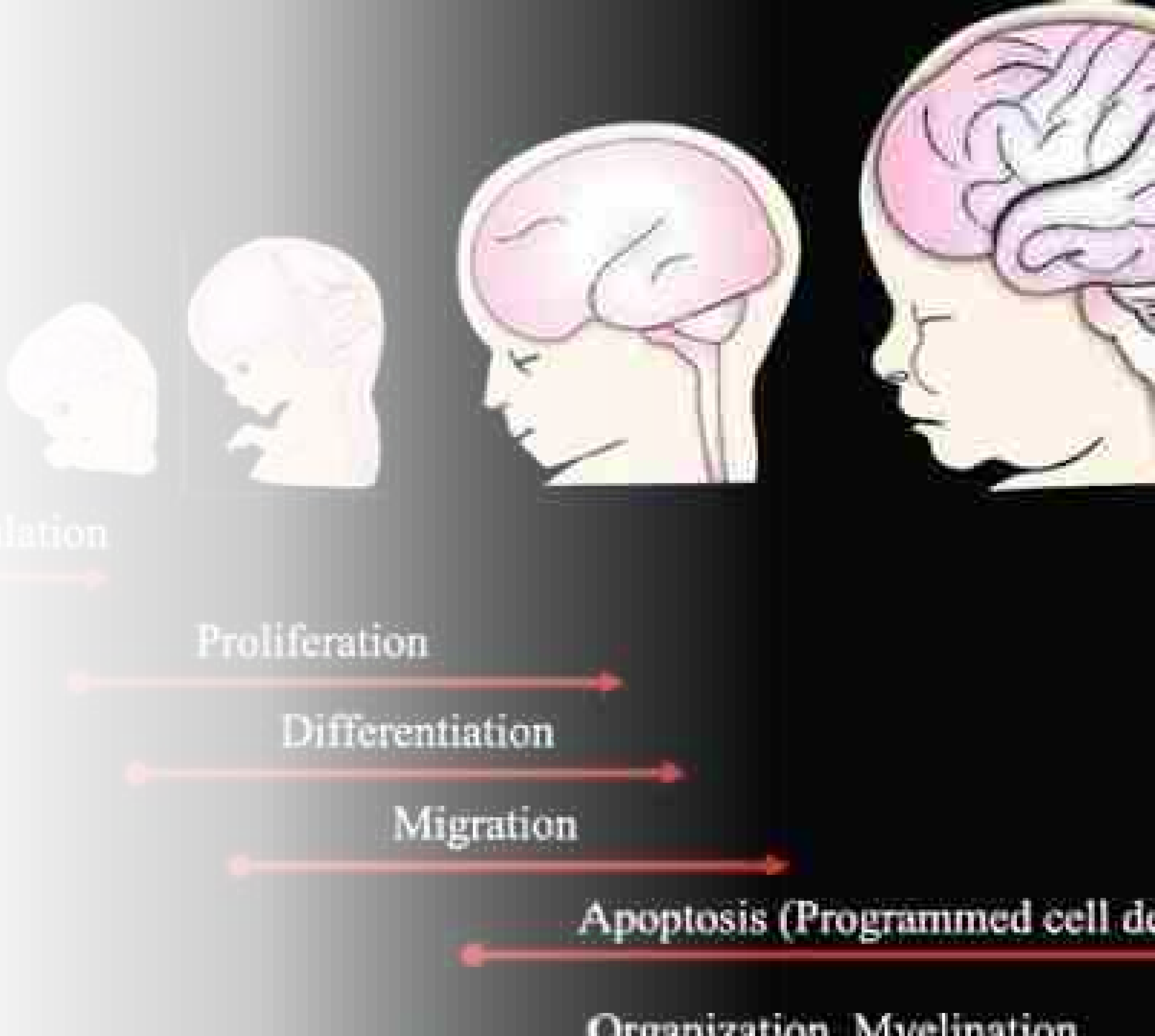
FETAL CORTICAL MALFORMATION



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- Fetal cortical development (corticogenesis) is a highly organized process that occurs mainly between **5 and 40 weeks of gestation**. Understanding the timing of each stage is essential for interpreting fetal neurosonography and MRI findings.

  Overview of Normal Cortical Development

  1. Neural Proliferation (5–20 weeks)

  Neural stem cells proliferate in the ventricular and subventricular zones.
  Produces neurons and glial cells.
  Peak neuronal production occurs between **8–16 weeks**.
  Abnormalities → microcephaly, megalencephaly, some forms of cortical dysplasia.

  2. Neuronal Migration (8–24 weeks)

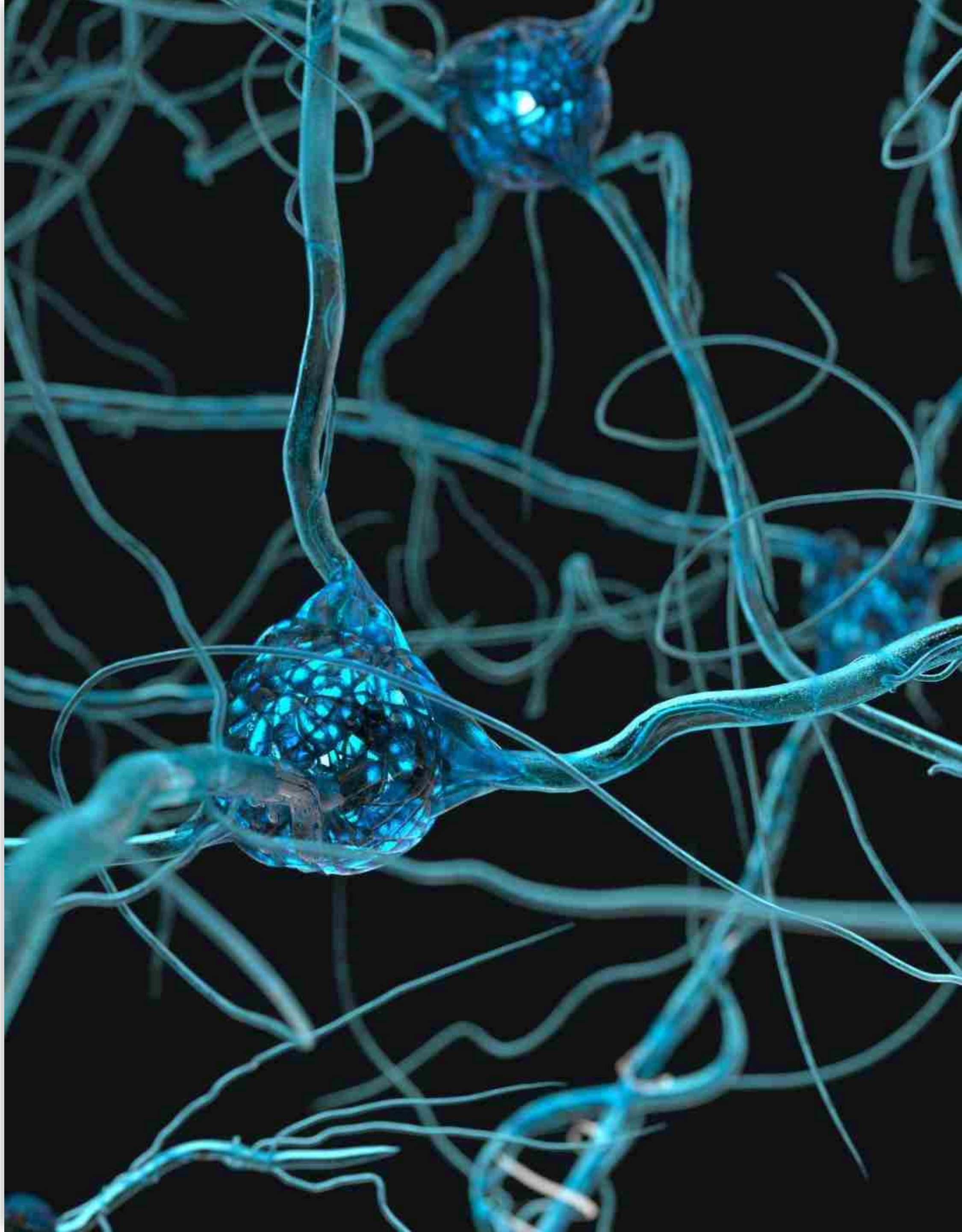
  Newly formed neurons migrate from the germinal matrix to the cerebral cortex.
  Migration occurs along radial glial fibers.
  Most cortical neurons reach their final destination by **24 weeks**.
  Abnormalities → Lissencephaly, Periventricular Heterotopia, subcortical band heterotopia.

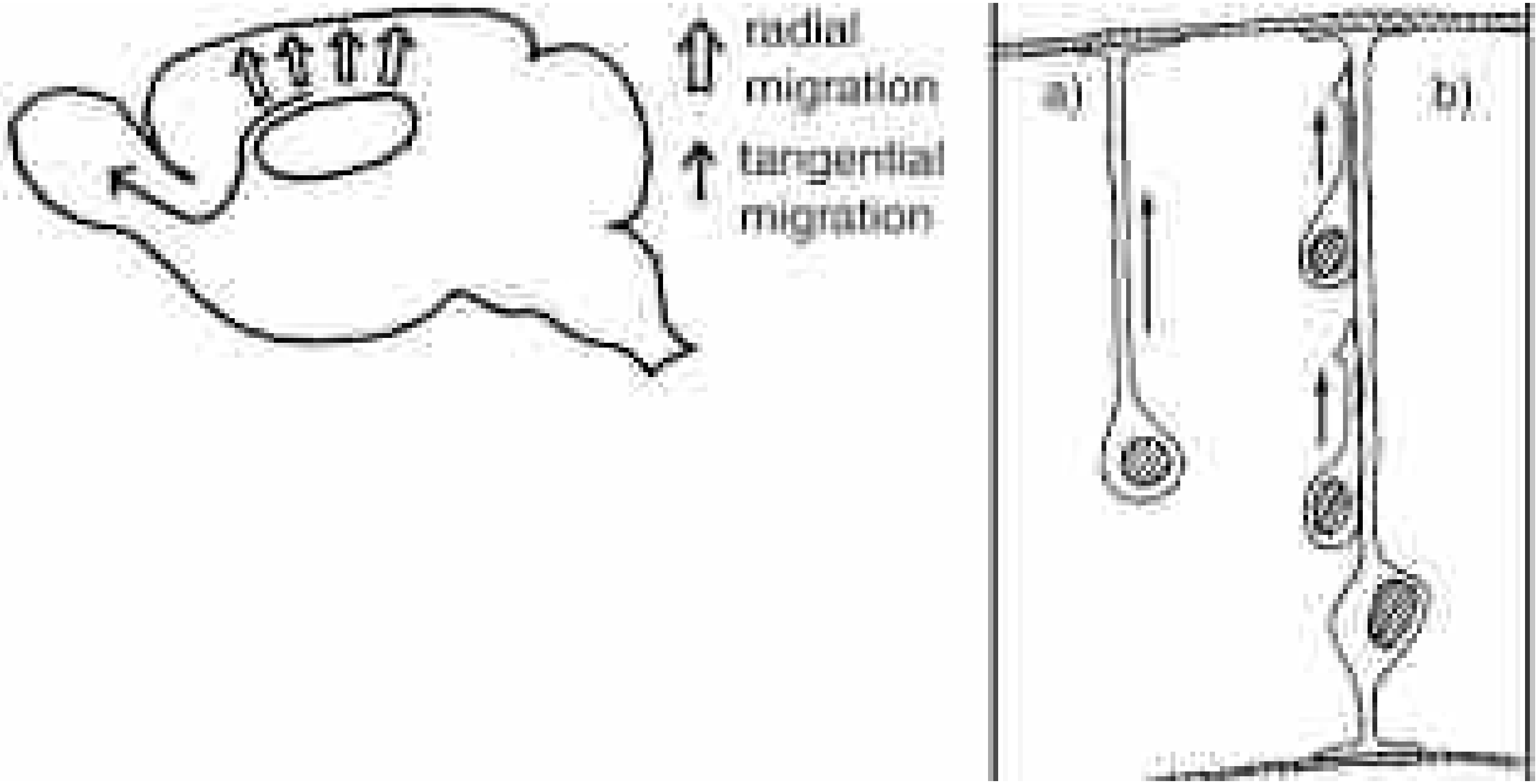
  3. Cortical Organization (22 weeks–birth and beyond)

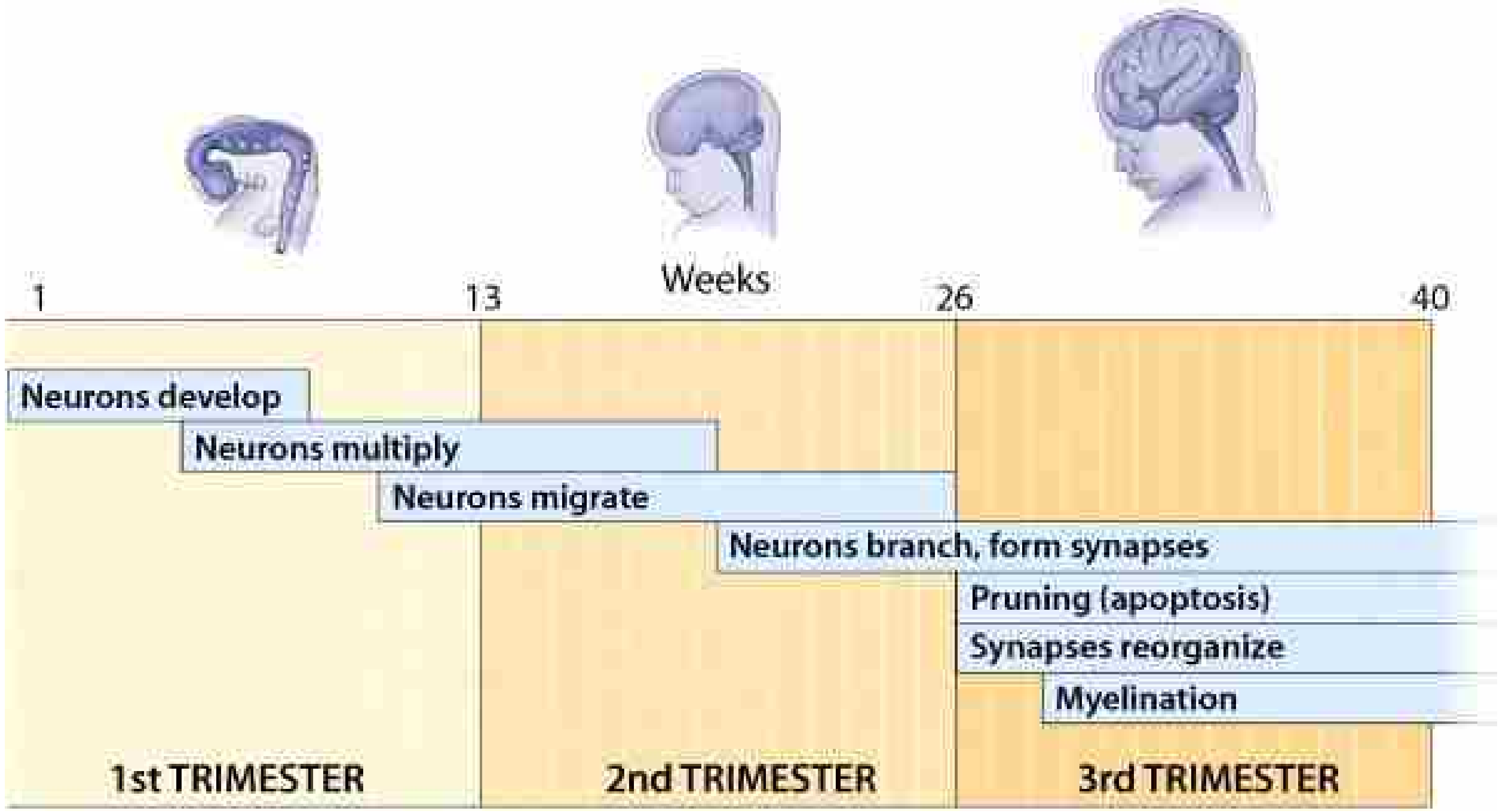
  Neurons organize into the normal six-layered cortex.
  Synaptogenesis and cortical connectivity develop.
  Sulci and gyri progressively form.
  Abnormalities → polymicrogyria, schizencephaly, focal cortical dysplasia.

Normal Brain Development

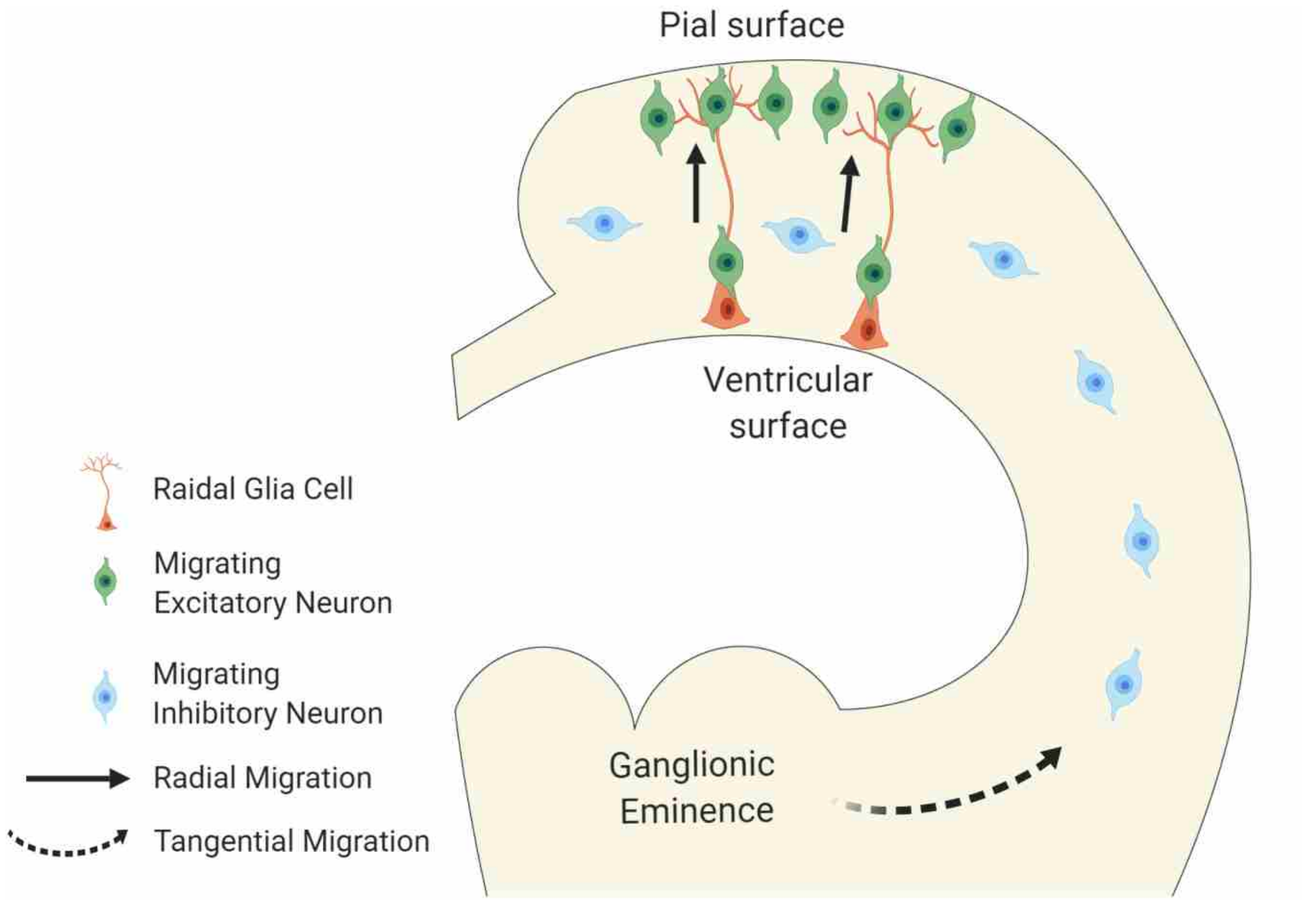
- Human brain development begins shortly after conception and continues through adolescence until adulthood. During **the first 10 weeks of pregnancy (the first trimester), a group of cells in the embryo called stem cell receive chemical signals to develop into the primary cells of the brain, called neurons and glia.**
- **The birth of new neurons and glia is referred to as neurogenesis and gliogenesis, respectively**. Ultimately, neurons will be responsible for communicating messages throughout the entire brain and the glial cells will provide both structural and chemical support to the neurons.
- Although most of the neurogenesis occurs in the fetus and newborn, the “birth” of new neurons actually continues in some parts of the brain right through old age! The fetal brain contains as many as **100 billion neurons at birth**.




radial
migration
tangential
migration
a)
b)

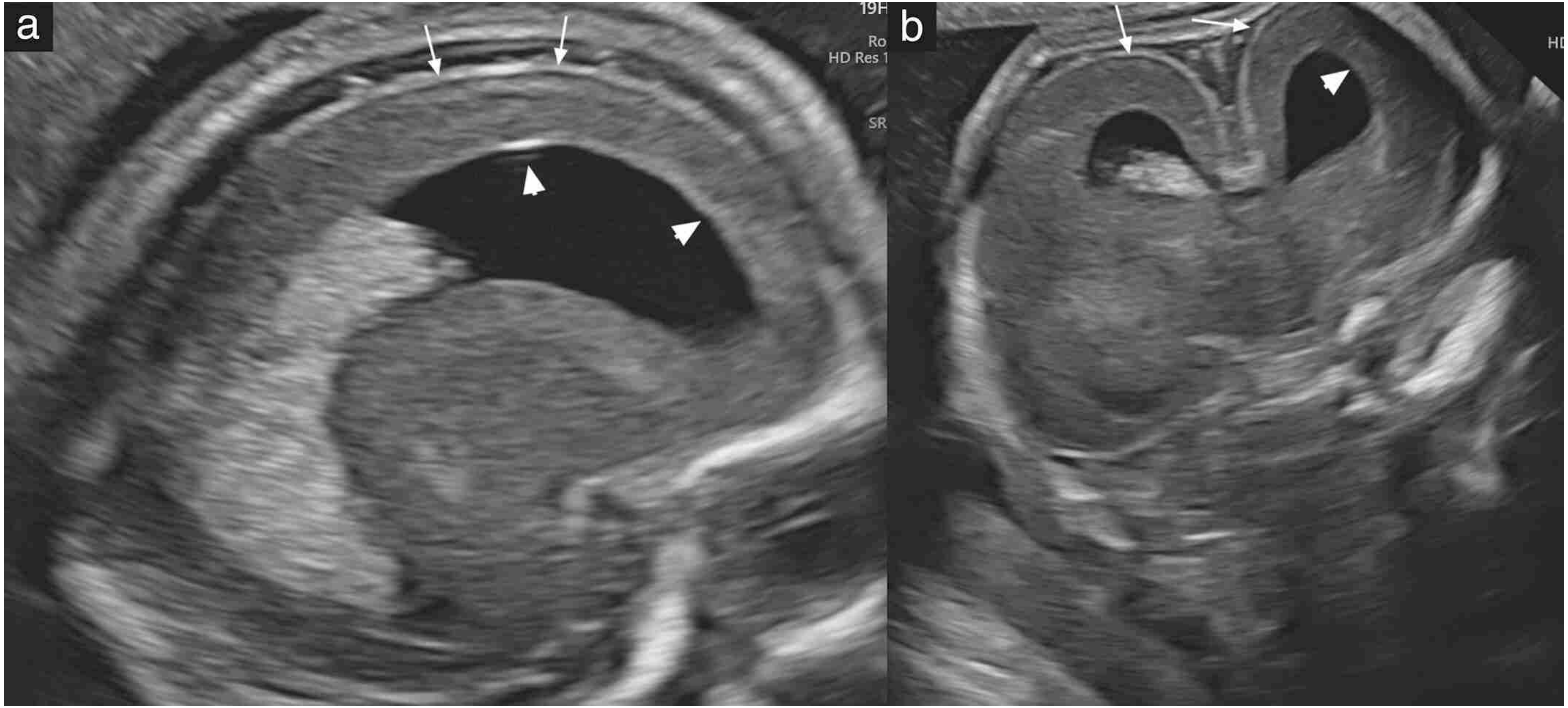


Weeks
1
13
26
40
Neurons develop
Neurons multiply
Neurons migrate
Neurons branch, form synapses
Pruning (apoptosis)
Synapses reorganize
Myelination
1st TRIMESTER
2nd TRIMESTER
3rd TRIMESTER


Pial surface
Ventricular
surface
Ganglionic
Eminence
Raidal Glia Cell
Migrating
Excitatory Neuron
Migrating
Inhibitory Neuron
Radial Migration
Tangential Migration

Imaging diagnosis

- Both dedicated neurosonography and MRI can depict fetal cortical malformations.
- Neurosonography is the most important imaging tool for prenatal malformation screening as it is widely available and safe for both mother and fetus.
- It can detect lissencephalies and PNH→
- MRI is a superior imaging modality →grey and white matter and topographical characterization of development of cortical gyri and sulci.
- **Most cortical abnormalities will be detected after 24 weeks, after 24 weeks, but some, particularly the severe severe lissencephaly seen in Miller-Dieker patients, can be patients, can be diagnosed prior to 24 weeks**
- With high resolution ultrasound transducers focused on the cortical rim, the more severe malformations can be detected even prior to 20 weeks.



Normal appearance of cortical rim at 16 weeks' gestation, demonstrated using a 6–12-MHz transvaginal transducer. Sagittal (a) and coronal (b) planes, showing regular shape of cortex (arrows). Note also regular shape of ventricular wall (arrowheads

Malformation of cortical development

Group 1	Group 2	Group 3
secondary to proliferative disorders, abnormal neurona and glial proliferation or apoptosis	abnormal neuronal migration and is further divided into four sub-categories	abnormal post-migrational development
1- microlissencephaly (decreased proliferation) 2- megalencephaly and hemimegalencephaly (increased proliferation) 3-focal cortical dysplasia (abnormal proliferation).	periventricular nodular lissencephalies. subcortical heterotopias cobblestone malformation	polymicrogyria schizencephaly

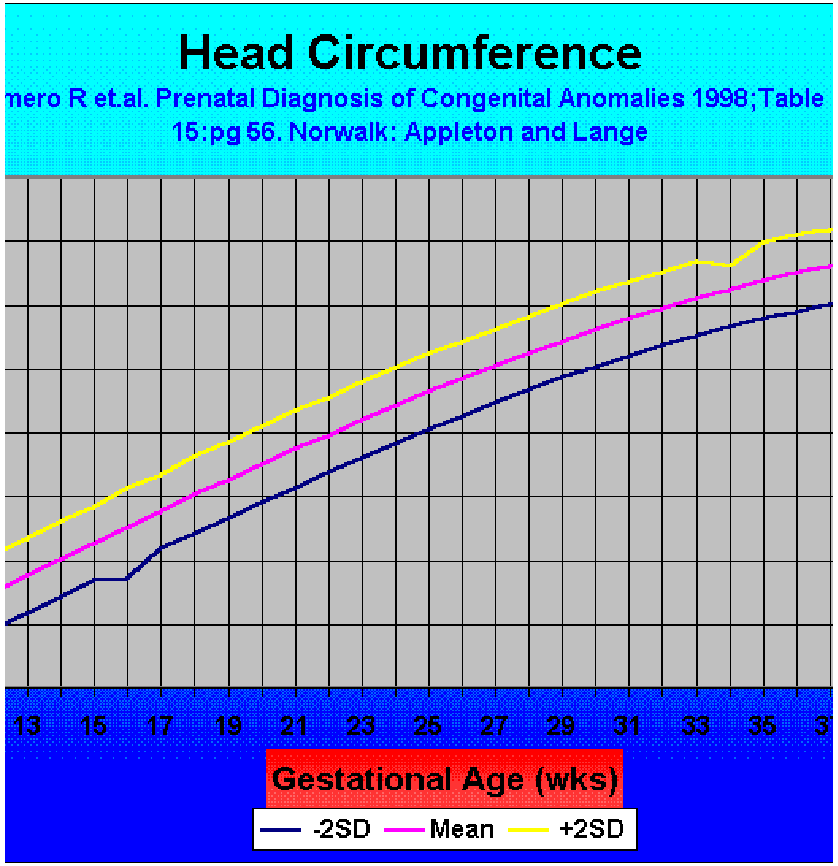
Megalencephaly

- Megalencephaly→The HC is greater than **2SD** and after exclusion of other causes of macrocephaly, such as CSF expansion.
- **→fetal sex, ethnicity, and parental HC; and inconsistencies between prenatal and postnatal HC growth curves and progression over time**

- The fetal HC should always be measured during a sonographic examination performed in the second or third trimester.
- HC larger than **+2 SD** from the mean

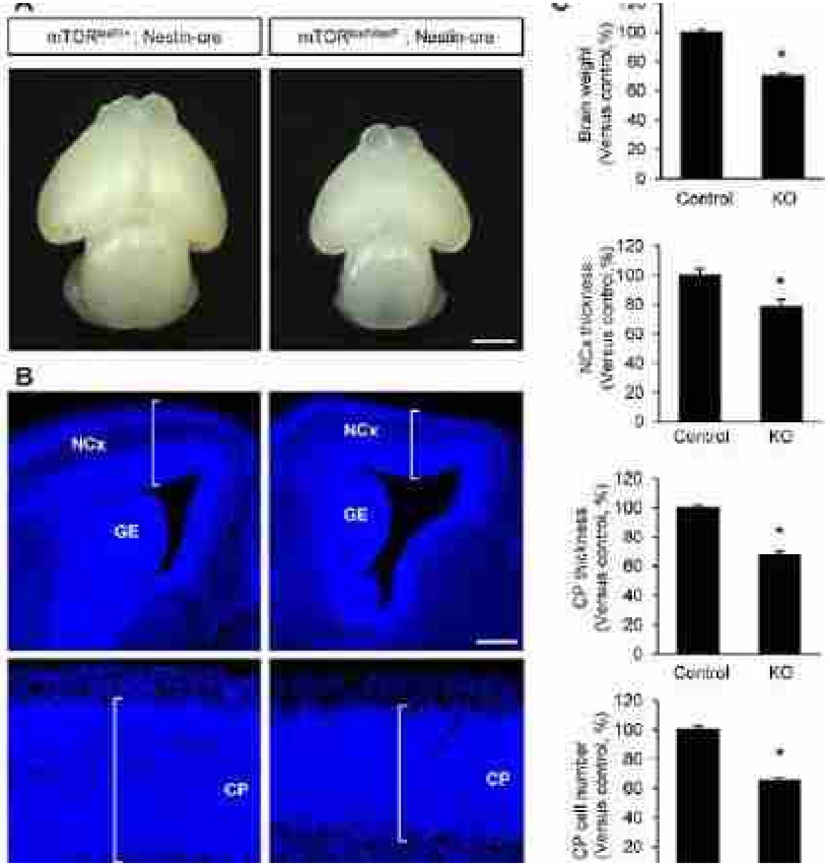
  and/or
- there is a **disproportion** with the size of the trunk or limbs, the possibility of megalencephaly should be considered.

- If other conditions associated with a relatively large head, such as **intrauterine growth restriction, hydrocephalus, fetal tumors and**



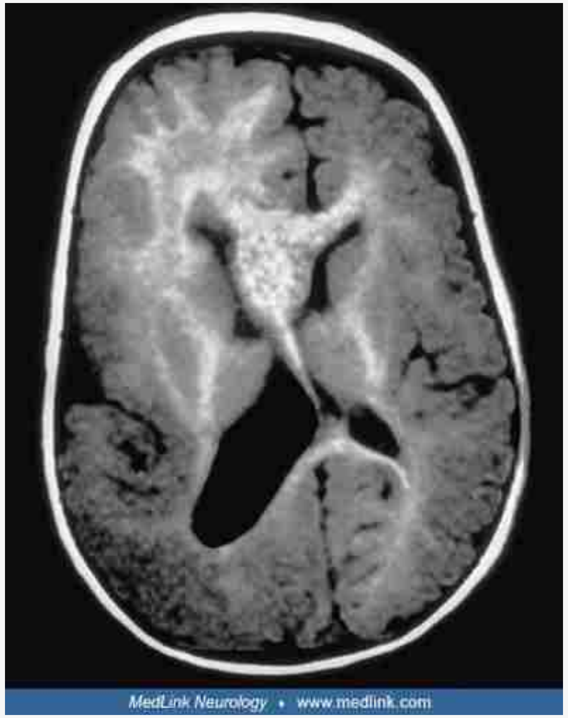
- Hemimegalencephaly (HME) **Hemimegalencephaly (HME)** is a rare congenital brain malformation characterized by the **asymmetric enlargement of all or part of one cerebral hemisphere**.

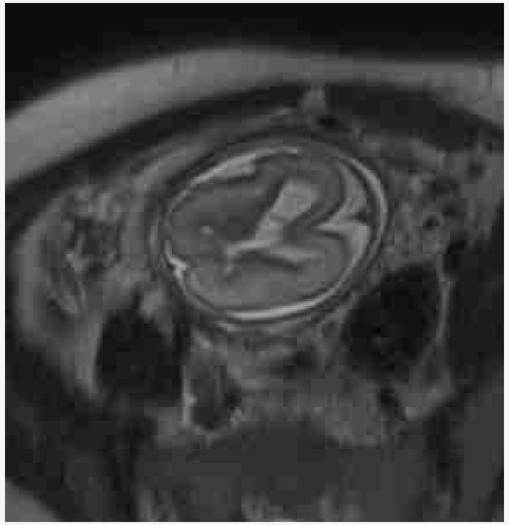
- Many cases of HME→hyperactivation of the **mTOR pathway** which is responsible for unilateral brain and spinal cord overgrowth.
- HME may be a part of **neurocutaneous or somatic hemihypertrophy syndromes→NF 1,TSC**



Hemimegalencephaly ultrasound

- **Asymmetric Cerebral Overgrowth**
- **Ipsilateral Ventriculomegaly**
- **Midline Shift**
- ***Cortical Dysplasia***: High-resolution neurosonography may reveal abnormal gyration patterns, such as thick, flat gyri (pachygyria) or tiny, disorganized folds (polymicrogyria) on the affected side.
- **Altered Echogenicity**: The white matter of the enlarged hemisphere can appear abnormally echogenic (brighter) due to underlying gliosis or heterotopia (displaced gray matter)





Group II (abnormal neuronal migration)

The **first** of these is related to abnormalities of the neuroependyma (ventricular epithelium), which result in the formation of periventricular nodular heterotopias.

The **second** describes generalized abnormalities of trans-mantle migration, mainly **lissencephalies**

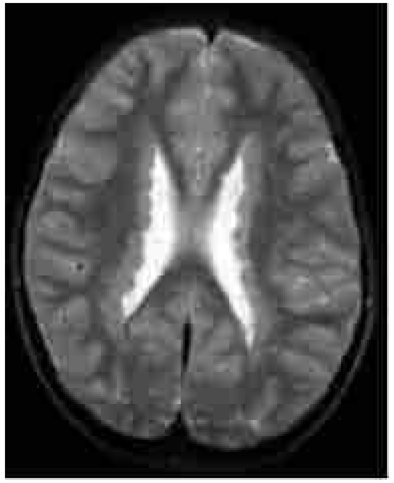
The **third** describes localized abnormalities of trans-mantle migration, mainly **subcortical heterotopias**

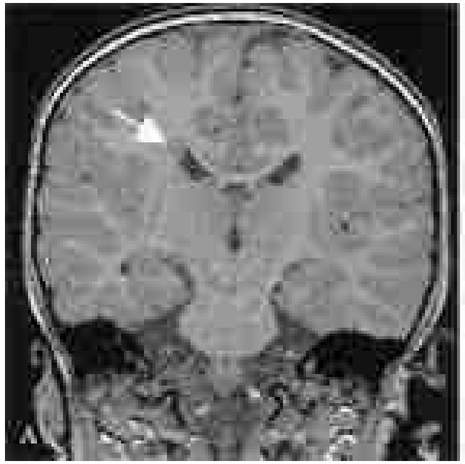
the **fourth** describes abnormalities due to abnormal terminal migration/defects in pial limiting membrane, mainly **cobblestone malformation**

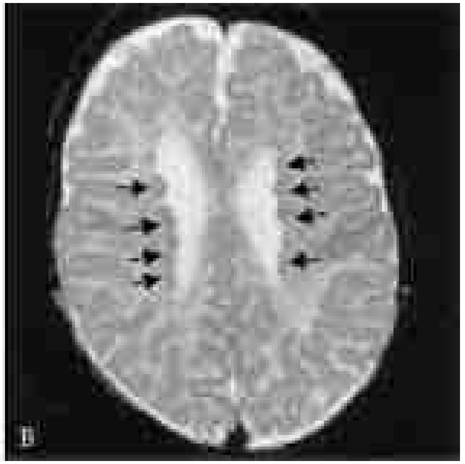
periventricular nodular heterotopias

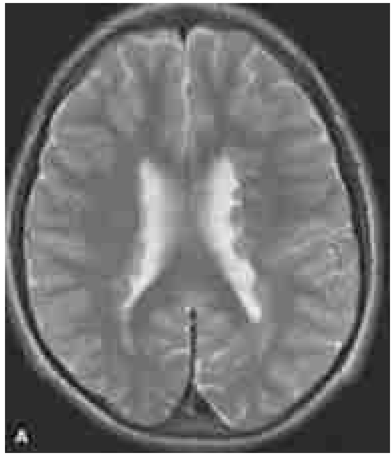
- **Sonography (Ultrasound) Findings**
- usually becoming most apparent in the **late second to third trimester:**
- **Irregular Ventricular Borders**: The normally smooth walls of the lateral ventricles may appear jagged or bumpy on axial views.
- **Dysmorphic Ventricles**: The frontal horns of the lateral ventricles can look square-shaped or distorted on coronal views.
- **Associated Anomalies**: Sonography may also reveal concurrent structural brain differences, such as mild ventriculomegaly (enlarged ventricles) or posterior fossa anomalies (like a mega cisterna magna)

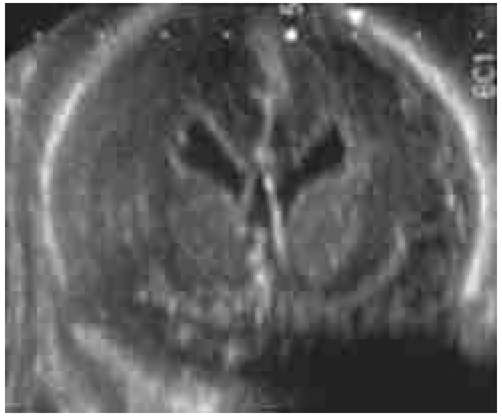
Irregular ventricular walls due to heterotopias should not be confused with ventricular wall irregularity secondary to clastic events, such as CMV infection, ischemia or hemorrhage.





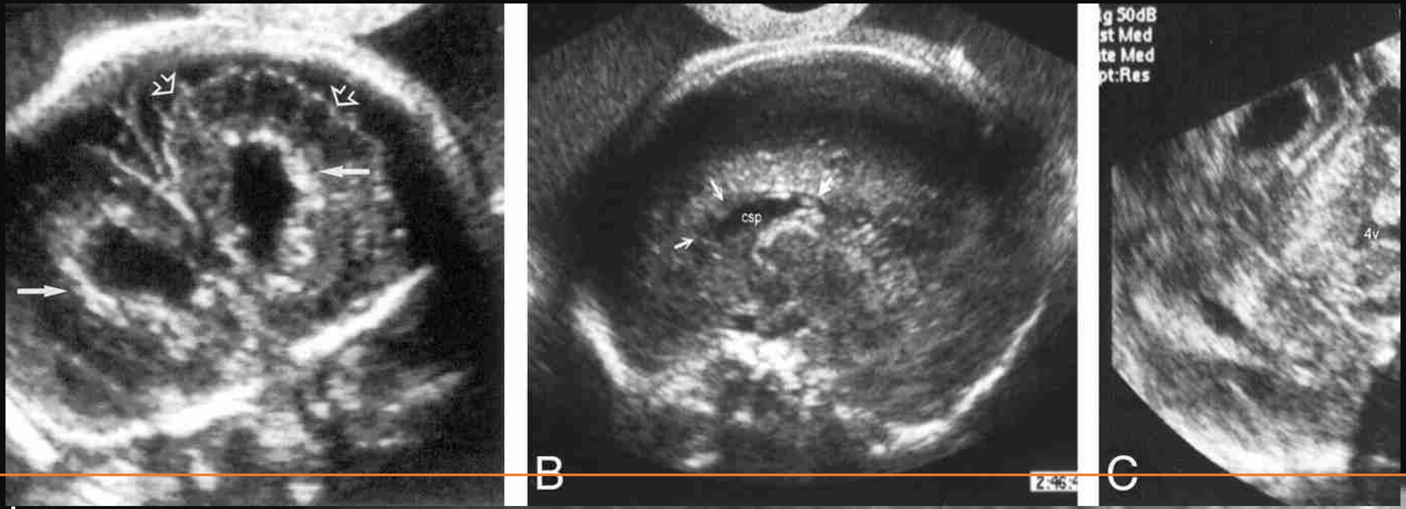




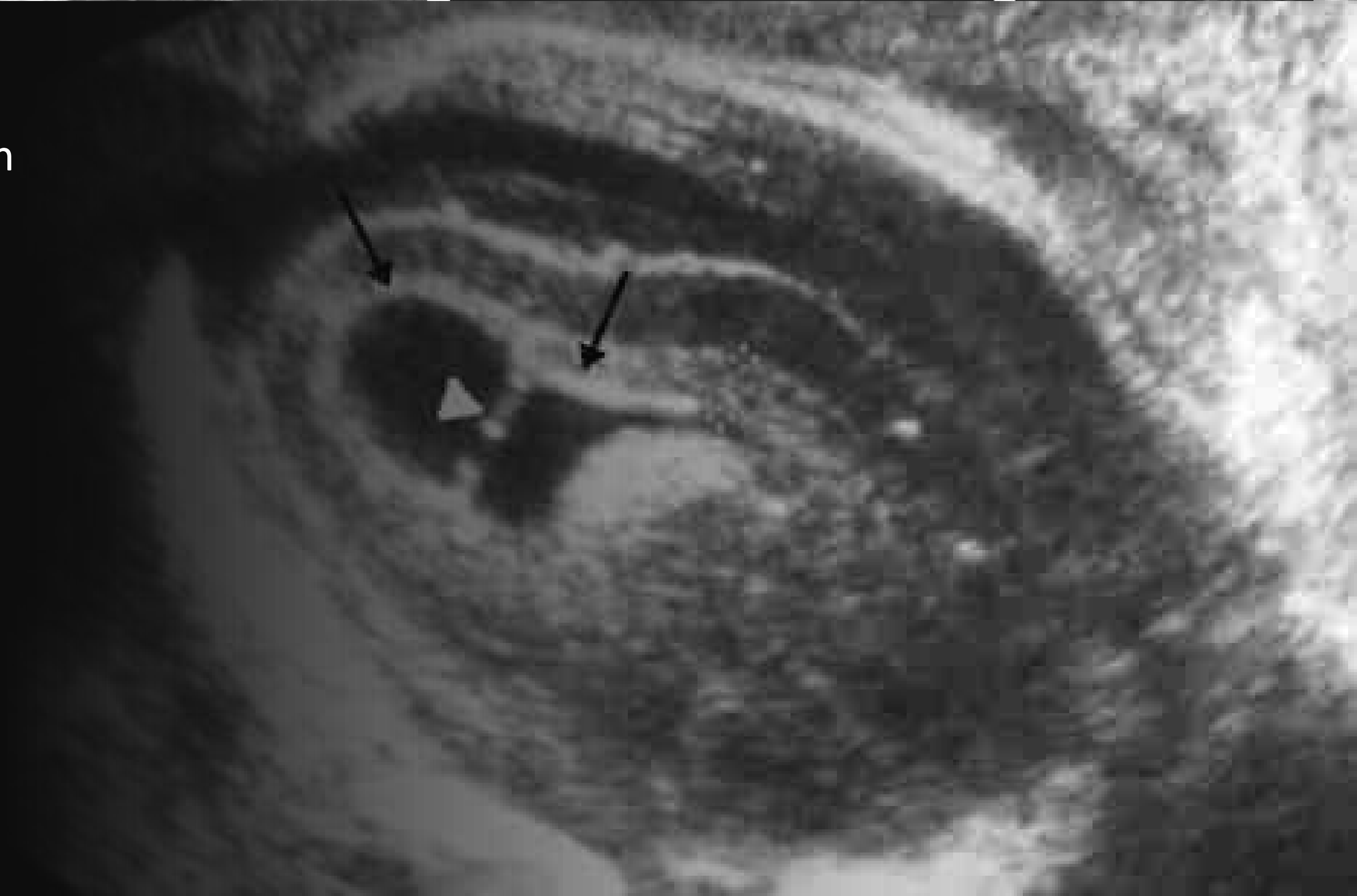


Periventricular Nodular Heterotopia (PNH)	Congenital CMV Infection
Pathogenesis: Neuronal migration disorder	**Pathogenesis:** Infectious/destructive brain injury
MRI hallmark: Gray-matter nodules lining ventricles	**MRI hallmark:** Ventriculomegaly + white matter injury
Ventricular wall: Smooth with protruding nodules	**Ventricular wall:** Irregular/rough
Signal characteristics: Nodules identical to cortex on all sequences	No cortical-signal nodules
Calcifications: Absent on MRI	Frequently present (better seen on US)
Temporal lobe cysts: Rare	Common and highly suggestive
Associated findings: Callosal anomalies, posterior fossa anomalies, FLNA mutation	Polymicrogyria, cerebellar hypoplasia, FGR

CMV→

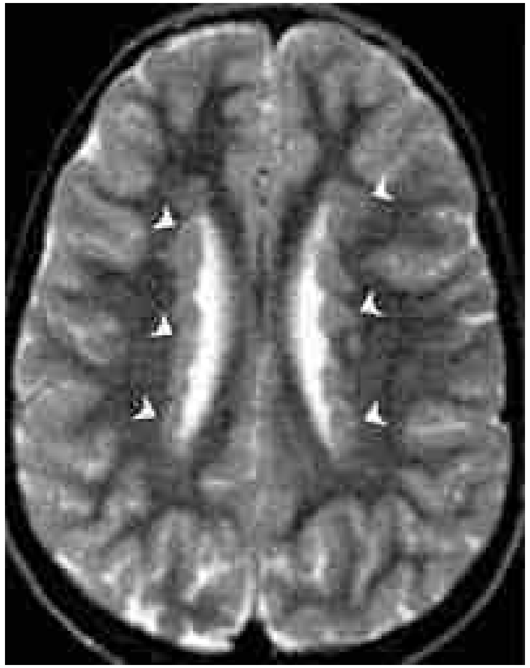


- A, Coronal transvaginal sonogram of the fetal brain at 29 weeks' gestation shows parenchymal foci of increased echogenicity consistent with calcifications (solid arrows) and abnormal sulcation (open arrows).
- B, Sagittal transvaginal sonogram shows hypoplastic, blurred corpus callosum. The genu of the corpus callosum is not observed (open arrows), the splenium is thin (solid arrow). csp indicates cavum septum pellucidum.
- C,Sagittal transvaginal sonogram shows cerebellar echogenic foci (arrow).
-

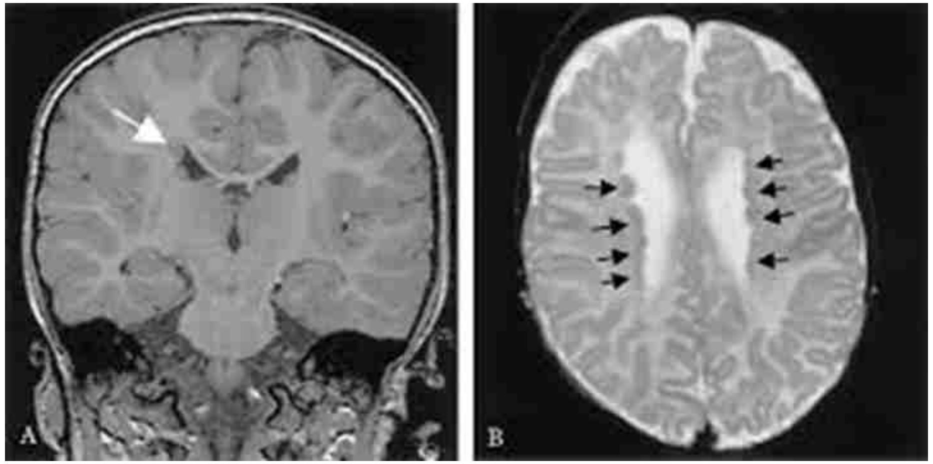


PNH→

- **Heterotopic nodules may be single, multiple, unilateral or bilateral (string-of-pearls appearance) and appear in various locations along the ventricular wall.**
- Single nodules may be found subependymal disruption as seen hydrocephalus.
- “String-of-pearls” lesions along the ventricular walls may be seen with **mutations.**

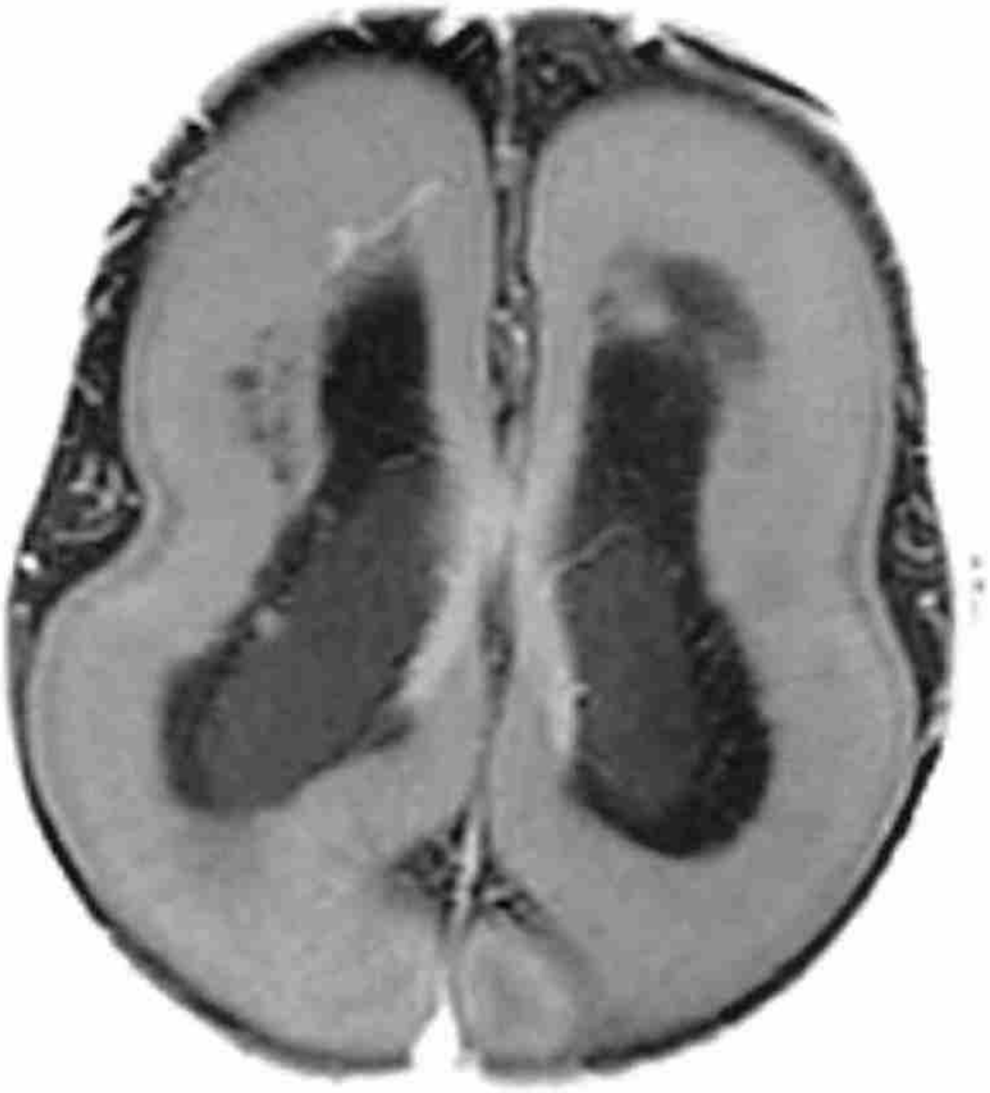


- Multiple nodules can be associated with **ACC and mega cisterna magna**.
- A posterior or trigonal location is associated with **hippocampal, cerebellar and brainstem anomalies**

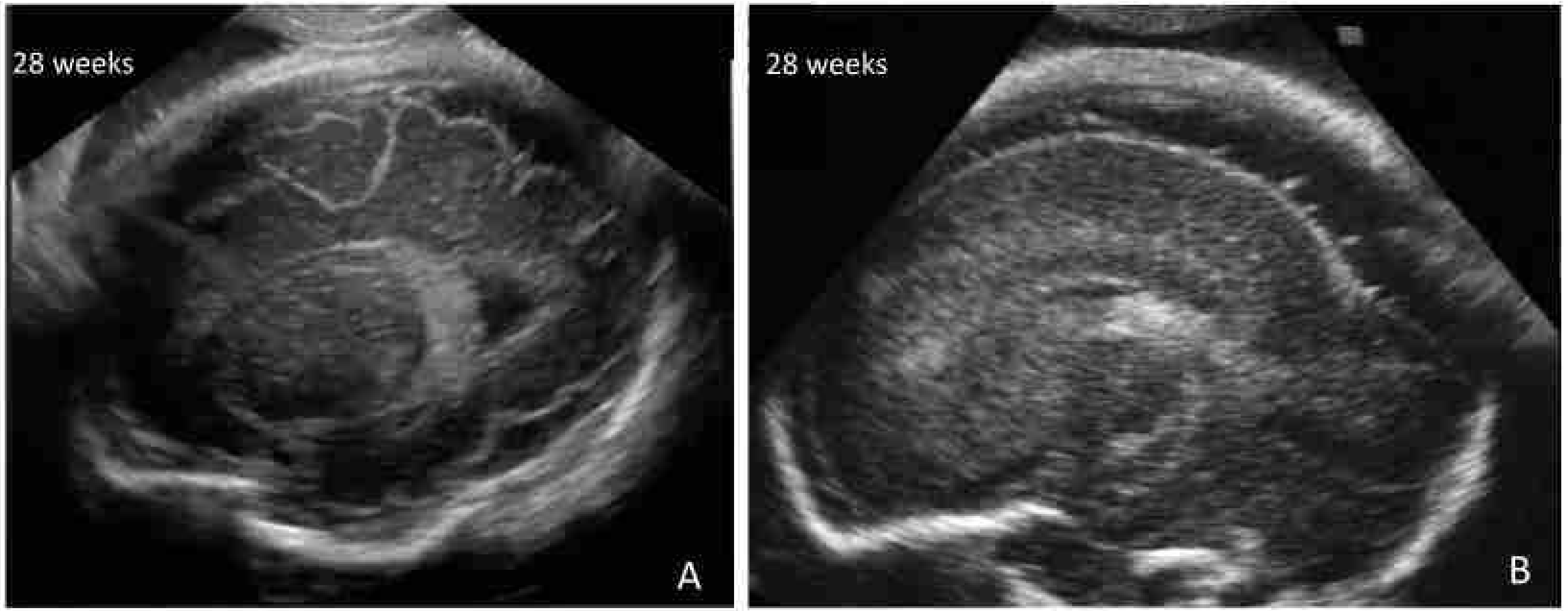


Detecting Lissencephaly

- Ultrasound (Sono) Features via fetal ultrasound is heavily dependent on gestational age and the severity of the condition.
- While primary structural anomalies can sometimes be hinted at earlier, the condition is most reliably visualized during the late second or third trimester.
- **Absent or Delayed Sulcation**: The most telling sign is the failure of the brain surface to develop normal grooves (sulci and fissures), particularly the Sylvian fissures, which should typically become visible between 20-24 weeks.
- **Smooth Cerebral Hemispheres:** The cortex appears abnormally smooth (agyria) or exhibits only a few broad, flat gyri (pachygyria).
- **Ventriculomegaly**: Mild to moderate enlargement of the cerebral ventricles is frequently observed.
- **Corpus Callosum Anomalies**: The bundle of nerves connecting the brain hemispheres may be underdeveloped or absent.

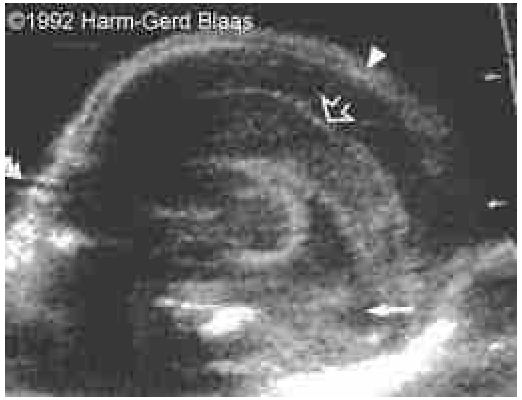


Lissencephaly type 1

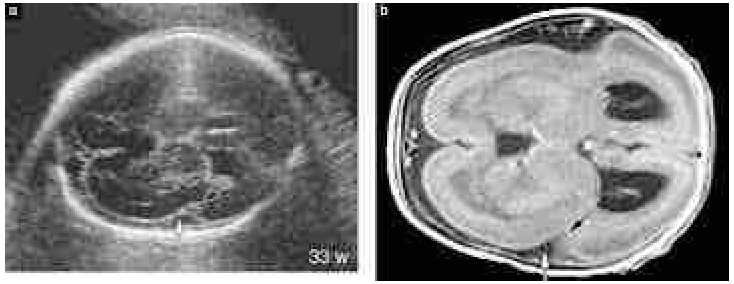


Sagittal images of 28-week fetuses with (A) normal cortical development with central (Rolandic) fissure and adjacent age-appropriate surface sulci (B) Lissencephaly with complete absence of surface sulci and increased extra-axial spaces.

The most common, known as classical lissencephaly or Type 1 lissencephaly→



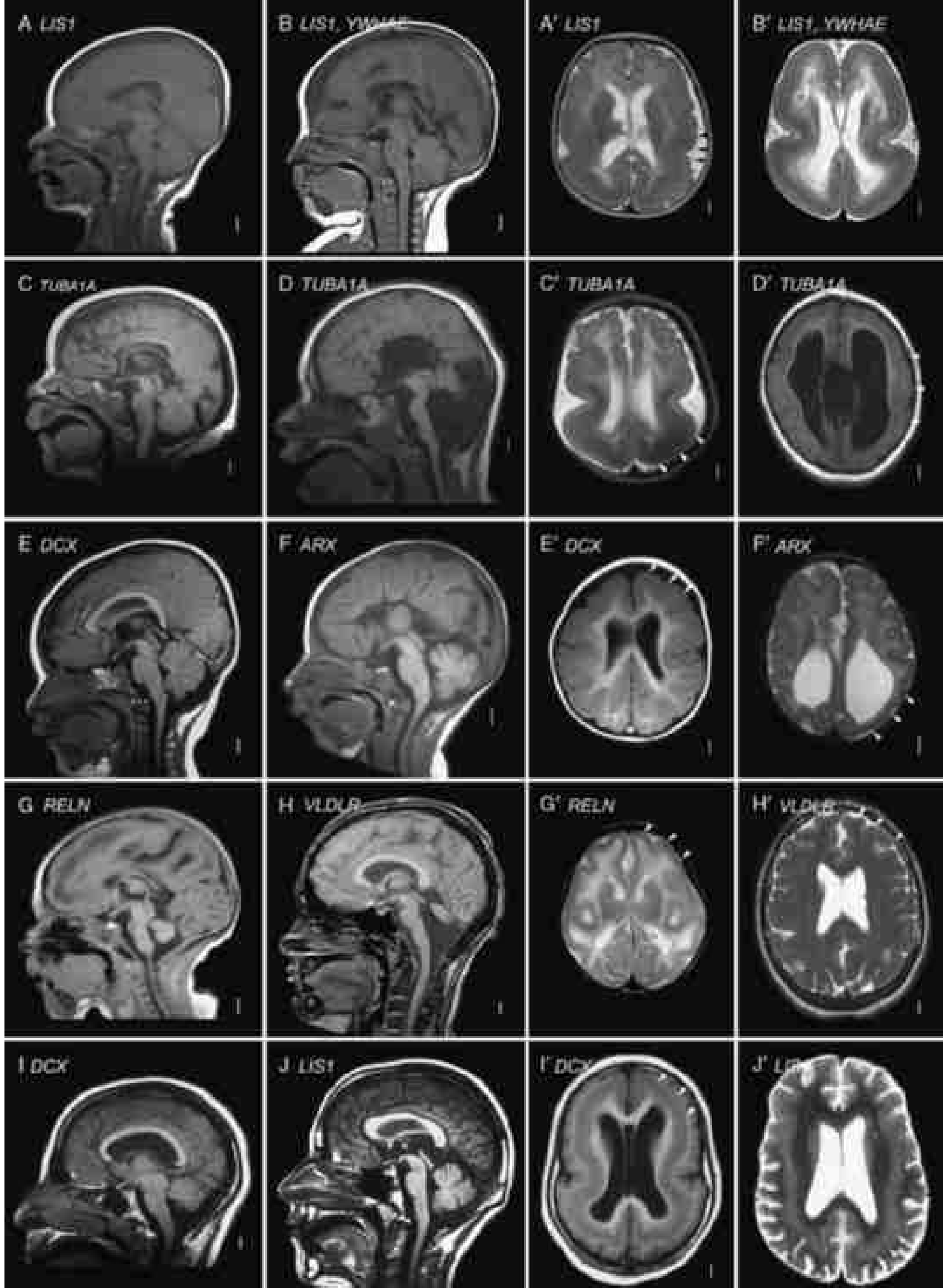
- a very thick and smooth cortex (10–20 mm) and no other major brain malformations.
- It can be isolated or can accompany multiple congenital anomaly syndromes, including
- **Miller-Dieker,**
- **Baraitser-Winter cerebrofrontofacial syndrome**
- **X-linked lissencephaly with abnormal genitalia or XLAG**

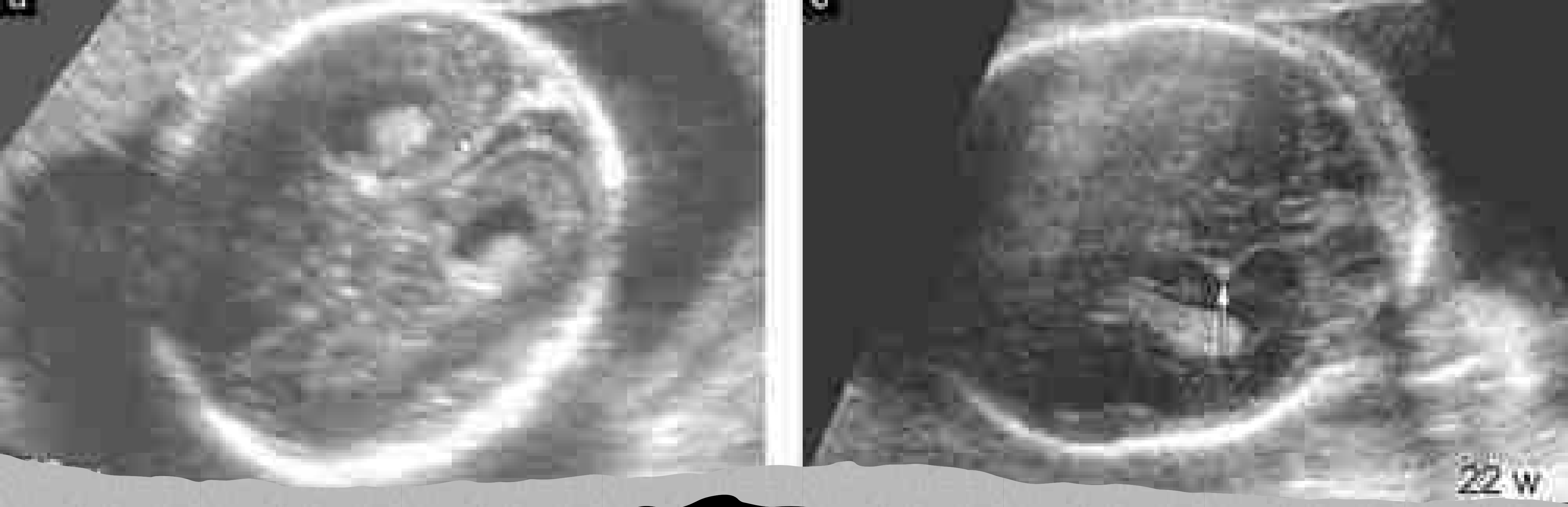


- Miller-Dieker

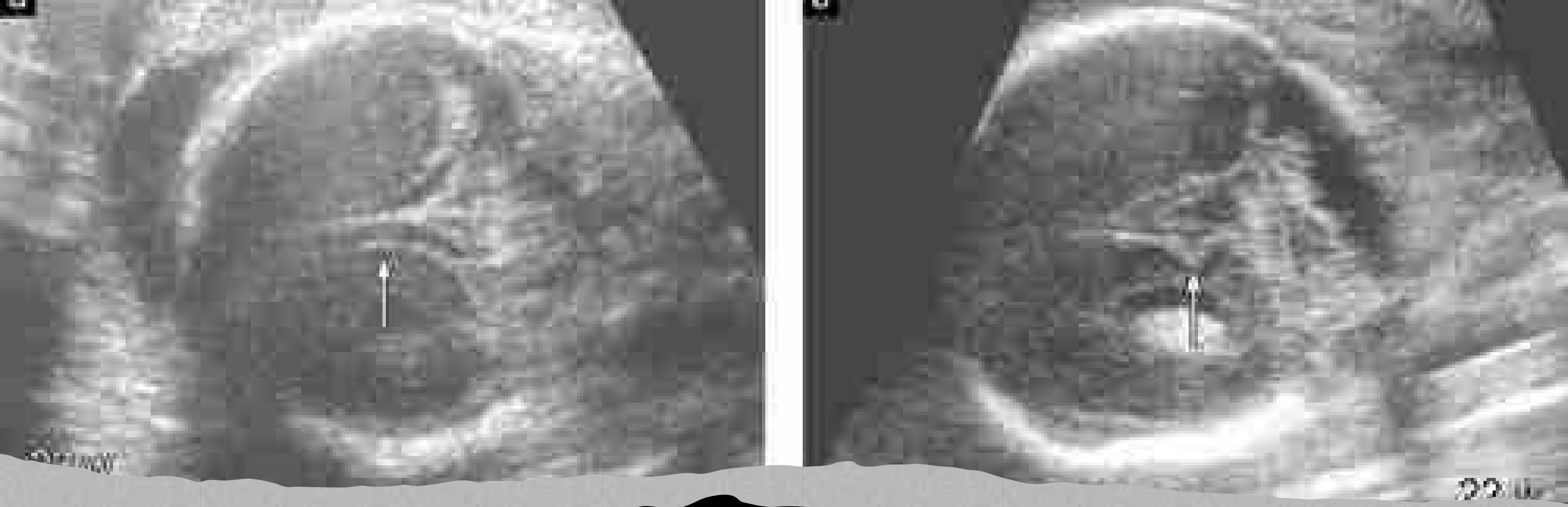
(17p13.3 mutation) is the most severe of these, with typical facies and a lack of sulcation.

- The other known genes responsible for lissencephaly Type 1 include **LIS1**, ARX, RELN, VLDLR, ACTB, ACTG1, **DCX**, DYNC1H1, KIF2A, TUBA1A, TUBB2B, and TUBG19



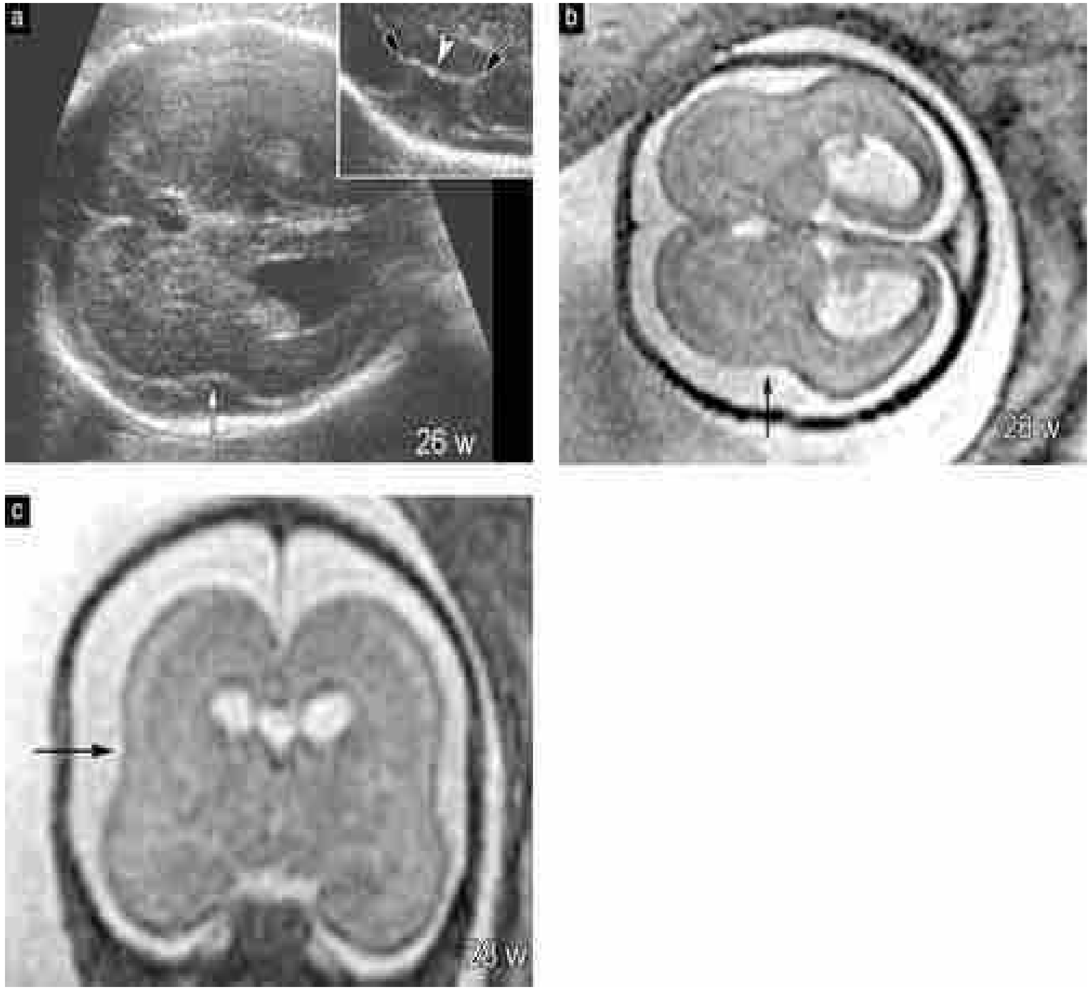


- Absent parieto-occipital fissure at 23 weeks.
- (a) Axial ultrasound image: the parieto-occipital fissure is not identified in the expected location (arrow) in a 23-week fetus with lissencephaly associated with Miller–Dieker syndrome
- (b) Normal sonographic appearance of the parieto-occipital fissure (arrow) in a 22-week fetus.



- The most common prenatal ultrasound findings of MDS were ventriculomegaly and polyhydramnios. CMA can improve diagnostic precision for detecting MDS.
- Absent calcarine fissure at 23 weeks. (a) Coronal ultrasound image: the calcarine fissure is not seen in the expected location (arrow) in a 23-week fetus with lissencephaly associated with Miller–Dieker syndrome
- (b) Normal sonographic appearance of the calcarine fissure (arrow) in a 22-week fetus.

- Abnormal Sylvian fissure/insula at 23 weeks. (a) Axial ultrasound image: the Sylvian fissure/insula appears shallow and flat (arrow) in a 23-week fetus with lissencephaly associated with Miller–Dieker syndrome (b) Normal ‘square’ appearance of the Sylvian fissure/insula in a 22-week fetus, with distinct angularity (black arrows) at the margins of the insula (white arrowhead).

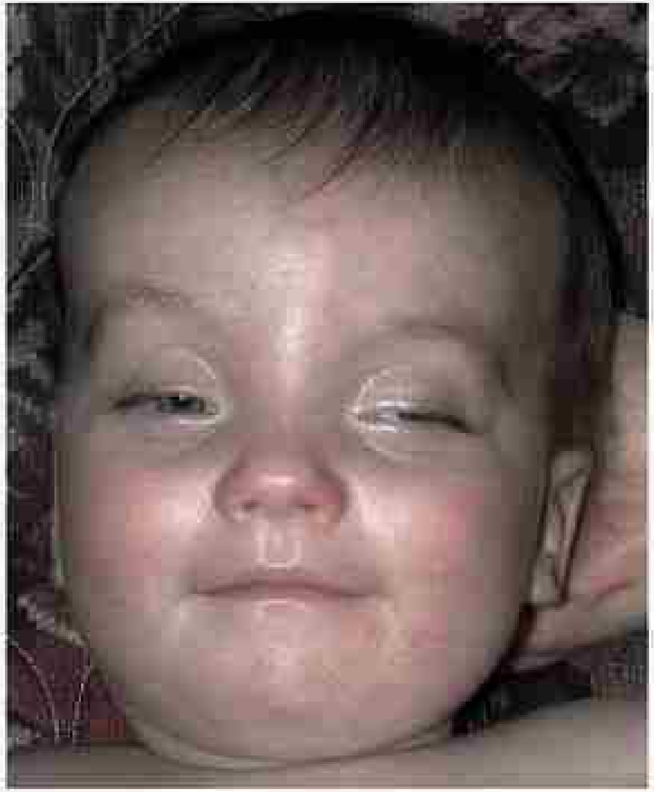


Abnormal Sylvian fissure/insula at 26 weeks.

- Axial ultrasound image at 26 weeks in a fetus with lissencephaly associated with Miller–Dieker syndrome (MDS) :
- a shallow, flat Sylvian fissure/insula (arrow) with absence of angularity at the insular margins
- Infolding of the operculum should be seen with acute angles (black arrows in inset) at the margins of the insula (white arrowhead in inset) at ≥ 24.5 weeks' gestation. (b) Axial and (c) coronal T2-weighted magnetic resonance images at 28 weeks in the same fetus with MDS (Case 3) showing a shallow Sylvian fissure (arrow). **The brain has an hourglass or figure-of-eight appearance on the axial image. Also note the agyria, large subarachnoid space and mildly dilated occipital horns.**

Miller-Dieker→

- Lissencephaly
- short nose with upturned nares
- thickened upper lip with a thin vermilion upper border
- frontal bossing,
- small jaw, low-set posteriorly rotated ears,
- hypertelorism of eyes

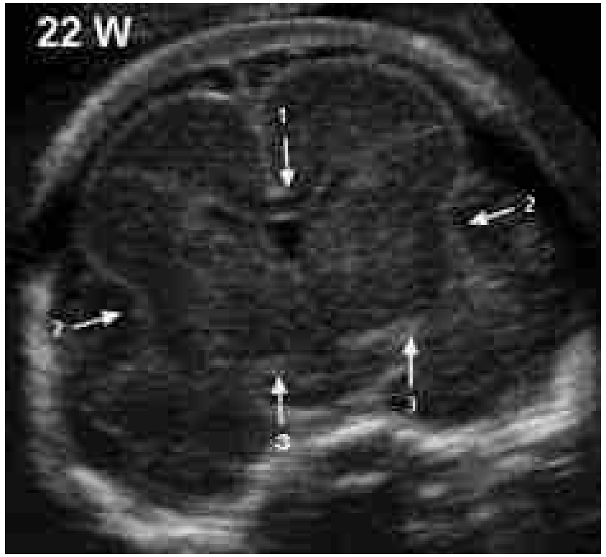


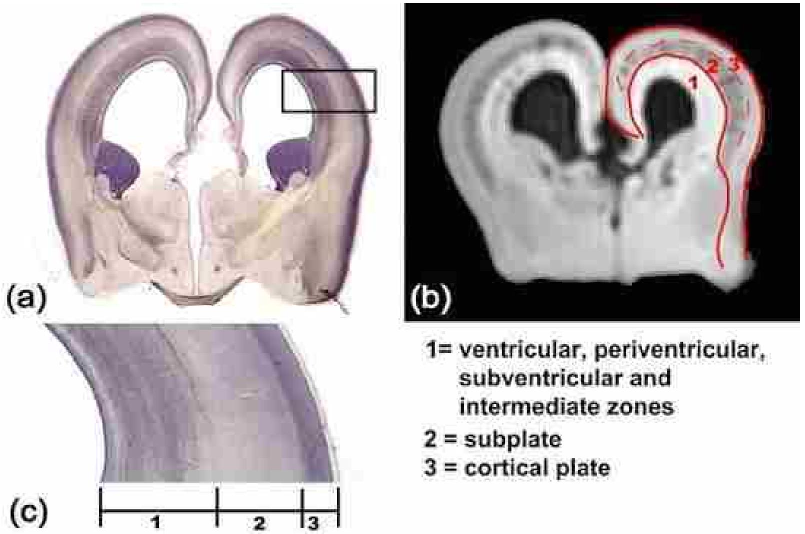
phenotype–genotype classification

Cortical thickness	Gradient	Gender	Cerebellum	Brainstem
	Lis 1 DCX	DCX BAND HETEROTOPIA XLAG	RELN gene XLAG TUBULINOPATHIES	COBBLESTONE

Cortical thickness

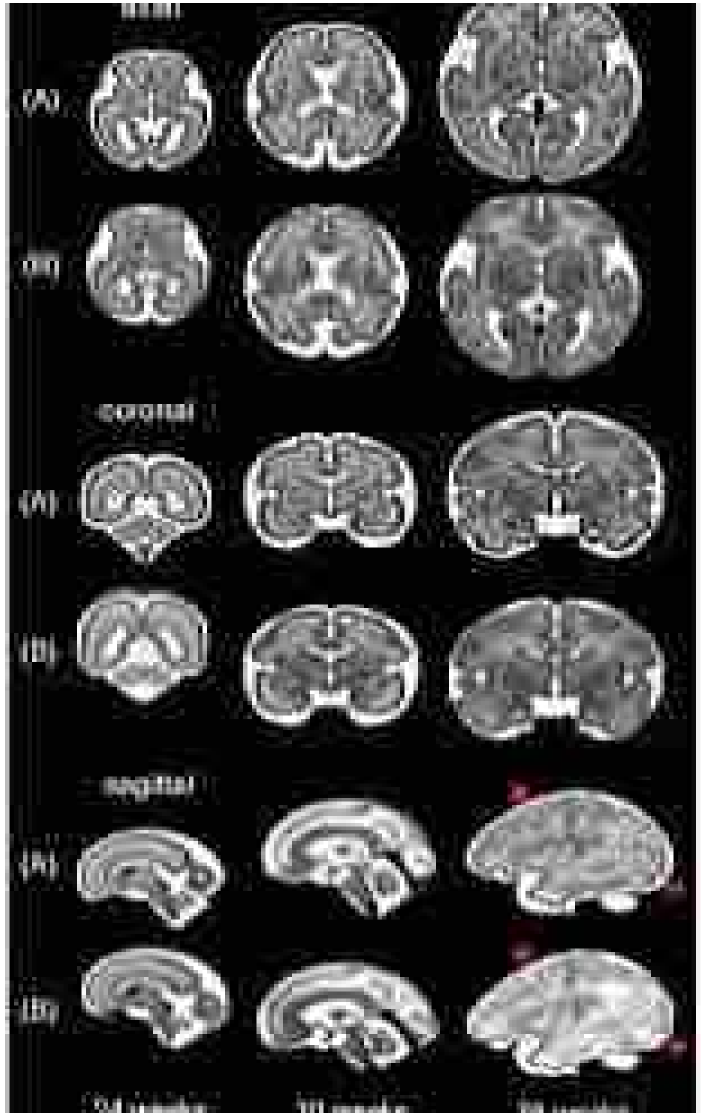
- Normal cortex is comprised of **six layers with an overall thickness of 4 mm,** in lissencephaly there are two to four layers, resulting in either a thick (10–20 mm), thin (5–10mm) or variable cortex, with the former being most common.





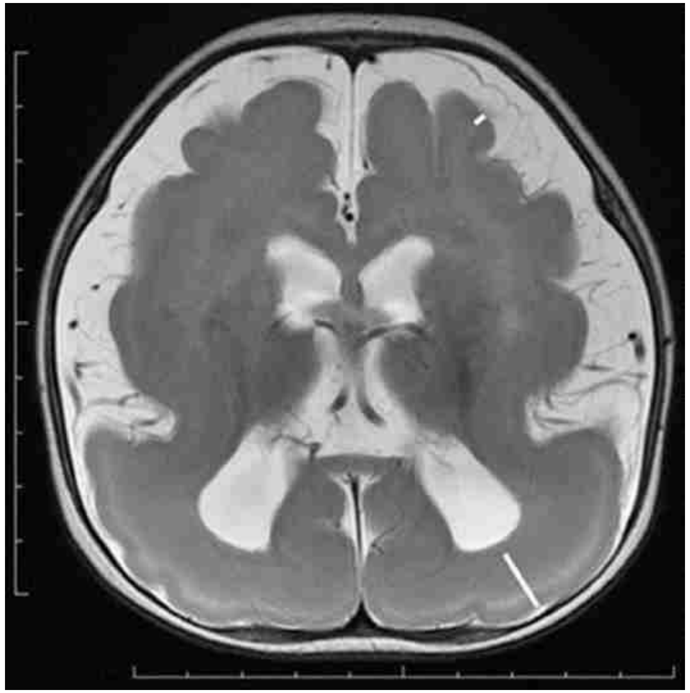
Gradient

- Important feature of lissencephaly, with **posterior predominant lissencephaly more common than anterior predominant or diffuse lissencephaly**
- *The gradient* of involvement in the gyral pattern can help differentiate the other LIS disorders.
- Involvement may be partial or demonstrate pachy/agyria with frontal or posterior severity reflecting the mutation.
- **Frontal pachygyria and posterior agyria is the most common pattern and suggests mutations of the LIS1 gene.**

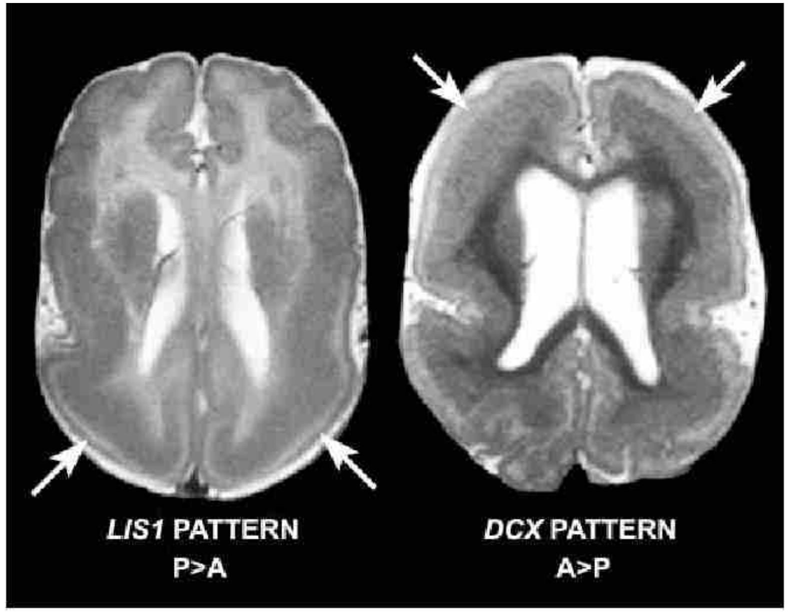


Gradient

- **LIS1→** also known as *PAFAH1B1 :*
- most severe in the posterior regions (parietal and occipital lobes), often showing complete agyria (smooth brain) there, while the frontal lobes may show pachygyria (broad, thick gyri).
- **(posterior-to-anterior gradient)**



- **DCX Mutation→** (Anterior-to-Posterior Gradient): Mutations in the DCX (Doublecortin) gene, which is X-linked,
- the frontal lobes are most severely affected, while the posterior regions are relatively spared or show milder pachygyria
- **(Anterior-to-Posterior Gradient)**



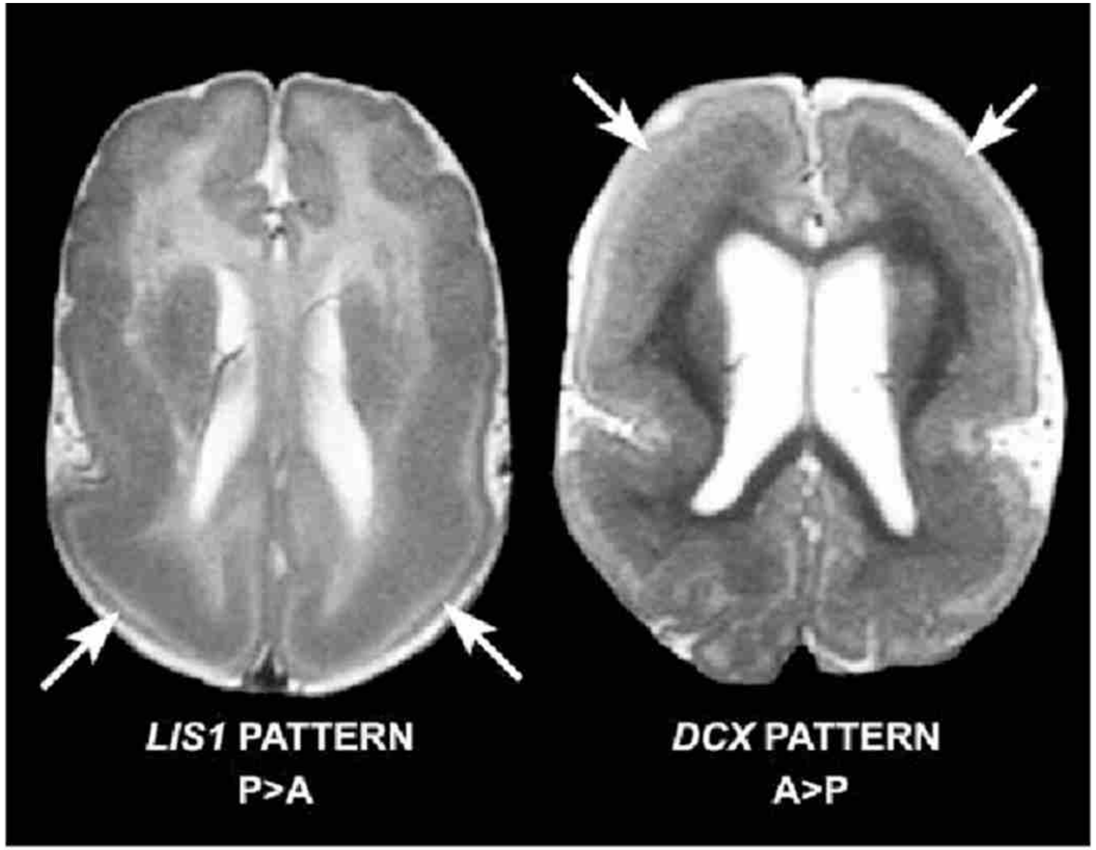
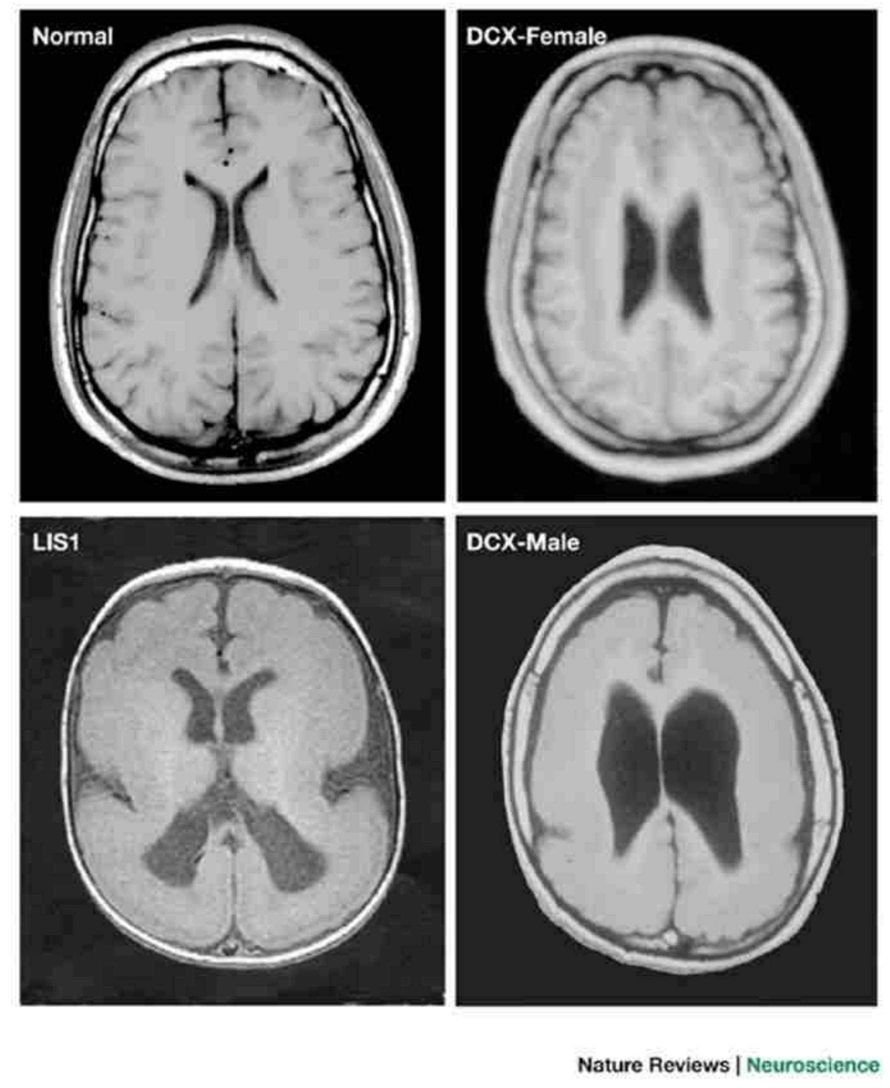


Figure 3. Different anteroposterior severity gradients in lissencephaly

Gender

- DCX mutations lead to **classic lissencephaly in males, but may exhibit subcortical band heterotopia in females**

- The band or double cortex, as can be seen in DCX mutations, would be difficult to confirm on prenatal imaging, although the dysgyria and vermian hypoplasia are helpful prenatal imaging features

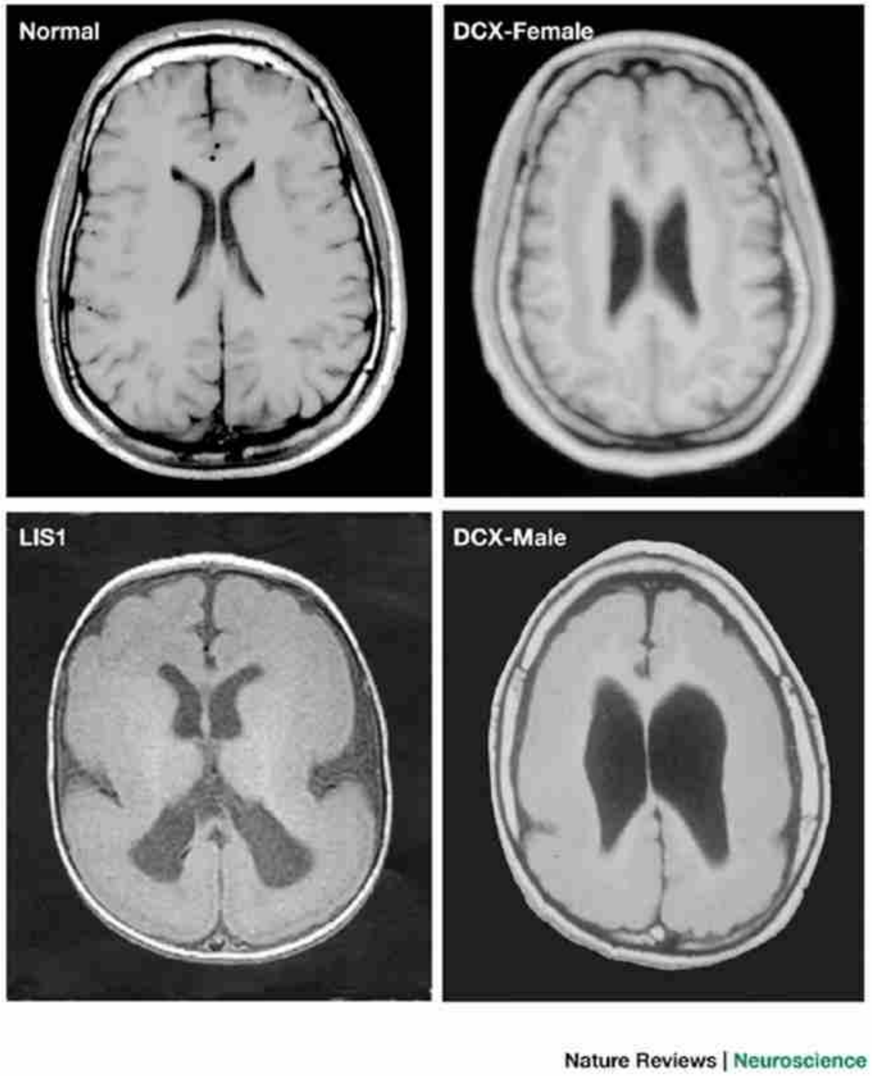


Clinical Presentation

In Males (Hemizygous): Usually causes **Lissencephaly** (a "smooth brain"), **developmental disabilities, severe language impairment, and intractable epilepsy (infantile spasms).**

In Females (Heterozygous): Typically causes Subcortical Band Heterotopia (SBH), also known as **Double Cortex Syndrome→→→**

In this condition, **a band of gray matter becomes trapped underneath the normal brain cortex.** The severity varies widely: some individuals may have average intelligence with mild focal epilepsy, while others experience moderate-to-severe developmental delays and hard-to-treat seizures



MRI appearance of human lissencephaly and double cortex syndrome→

MRI images of cerebral cortex in a normal human being (Normal), a patient with LIS1 mutation (LIS1), a female patient with DCX mutation (DCX-Female) and a male patient with DCX mutation (DCX-Male).

Notice that patients with mutations in LIS1 and male DCX patients show strikingly similar lissencephalies, whereas female patients with DCX mutations present with 'double cortex' syndrome, in which a band of grey matter is embedded within the white matter beneath the normal cortex.

Band→

- **MRI**
  As the name suggests, this condition is characterized by a band of grey matter located deep to, and roughly paralleling, the cortex, with either normal or pachygyric overlying cortex.
- The band of abnormal grey matter may be complete or incomplete and may even be duplicated (i.e. two concentric bands) within the temporal lobes
  The signal intensity is the same as normal cortex on all sequences.

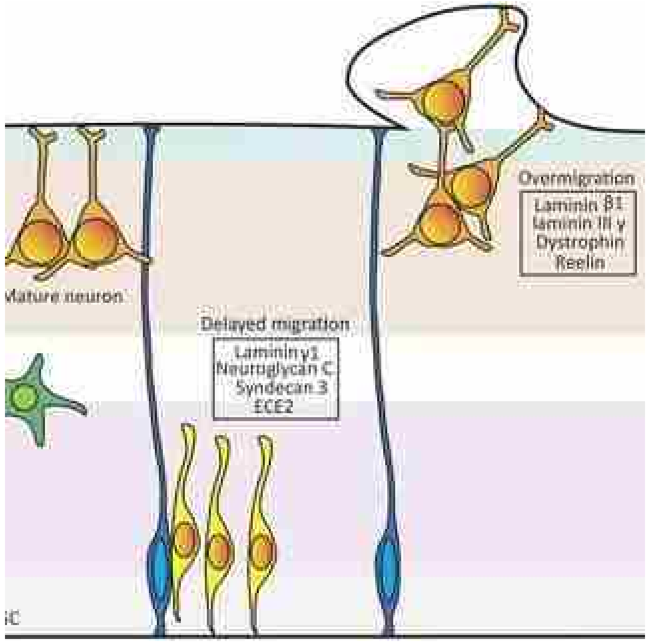
The cerebellum

- **RELN gene** mutation should be suspected when lissencephaly is associated with **cerebellar hypoplasia**
- while an **ARX gene mutation** should be suspected in chromosomal males with X-linked lissencephaly and ambiguous genitalia **(XLAG).**
- **Vermian hypoplasia** may be seen in DCX mutations
- **Thin, asymmetric or bent brainstem** in association with callosal deficiency, abnormal basal ganglia and hypoplastic cerebellum should suggest a tubulinopathy.

Brainstem involvement

- Cobblestone lissencephaly (formerly called Type 2 lissencephaly) is genetically, embryologically, and pathologically distinct from type 1 lissencephaly.
- It results from **defects in dystroglycan glycosylation**, which affects linkage of radial glial cells with the pial limiting membrane, leading to neuronal over-migration through pial gaps

```
Pia
↑
Marginal Zone
↑
Cortical Plate
↑
Intermediate Zone
↑
Subventricular Zone
↑
Ventricular Zone  ← Neurons are generated
↑
Lateral Ventricle
```



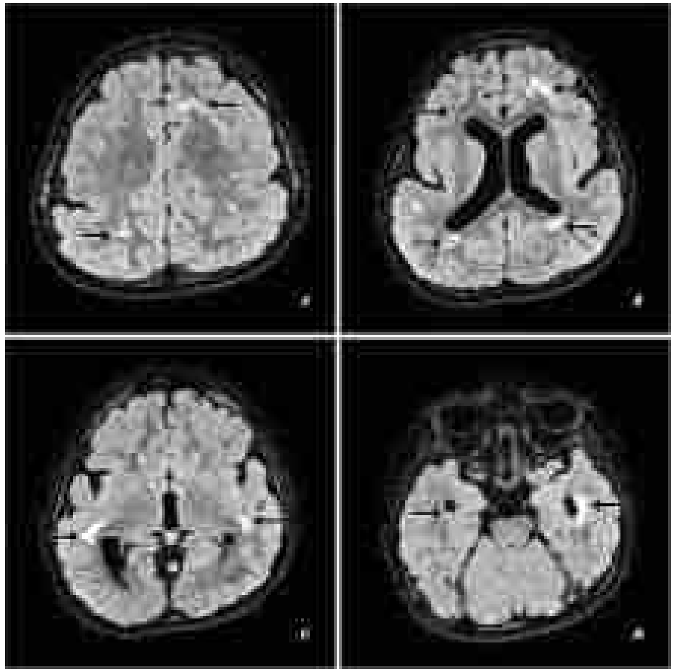
- The dystroglycanopathies with brain and eye anomalies→
- Walker–Warburg syndrome (WWS)
- muscle–eye–brain disease (MEB)
- Fukuyama muscular dystrophy.

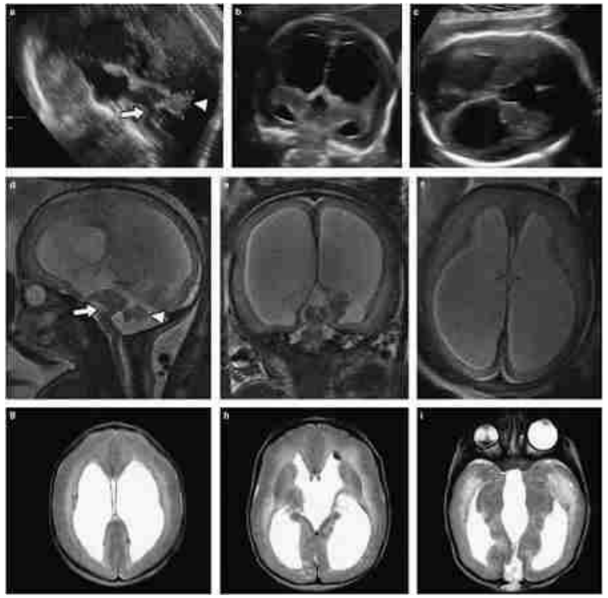
- In these conditions the brain surface lacks normal sulcation and has an uneven appearance, thus the name cobblestone cortex.

Type	Eye	Cortex	Cerebellum	Brain stem	Hydrocephalus	Intellectual disability/epilepsy
Walker-Warburg syndrome	Severe	Cobblestone lissencephaly	Very hypoplastic	Severely hypoplastic	Constant	Severe
Muscle eye brain disease	Common	Frontoparietal pachygyria, polymicrogyria	Vermis hypoplasia, cysts	Usually hypoplastic	Common	Severe
Fukuyama CMD	Variable/mild	Variable	Hypoplasia, cysts, polymicrogyria	Usually normal	Rare	Moderate

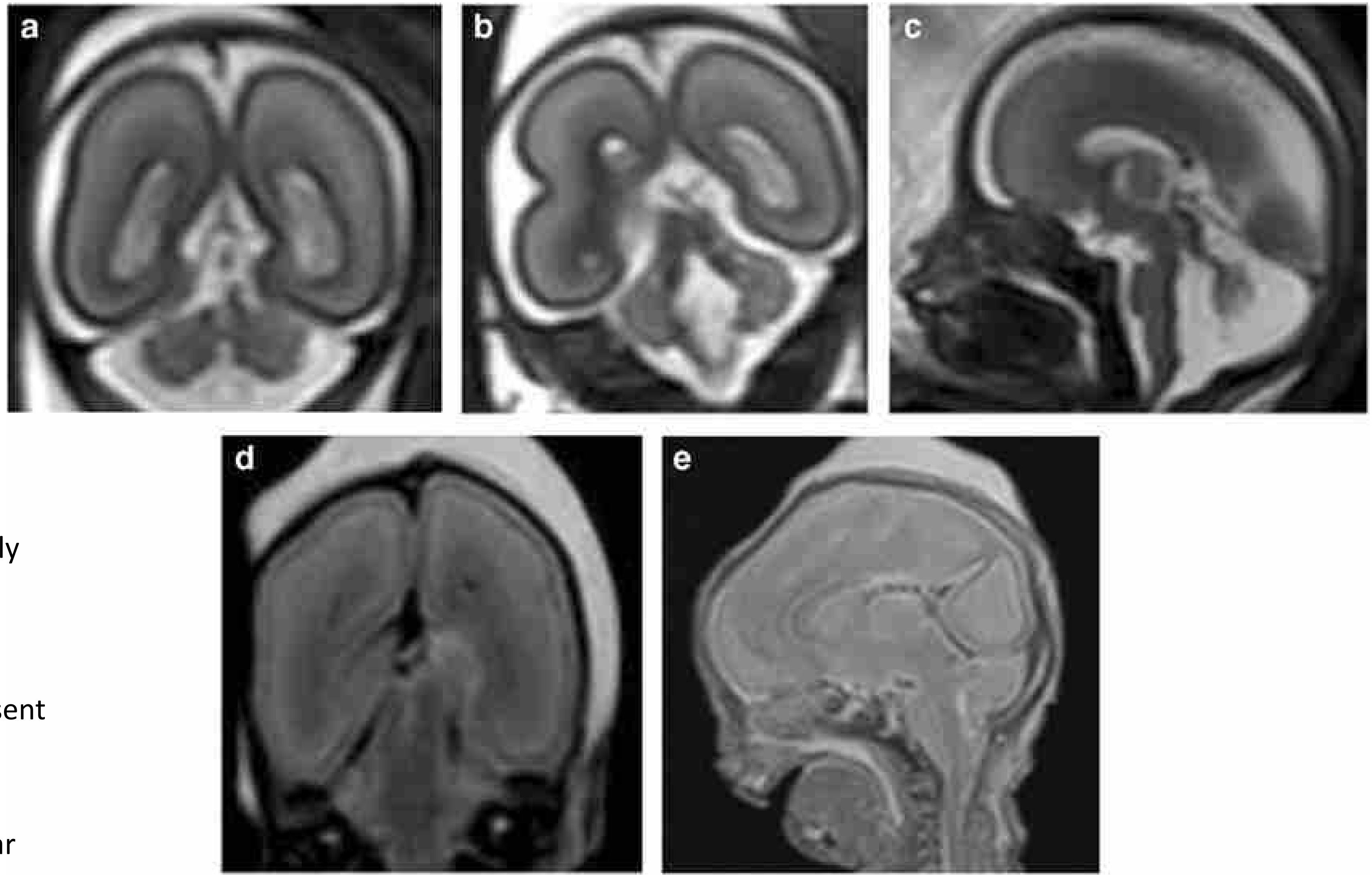
CMDs: Congenital muscular dystrophies

Cobblestone→





- **Abnormal Cortical Surface:** A **lack of normal sulcation** resulting in a smooth or irregular "pebbly" outline of the brain's cortex.
- **Ventriculomegaly:** Enlargement of the brain's fluid-filled cavities, often one of the earliest indicators.
- **Posterior Fossa Anomalies:** Severe underdevelopment or malformation of the cerebellum (cerebellar hypoplasia) and the cerebellar vermis.
- **Brainstem Kinking:** A distinctive, primitive 'Z'-shaped appearance of the brainstem in midsagittal views.
- **Associated Extracerebral Findings:** Ocular abnormalities (such as microphthalmia or cataracts) and/or occipital encephalocele



- Tubulinopathy in a 23-week gestation fetus. a Axial T2-weighted iuMR demonstrates microcephaly, severely thinned hemispheric parenchyma, thinly kinked brainstem (black arrows), small malformed cerebellum with enlarged ganglionic eminence (arrowhead). b Coronal single shot T2-weighted iuMR image demonstrates bilateral lateral ventriculomegaly (asterisks) and an absent corpus callosum (black arrow). c, d Coronal and axial T2-weighted PMMR images show decompressed lateral ventricles. There is also difficulty in appreciating the intra-uterine cerebellar abnormalities

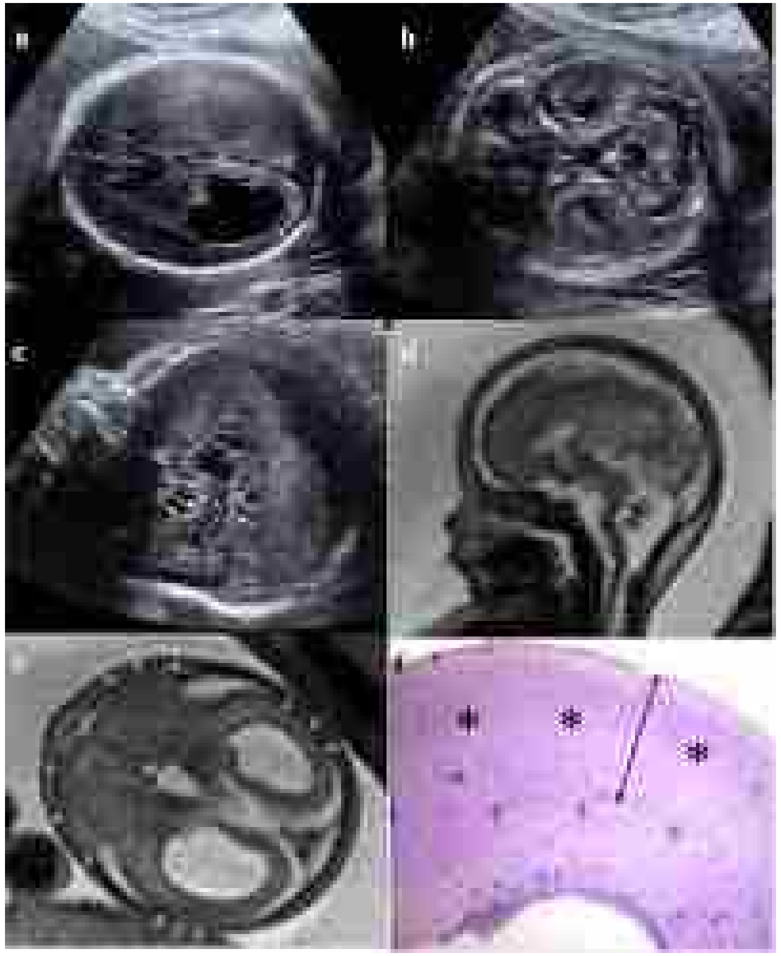
Characteristic features of Lissencephaly Type 1 and Type 2

Type 1 - classic

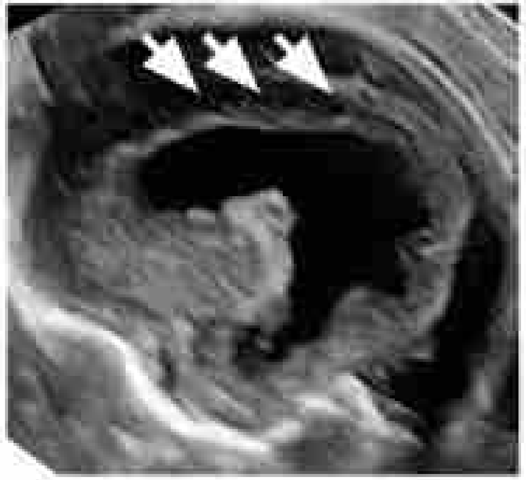
- Smooth and thick cortex
- Abnormal operculization
- Abnormal lamination
- Ventriculomegaly
- Sulcation gradient
- Associated cerebellar and/or callosal anomalies

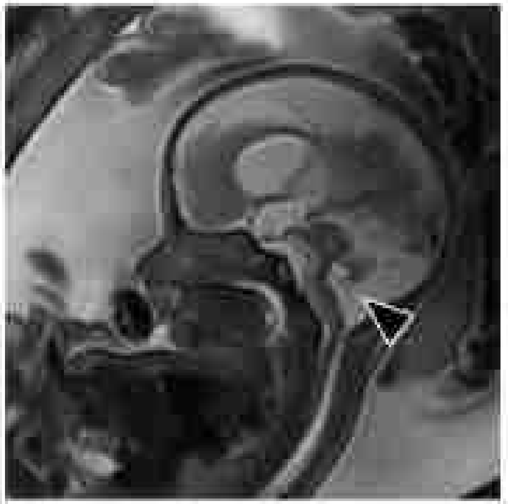
Type 2 - Cobblestone

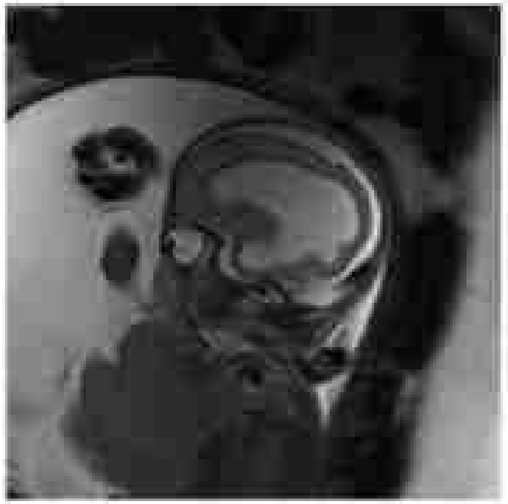
- Ventriculomegaly
- Abnormal operculization
- Abnormal lamination
- Irregular cortical surface
- Z shaped brainstem
- Cerebellar hypoplasia and cerebellar cysts
- Encephalocele
- Retinal detachment and cataracts



Cobblestone lissencephaly (lissencephaly type 2)

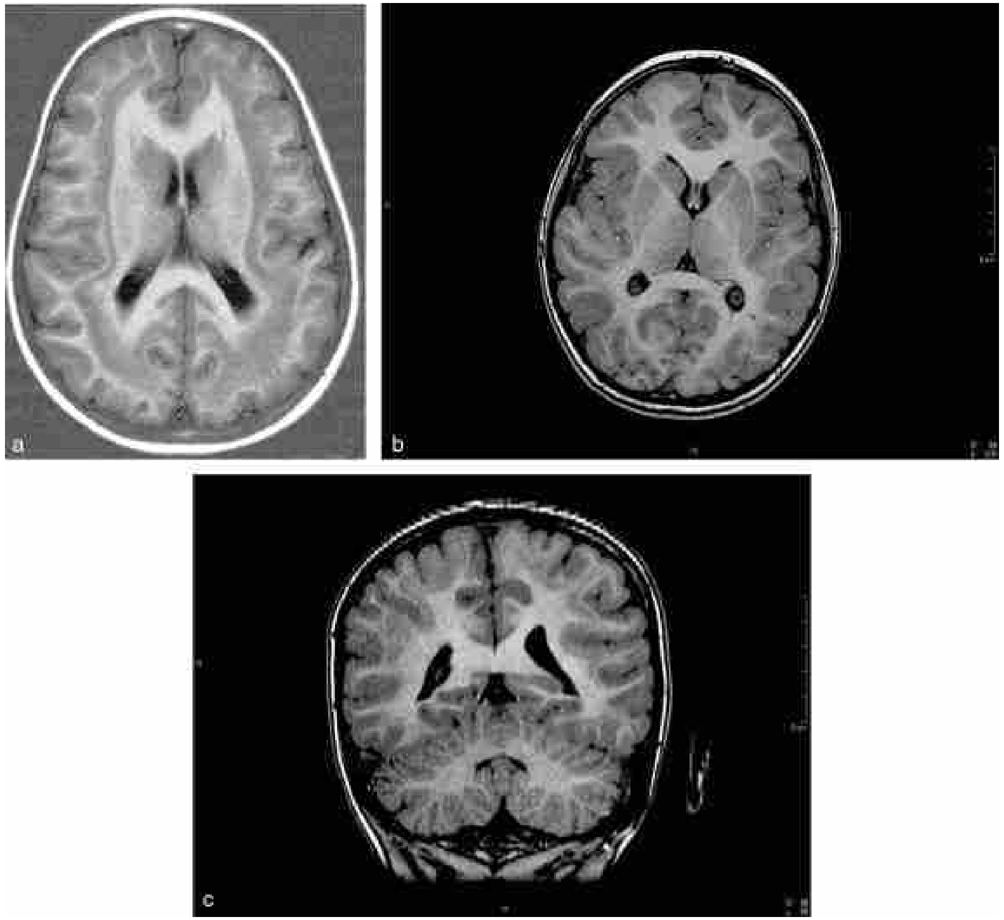






Note elongated midbrain on axial section because of cutting through a bent shaped brainstem.
Great clue to the diagnosis!

Walker Warburg Syndrome (WWS) in a fetus of a consanguineous couple. Note severe bilateral ventriculomegaly with third ventricle dilation, echogenic cortical rim (orange arrows) abnormal corpus callosum, kinked Z-shaped


a
b
c

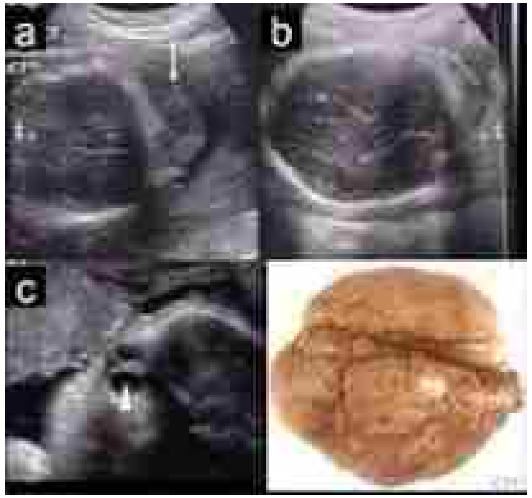
WWS→

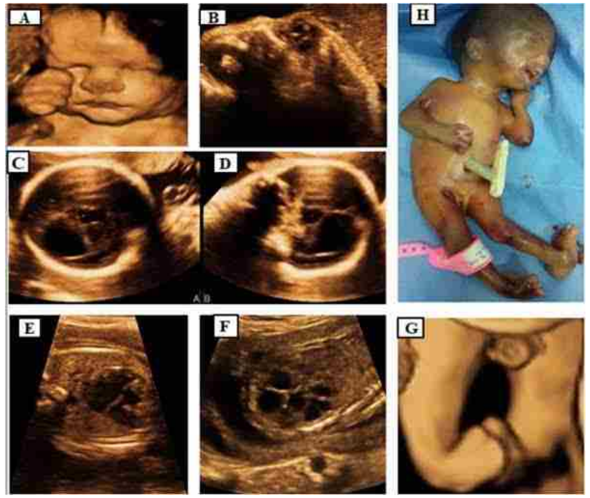
- type II lissencephaly
- cerebellar malformations, including
- Dandy-Walker continuum
- posterior fossa encephalocoele
- retinal malformation/retinal dysplasia
- congenital muscular dystrophy

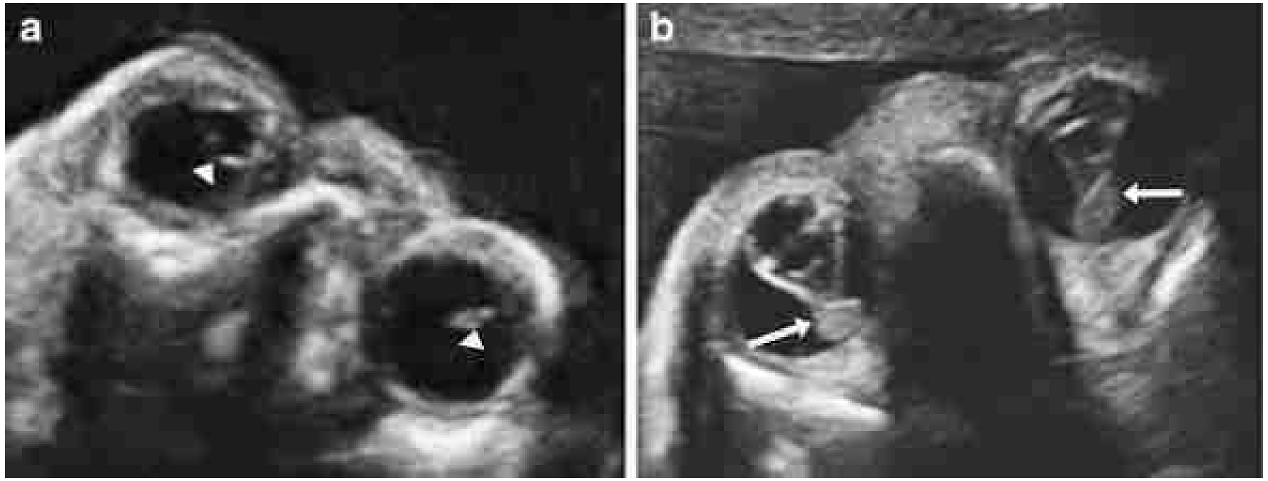
- **fetal hydrocephalus: almost always present**
- **kinked brainstem**
- **agenesis of the corpus callosum**
- **other ocular abnormalities**
- **microphthalmia or unilateral buphthalmos**
- **ocular colobomas**
- **persistent hyperplastic primary vitreous (PHPV) 10**
- **congenital cataracts**
- **microtia**
- **cleft lip +/- palate**
- **genital anomalies in males**

Walker-Warburg Syndrome (WWS)

- is a rare form of autosomal recessive congenital muscular dystrophy associated with brain and eye abnormalities







Key Fetal Ultrasound Findings

- Because the brain's cerebral cortex is supposed to develop folds (sulci and gyri) between the 12th and 24th weeks of pregnancy, a lack of normal development results in very specific, yet late-appearing signs:
- Smooth Cerebral Surface: The most defining feature is the absence or severe reduction of sulci, giving the brain an "agyric" (smooth) or "pachygyric" (thickened, poorly formed folds) appearance.
- Absent Sylvian Fissures: A normal brain shows a distinctive, branching, Y-shape in the Sylvian fissure.
- In lissencephaly type 1, this fissure appears shallow, widened, and unbranched.
- Mild to moderate enlargement of the lateral ventricles is a common, nonspecific secondary sign.
- Corpus Callosum Abnormalities: Agenesis or hypoplasia (underdevelopment) of the corpus callosum frequently accompanies this type of cortical malformation

Obstetrical management

- Following the suspicion of MCD by dedicated neurosonography and/or MRI, when appropriate and possible (depending on gestational age), the imaging diagnosis is supplemented by genetic

- **studies (CMA and whole exome sequencing of the fetus and both parents). When multiple PNH are seen in a female fetus, FLNA should be suspected and brain MR imaging of the mother should be completed.**

- In some instances, no further studies are required during pregnancy due to the clear and dire prognosis (i.e non development of cortical landmarks at an advanced gestational age, association of other CNS or systemic anomalies) and then the genetic evaluation can be deferred until after delivery or termination of pregnancy.