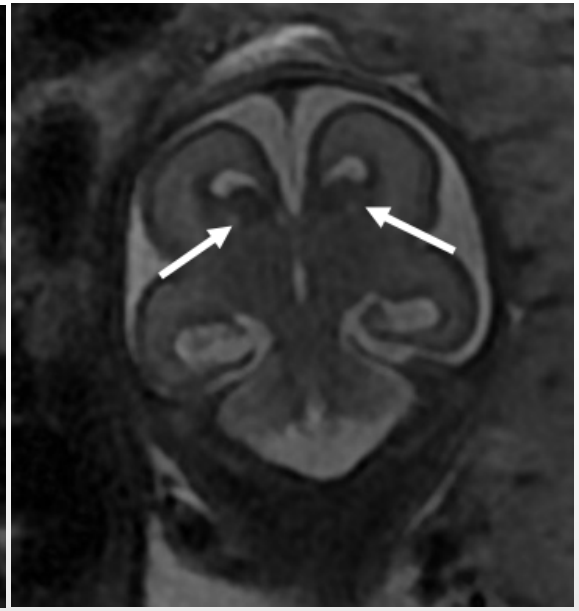
- Additional anomalies:
  - Unilateral volume reduction of one lobe or part of it

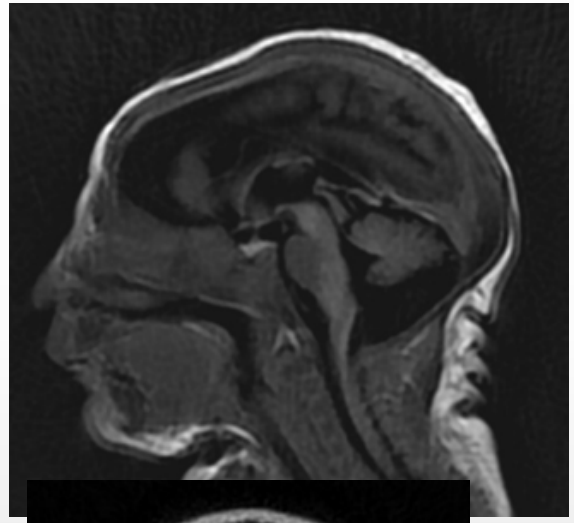


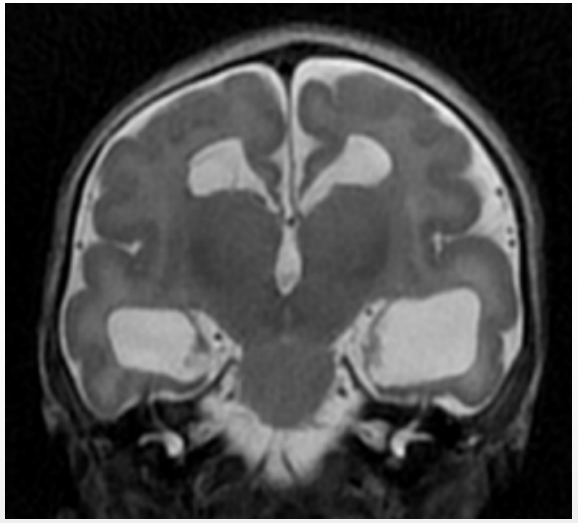


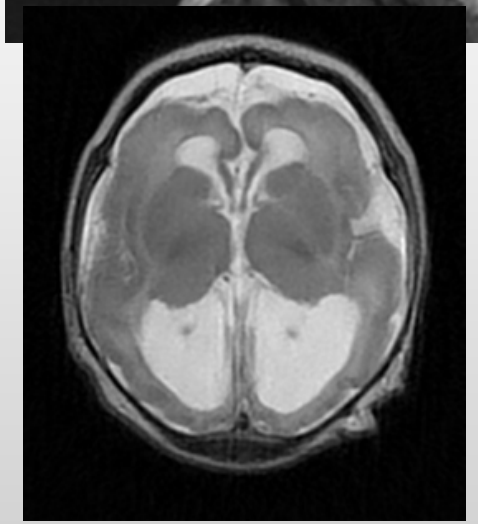
27 w GA
US: microcephaly with enlarged CSF spaces









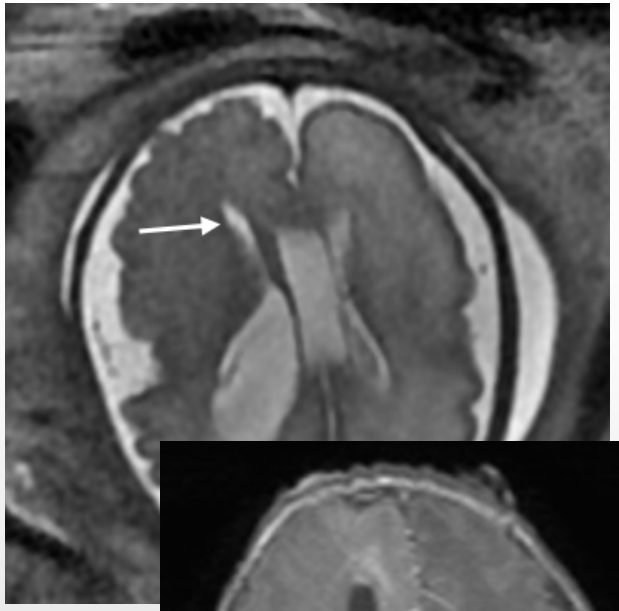


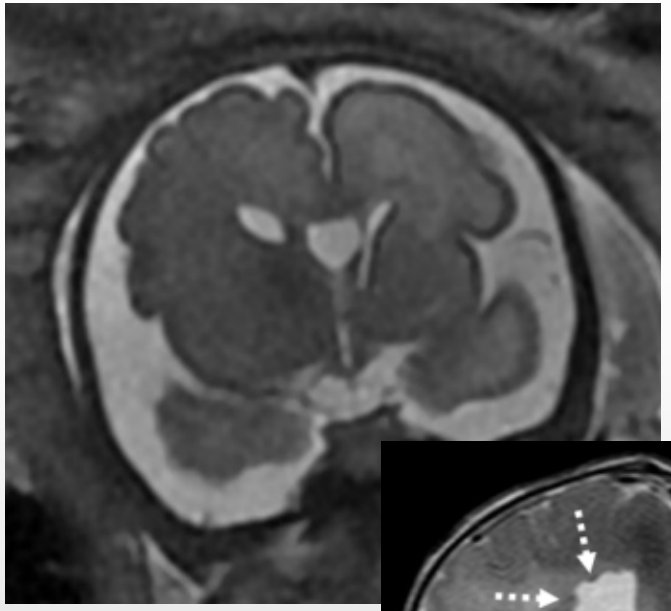
- enlarged pericerebral space
- enlarged ganglionic eminence
- agenesis of the corpus callosum
- cerebral measurements <<3rd centile
- gyration markedly delayed

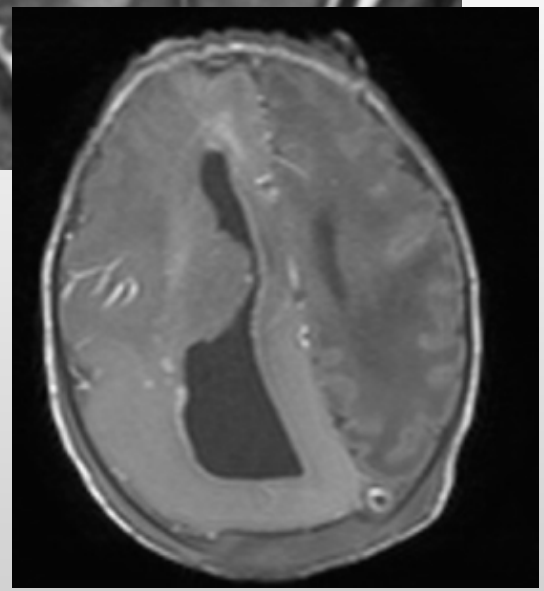
- receded forehead
- agenesis of corpus callosum
- simplified gyral pattern

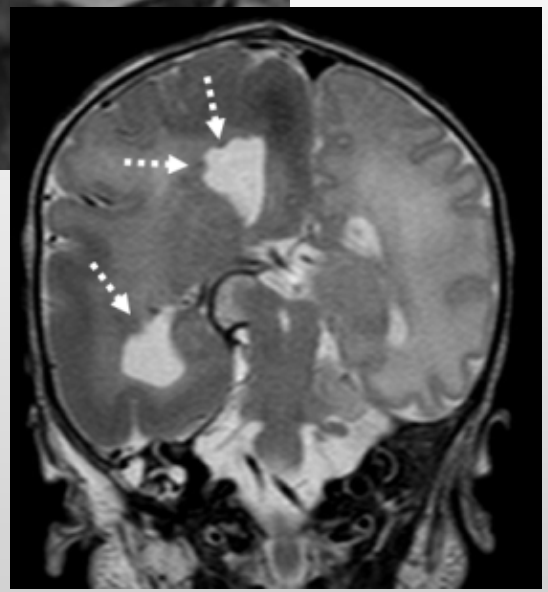
Whole genome sequencing: several breakpoints on Chromosome 2

Hemimegalencephaly









28+4 w GA:

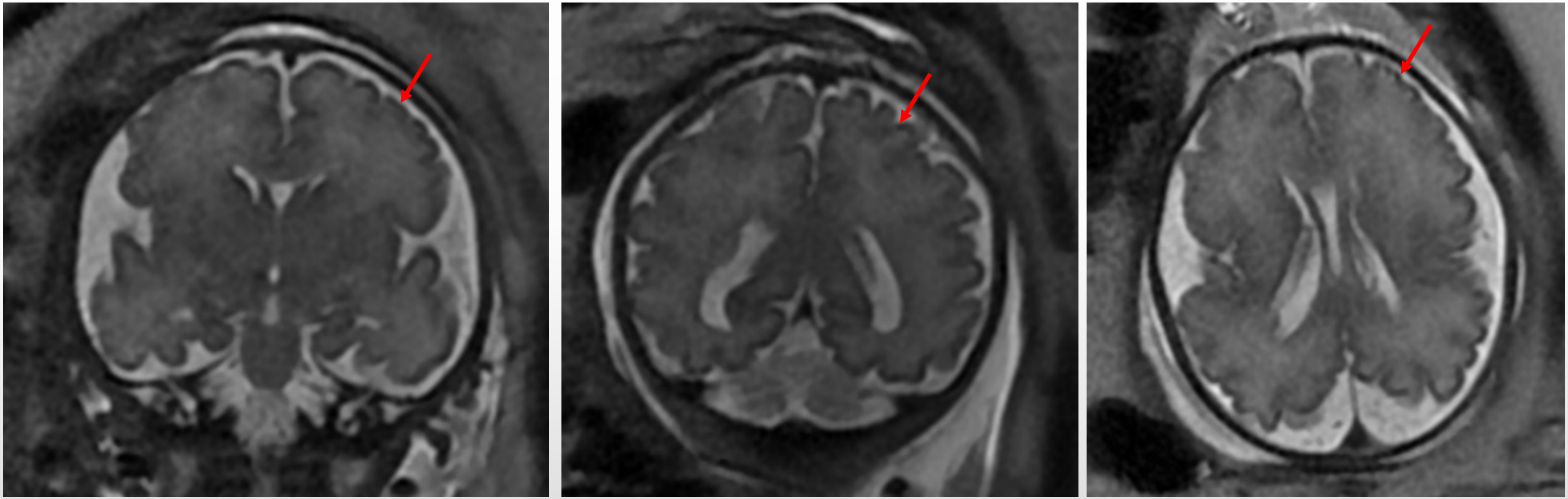
- enlargement of the right hemisphere
- typical straightening of the frontal horn
- diffuse polymicrogyria of the right hemisphere with abnormal insula
- T2 signal hypointensity of the parenchyma

- Postzygotic mutation in the *PIK3CA* gene

1 d-o, intractable seizures (no prenatal diagnosis)

- same findings
- additionally, several foci of subependymal heterotopia

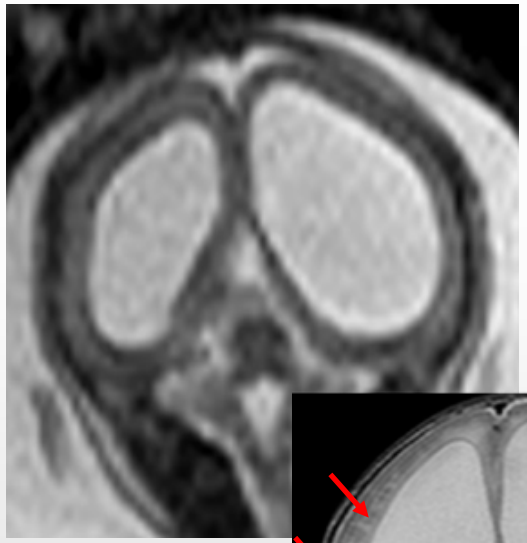
31 w GA with marked macrocrania

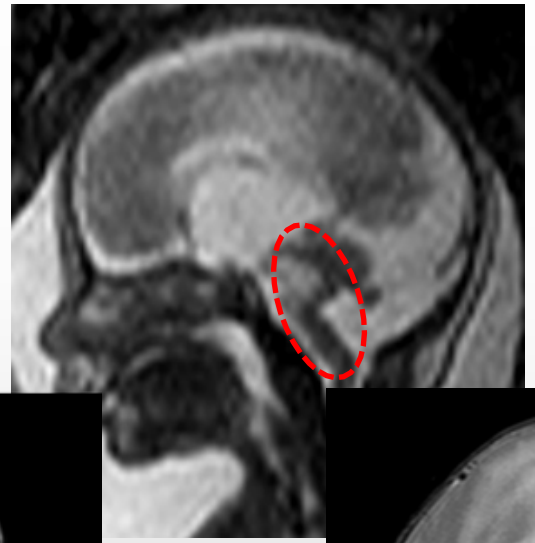


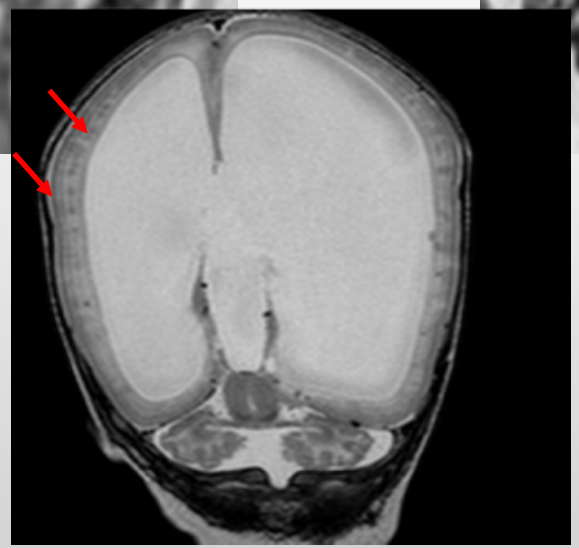
polymicrogyria

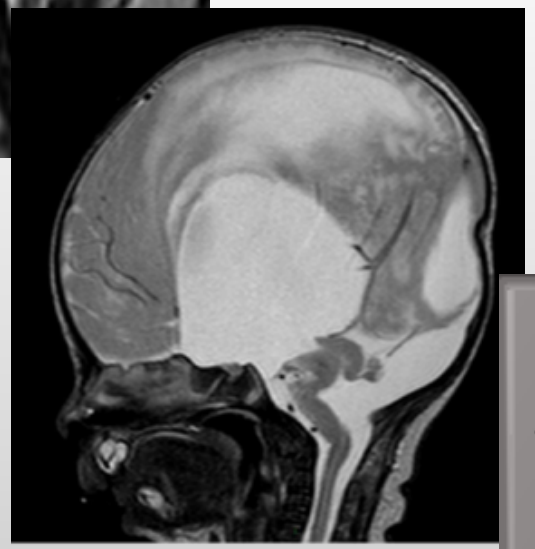
missense variant in *PIK3R2* gene, part of *mTOR* pathway

Cobblestone lissencephaly: Walker-Warburg syndrome









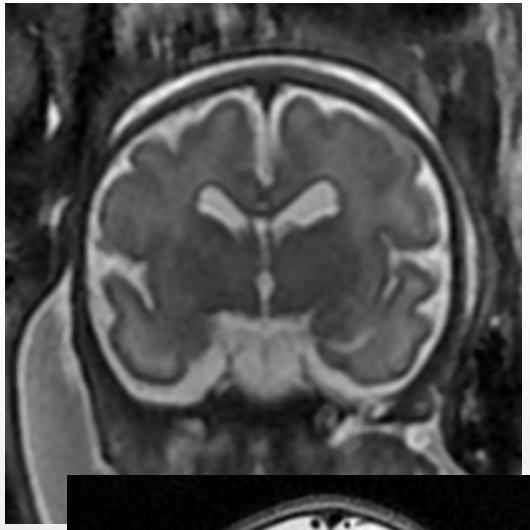
24+3 w GA:

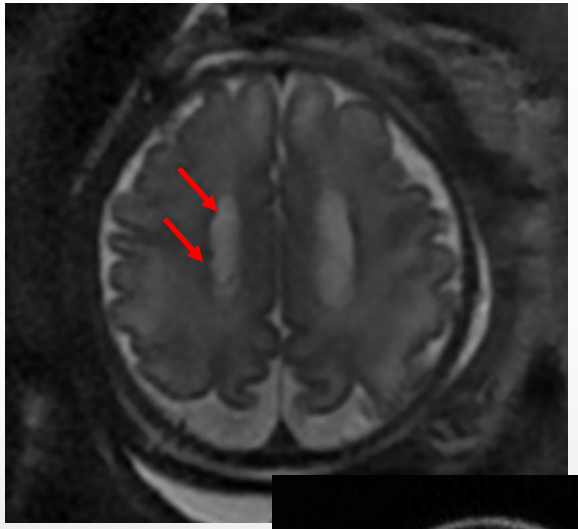
- kinked brainstem
- dysgenesis of the vermis
- very thin corpus callosum
- marked ventricular dilatation
- small cerebellar hemispheres
- no gyration

17 d-o

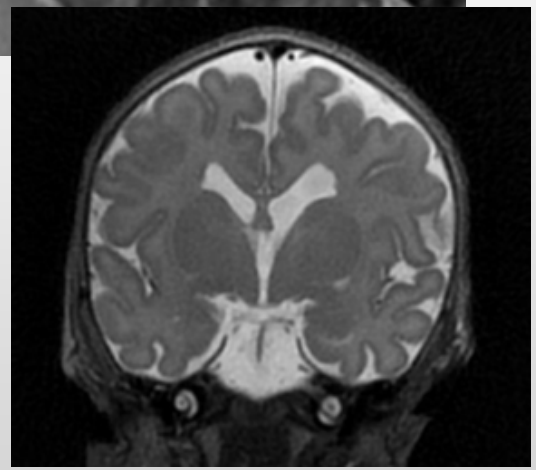
- prenatal findings confirmed
- pachygyria due to overmigration of neurons through the pia (cobblestone appearance)

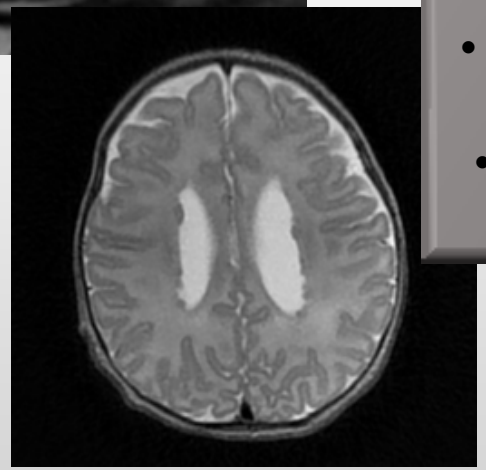
Subependymal nodular heterotopia in a female fetus and her mother



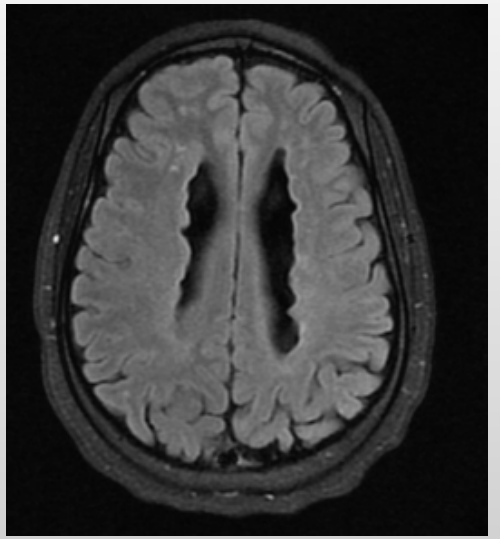


32 w GA
- Irregular wall of the lateral ventricles
- Numerous nodules protruding into the lumen

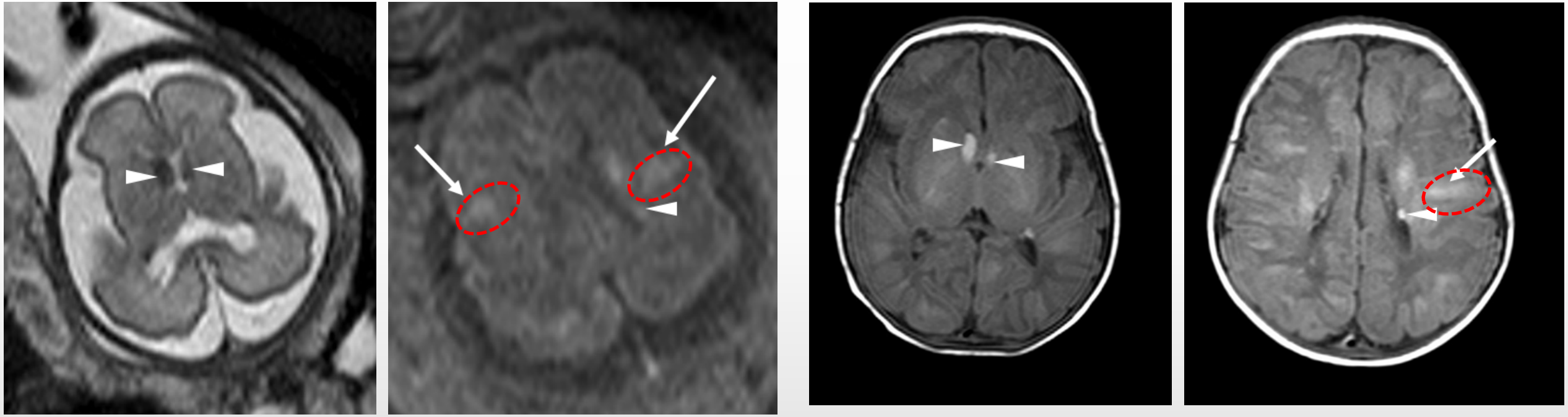




6 w-o
- same findings are observed in mother
- mutation in *FLNA* gene is strongly suspected



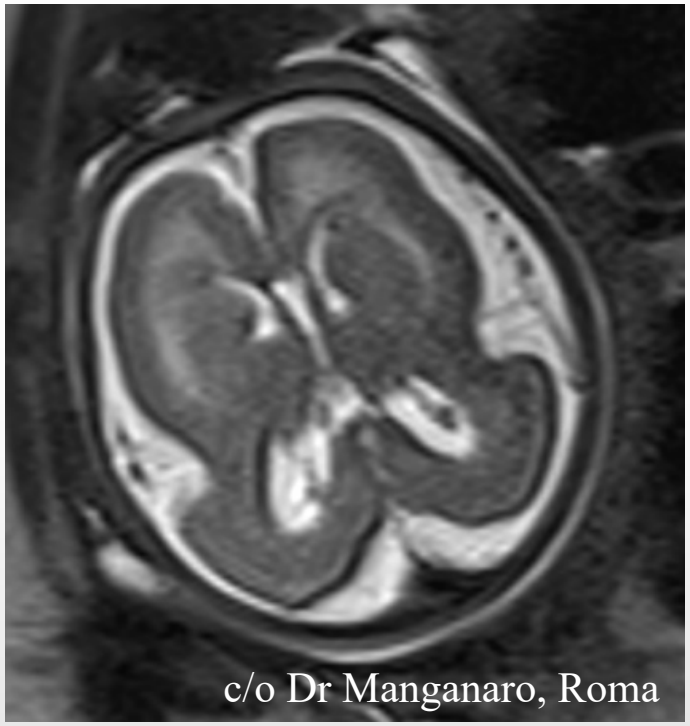
28 w GA
US: cardiac rhabdomyomas and multiple cortical tubers



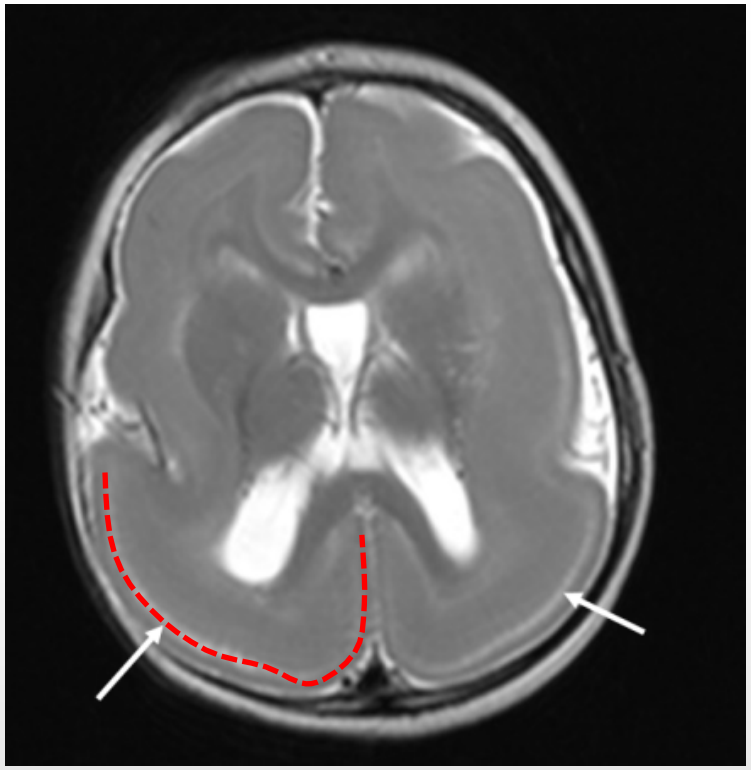
- subependymal nodules at the level of the Monro foramina
- abnormalities of the white matter

Tuberous sclerosis
de novo deletion of *TSC2* gene

Lissencephaly type I



32 w GA, US: agyria
- Agyria with very poor operculization of the insula
- terminated pregnancy
- deletion of the *LIS1* gene



6 m-o boy (w/o prenatal US) and intractable seizures
- agyria
- thin parieto-occipital T2-hyperintense layer "cell-spare zone"

Pitfalls in imaging

- Gyration should be scrutinized
  - particularly in unexpected cerebral findings
- Abnormal operculization on prenatal imaging may reflect
  - underlying cortical dysplasia
  - extracortical factors, such as abnormal cerebral volume or developmental anomalies

- Lissencephaly type 1
  - diagnosed after 27 - 30 weeks of gestation in lack of primary sulci development
  - better appreciated on MRI during late gestation
- Identification of heterotopia before the 24th gestational week is difficult
  - sensitivity 44% as opposed to 100% after 24 weeks of gestation

- *Guibaud L et al. Ultrasound Obstet Gynecol 2008*
- *Lerman-Sagie T, Leibovitz Z. Can J Neurol 2016*

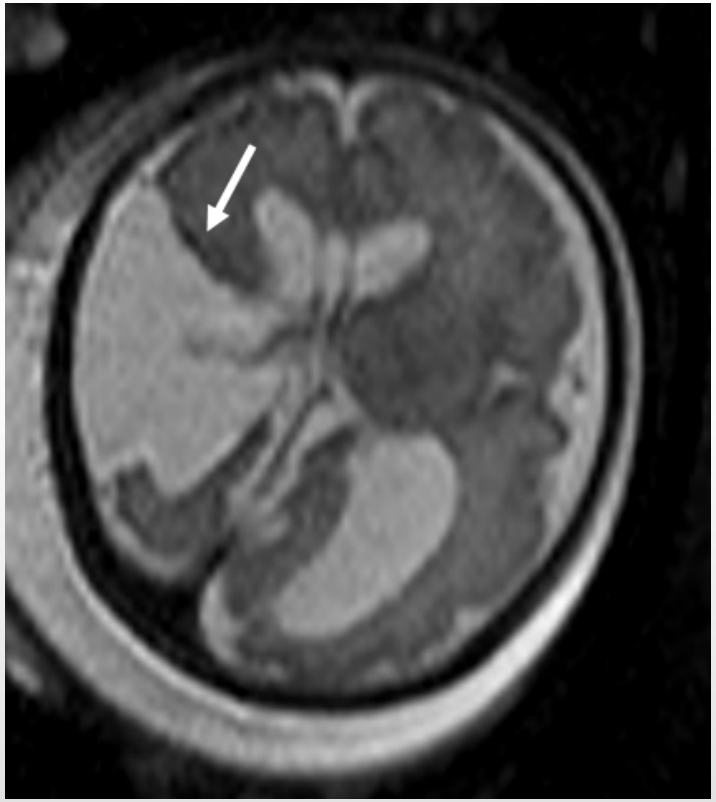
Pearls in fetal MRI

- Polymicrogyria
  - discernable before the expected normal appearance of primary sulci

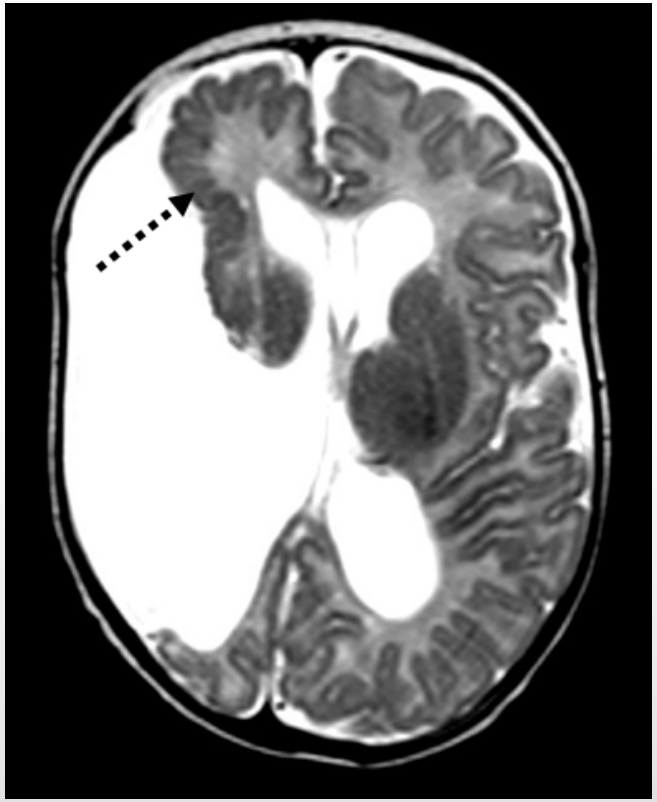
- Schizencephaly
  - the grey matter lining of the cleft has the appearance of polymicrogyria
  - look for additional findings
    - absent septum pellucidum
    - milder clefts or polymicrogyria without cleft in the contralateral hemisphere

- *Guerrini R, et al. Lancet Neurol 2014*
- *Robinson AJ, Ederies MA. Pediatr Radiol 2018*

Open-lip schizencephaly



32 w GA
- large cleft extending from pial surface to the ependymal lining of the right lateral ventricle
- cortex lining the anterior lip is slightly irregular



2-mo
- findings confirmed

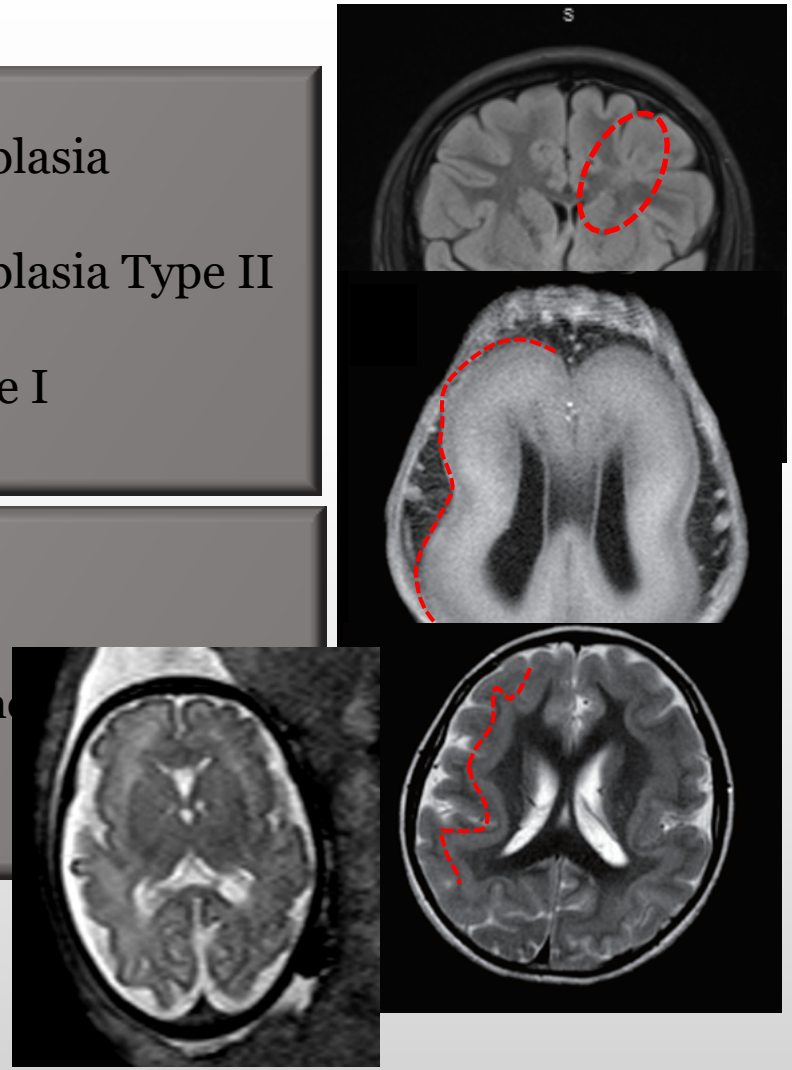
Neonatal MRI – contribution in antenatally missed findings

- Better spatial resolution
- High quality scan is mandatory
  - to assess
    - cortical surface
    - grey – white matter differentiation
    - cortical thickness
    - associated malformations
  - to define cortical malformation
    - distribution
    - type
    - severity

- Focal cortical dysplasia
- Focal cortical dysplasia Type II
- Lissencephaly type I

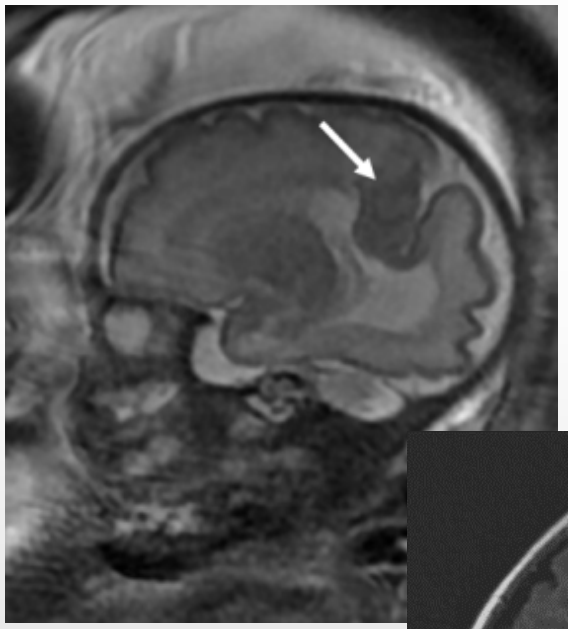
- Heterotopias

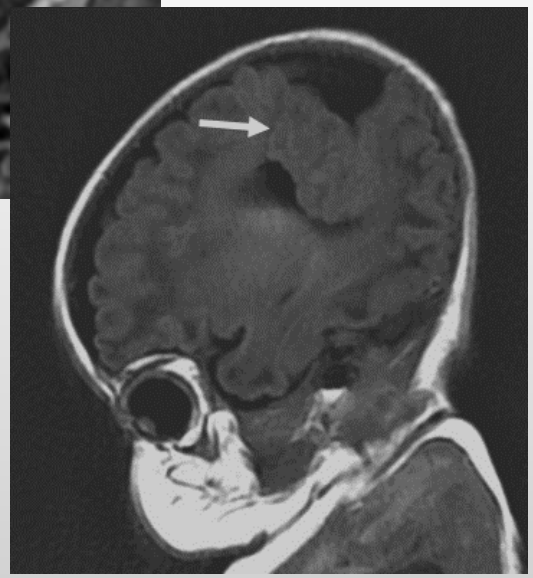
  subcortical band h
- Polymicrogyria

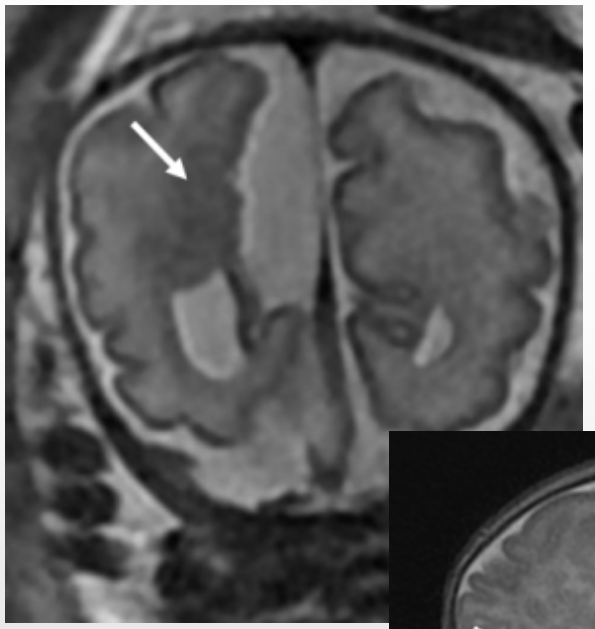


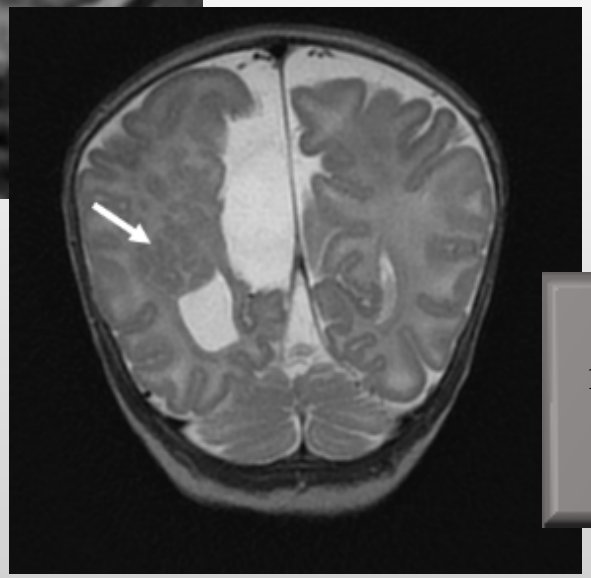
- *Lermal-Sagie T, Leibovitz Z. Can J Neurol Sci 2016*
- *Guerrini R, Dobyns WB. Lancet Neurol 2014*

31+4 w GA, US: partial agenesis of the corpus callosum with an interhemispheric cyst





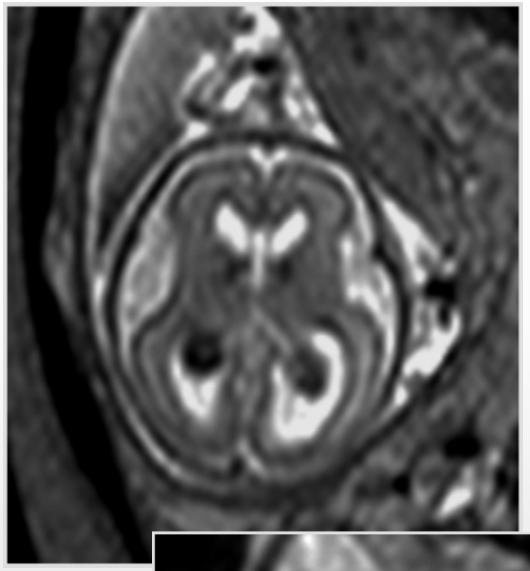


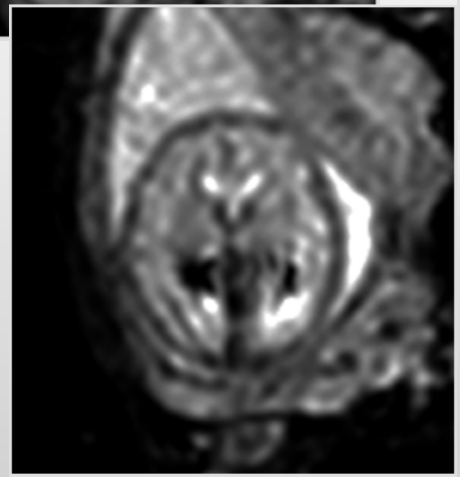


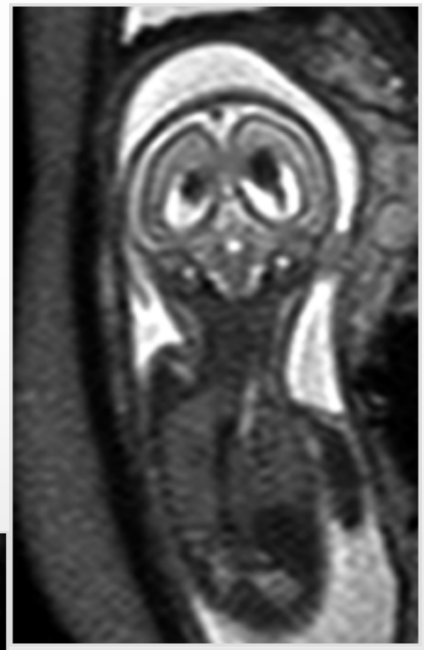
hypointense area adjacent to the lateral border of the cyst, which is irregular

6 w-o:
numerous foci of subcortical heterotopias adjacent to the lateral border of the cyst

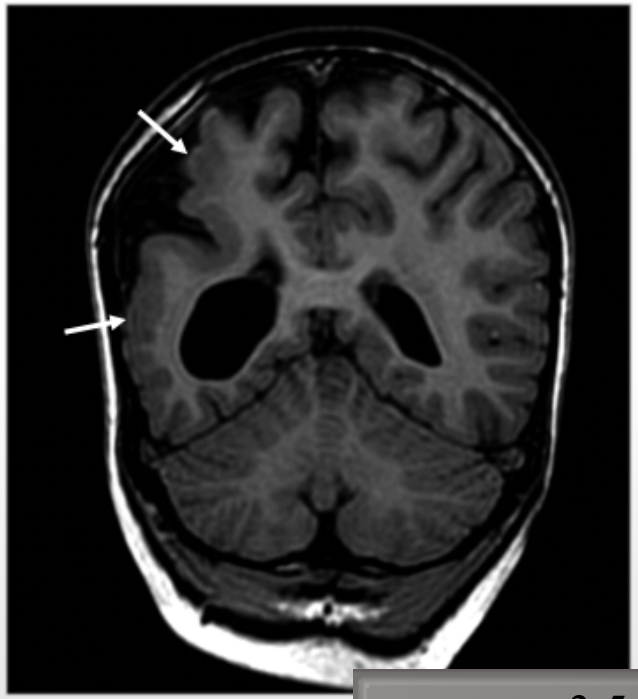
Polymicrogyria secondary to in utero ischemic insult, missed antenatally







22+1 w GA, US: ventriculomegaly
- intraventricular hemorrhage
- no abnormality of the cortical ribbon



3.5 y-o, seizures
- thickening and blurring of the cortical – subcortical junction

Conclusion

- MCD are a fascinating, large group of disorders, common causes of developmental delay and epilepsy
- Accurate diagnosis is essential and ideally should be performed prenatally to guide genetic investigation and allow parental counseling
- Detailed knowledge of the normal fetal cortical developmental landmarks and awareness of the indicative signs of MCD is required
- However, prenatal diagnosis of certain MCD (such as FCD, focal polymicrogyria or heterotopia) remains extremely challenging whatever the imaging modality applied and high quality postnatal MRI is required

Acknowledgements

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