

Forebrain Anomalies

Neuronal generation • migration • gyration • midline organization

Pathology of cerebral development

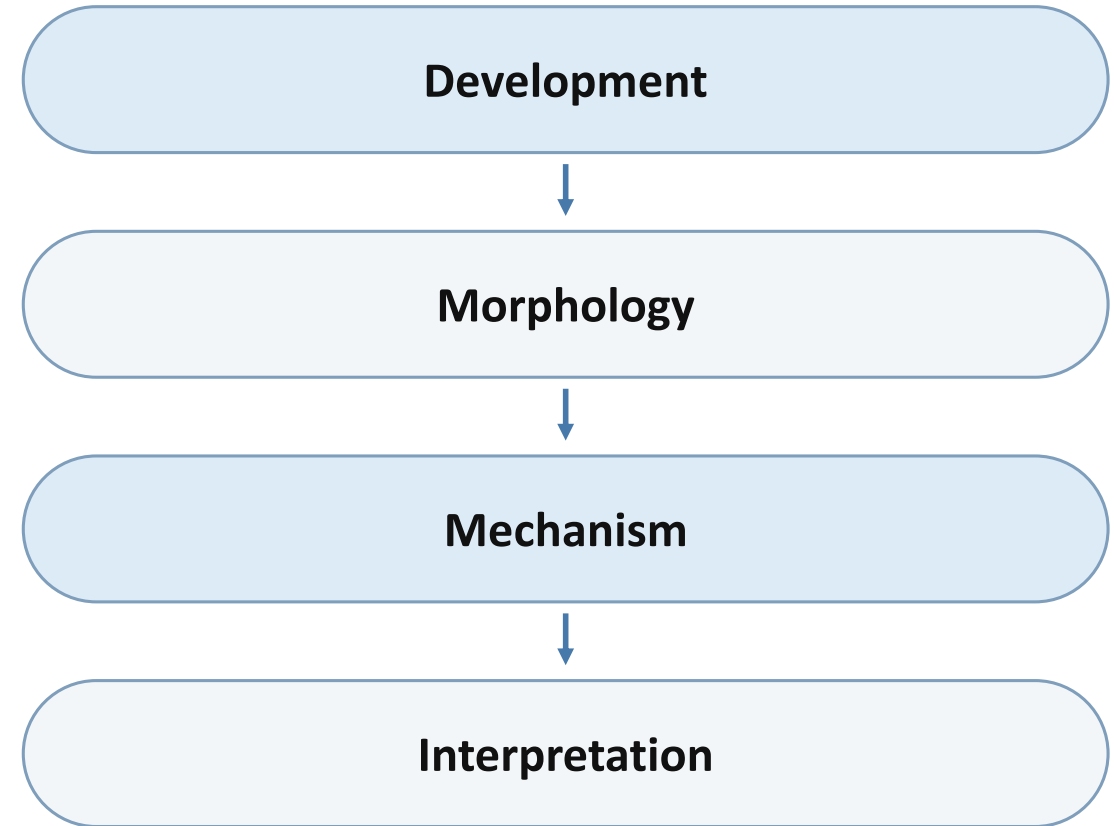
Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

- Trace neuronal production and the radial versus tangential migration routes
- Distinguish defects in brain size, gyration, cortical location, and midline formation
- Connect distinctive phenotypes with mechanisms and gene examples reported by Robbins
- Interpret representative morphologic patterns without overcalling clinical outcomes



Schematic: Conceptual sequence

Four dimensions of abnormal development

- Brain volume may be increased or reduced
- Cortical surface may have too few or numerous abnormal convolutions
- Neurons may form an abnormal cortical architecture or occupy ectopic sites
- Midline separation and interhemispheric connections may be defective

Volume

Gyrations

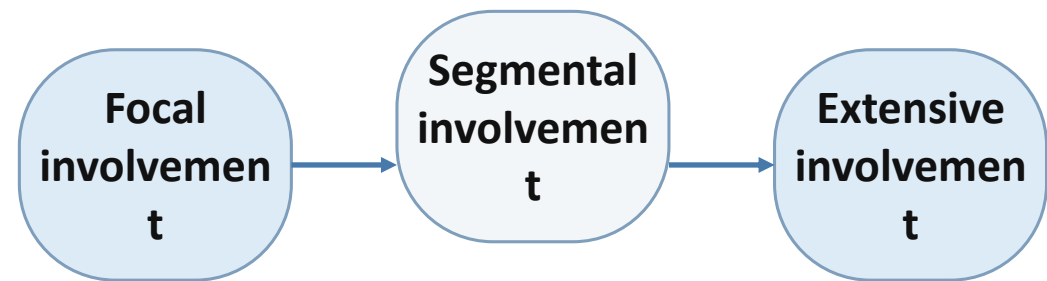
Cell location

Midline

Classification schematic

A lesion can be focal or extensive

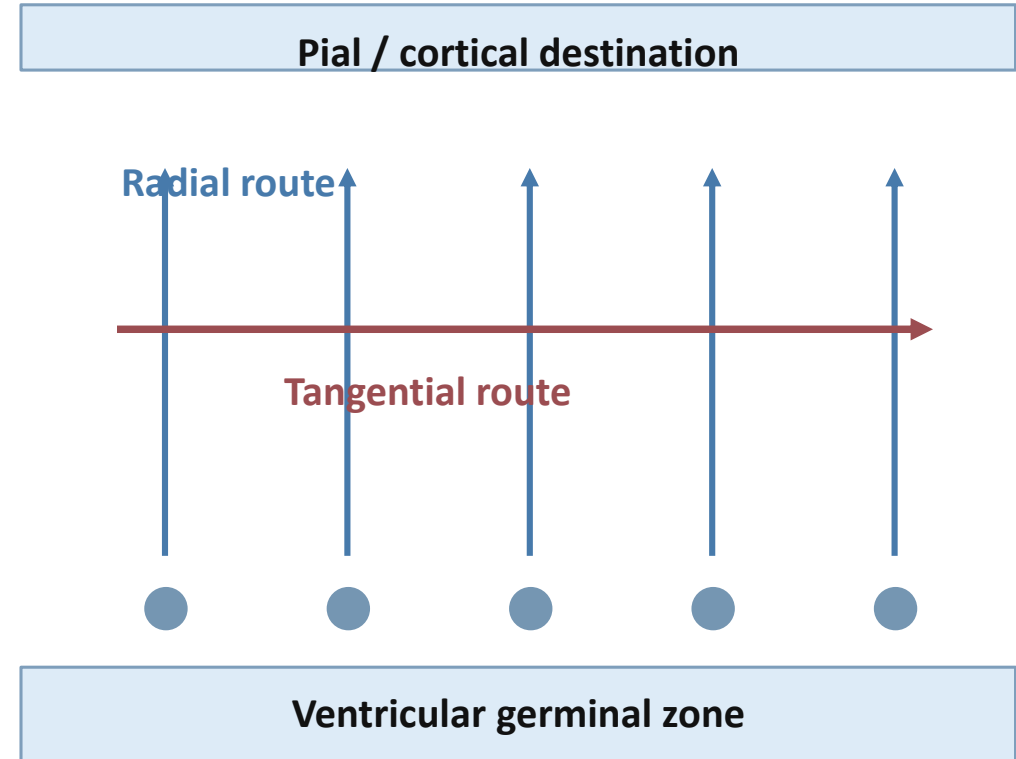
- Abnormal neuronal production or migration can affect selected regions
- Other malformations involve large segments of forebrain
- Distribution and anatomy should be described before assigning etiology



Phenotype spectrum / alternatives (schematic)

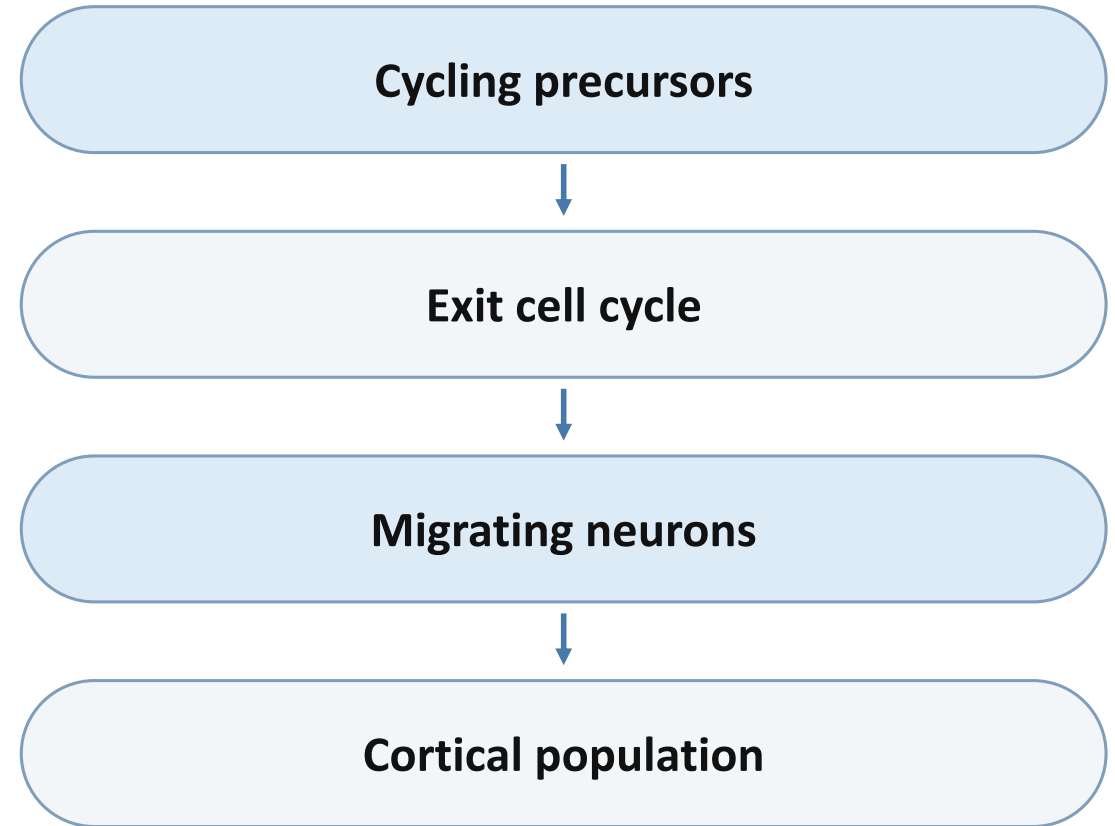
The germinal matrix is the neuronal source

- Proliferating precursor cells reside adjacent to the ventricular system
- These precursors contribute neurons to the developing neocortex
- Their proliferative behavior influences the final neuronal population



Precursor cell fate determines neuronal number

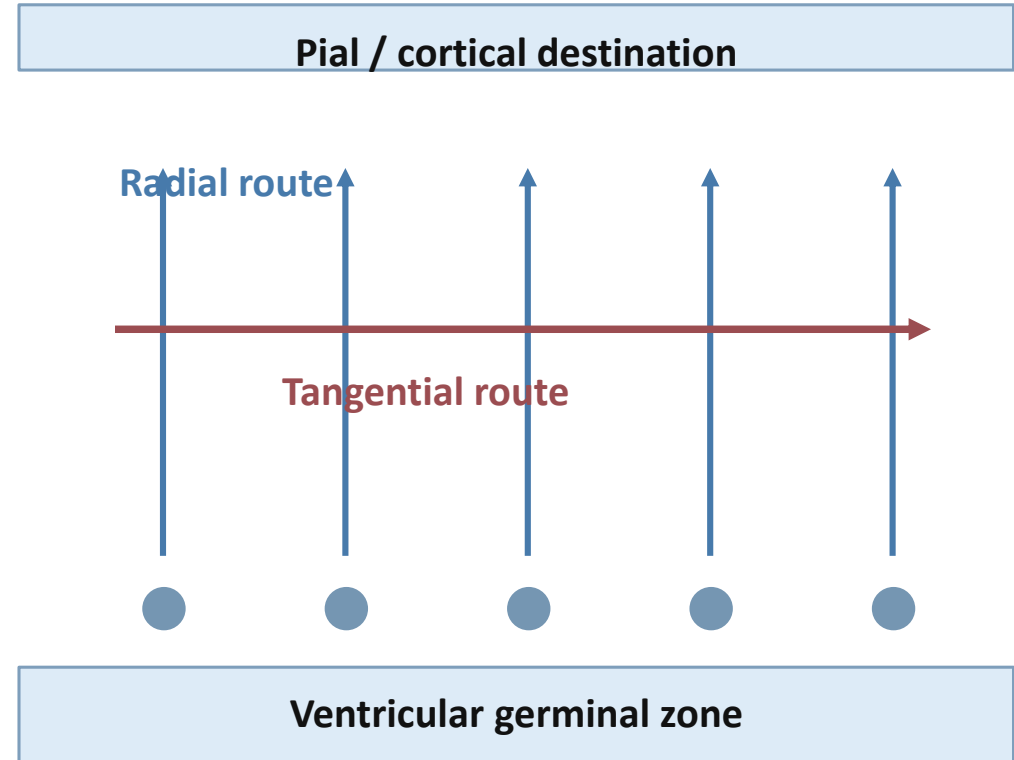
- At each cell cycle, some precursors continue to proliferate
- Others leave the proliferative pool and begin migration
- The balance between these choices helps determine neuron number



Schematic: Conceptual sequence

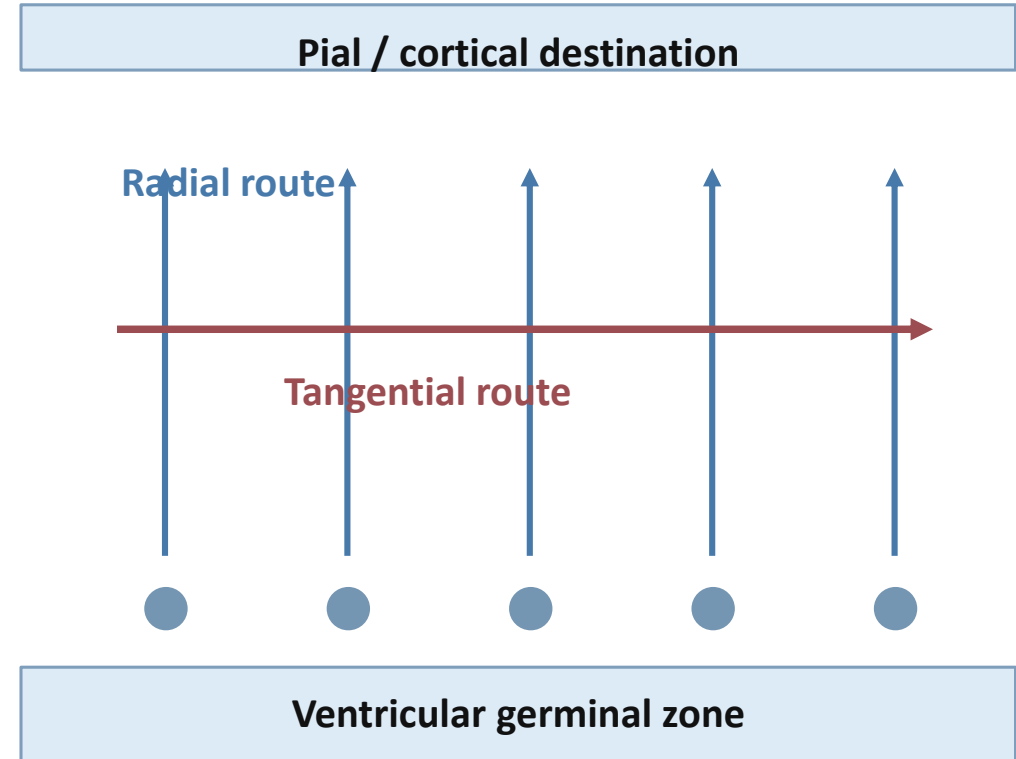
Radial migration builds cortical populations

- One developmental migration route runs radially toward the cerebral cortex
- This route with progenitors destined to become excitatory neurons
- Successful migration requires coordinated movement from germinal zones



Tangential migration supplies interneurons

- A distinct route is tangential rather than primarily radial
- Tangential migration with inhibitory interneurons
- Separate pathways explain why migration defects may yield different phenotypes



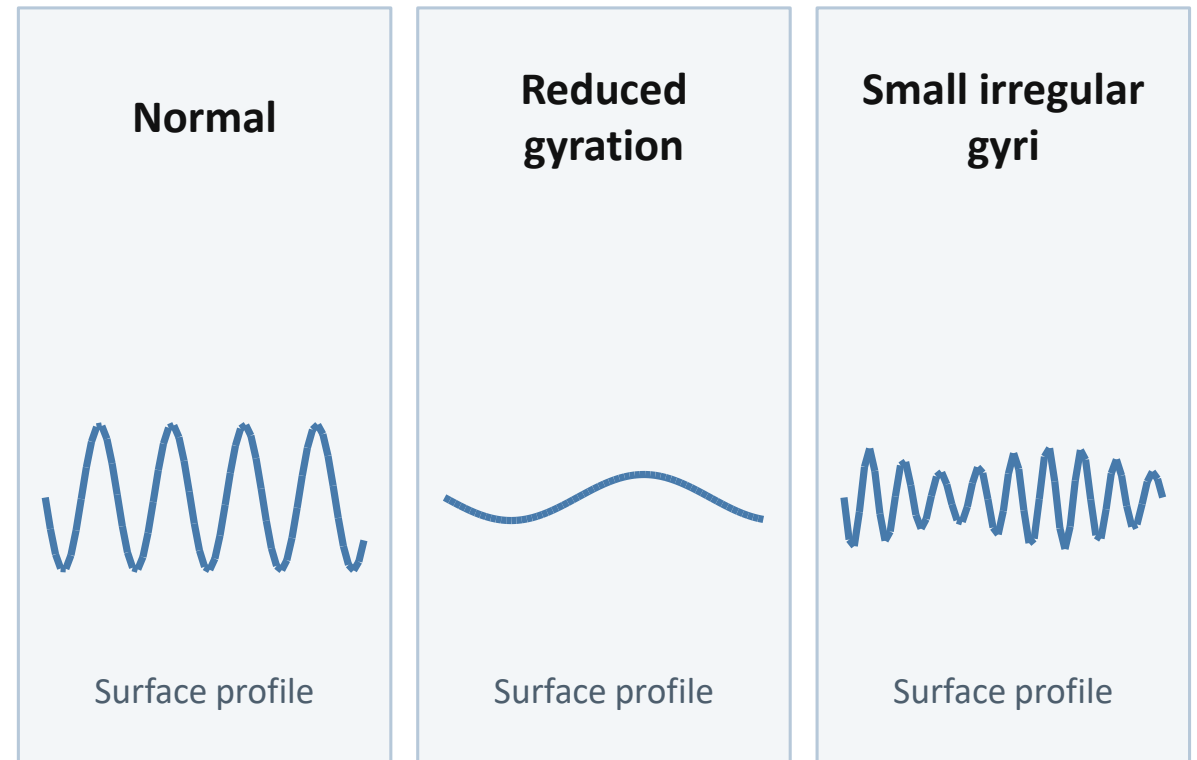
Neuronal generation and migration are distinct

- Production governs how many neurons are available
- Migration governs where those neurons ultimately reside
- Morphologic assessment should ask whether number, location, or both are abnormal

Process	Developmental consequence
Generation	Number of available neurons
Migration	Placement of neurons

Gyration reflects organized cortical growth

- Normal cortical surfaces develop a structured pattern of gyri and sulci
- Reduced gyration and irregular excess small convolutions are different defects
- Cortical appearance alone does not identify a single molecular cause



Schematic profiles—not microscopic sections

Cortical layers are a separate clue

- Normal neocortex has six principal layers
- Polymicrogyria is as four or fewer layers
- The number and organization of layers can distinguish malformations

Six-layer pattern



6 illustrated layers

Four-or-fewer layers

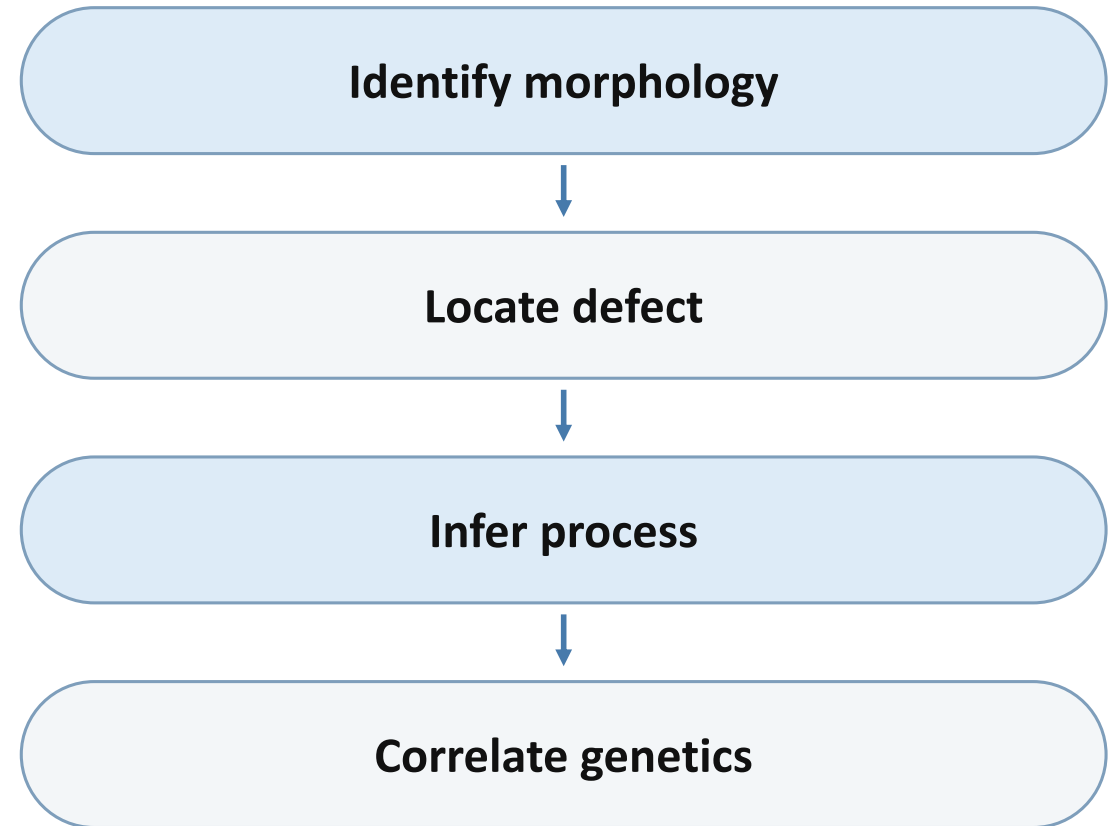


4 illustrated layers

Schematic; Layer counts reflect only depicted concept

Phenotype first; Mechanism second

- Document brain size, surface, cortical lamination, and ectopic gray matter
- Next evaluate midline division and callosal connections
- Use molecular examples to explain phenotype, not as interchangeable labels



Schematic: Conceptual sequence

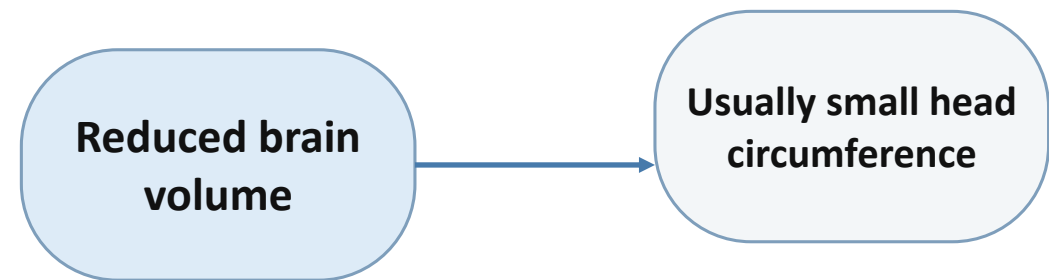
Megalencephaly and microencephaly

- Megalencephaly denotes an abnormally large brain volume
- Microencephaly denotes an abnormally small brain volume
- Microencephaly as much more common in this comparison

Feature	Megalencephaly	Microencephaly
Brain volume	Increased	Decreased
Relative frequency	Less common	More common

Microencephaly: Brain size and head size

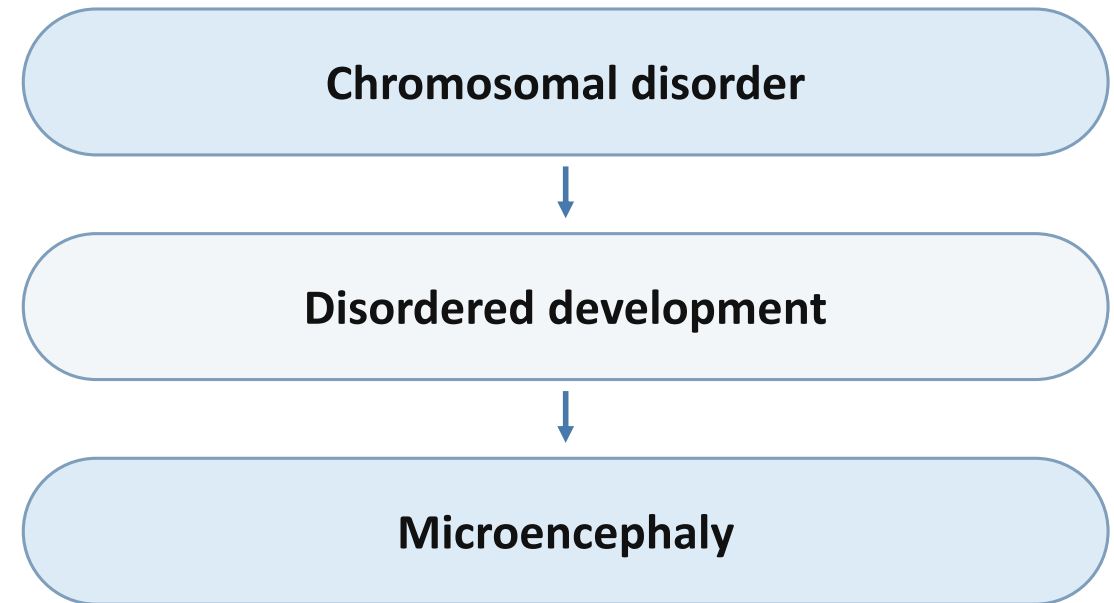
- The primary tissue abnormality is reduced brain volume
- It is typically accompanied by a small head circumference
- Head circumference is a clinical correlate, not a direct measurement of cortical neuronal number



Phenotype spectrum / alternatives (schematic)

Chromosomal abnormalities are an association

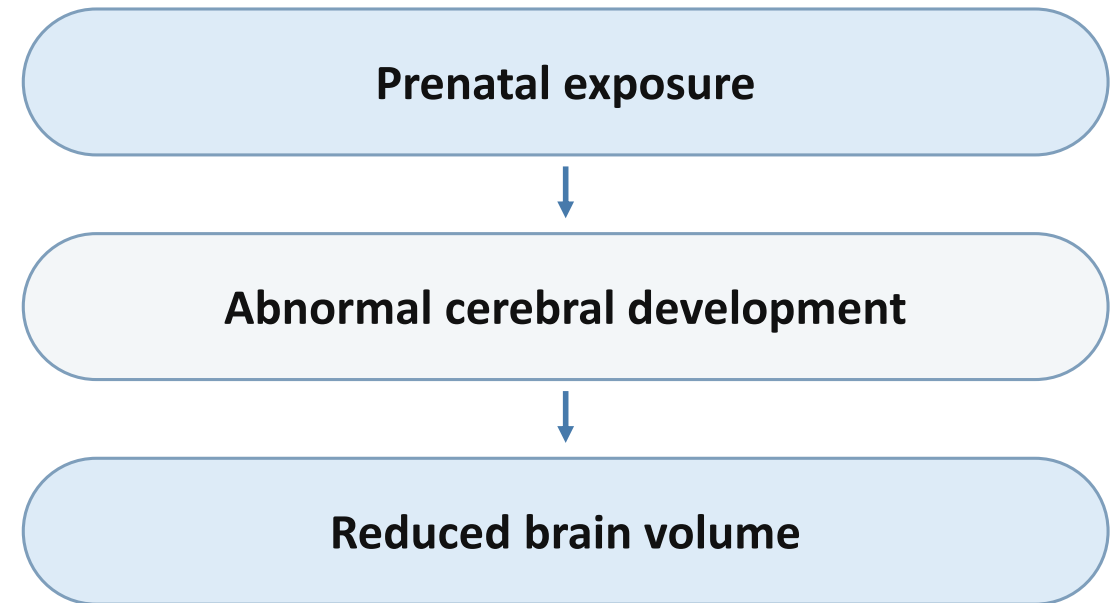
- Chromosome abnormalities among conditions linked to microencephaly
- The association is broad; The excerpt does not specify a unique chromosome or mechanism
- Avoid equating microencephaly with a single chromosomal diagnosis



Schematic: Conceptual sequence

Fetal alcohol syndrome is another association

- Microencephaly can accompany fetal alcohol syndrome
- This links an in-utero developmental exposure to abnormal brain growth
- The source does not quantify risk or specify a cortical histologic pattern for this association



Schematic: Conceptual sequence

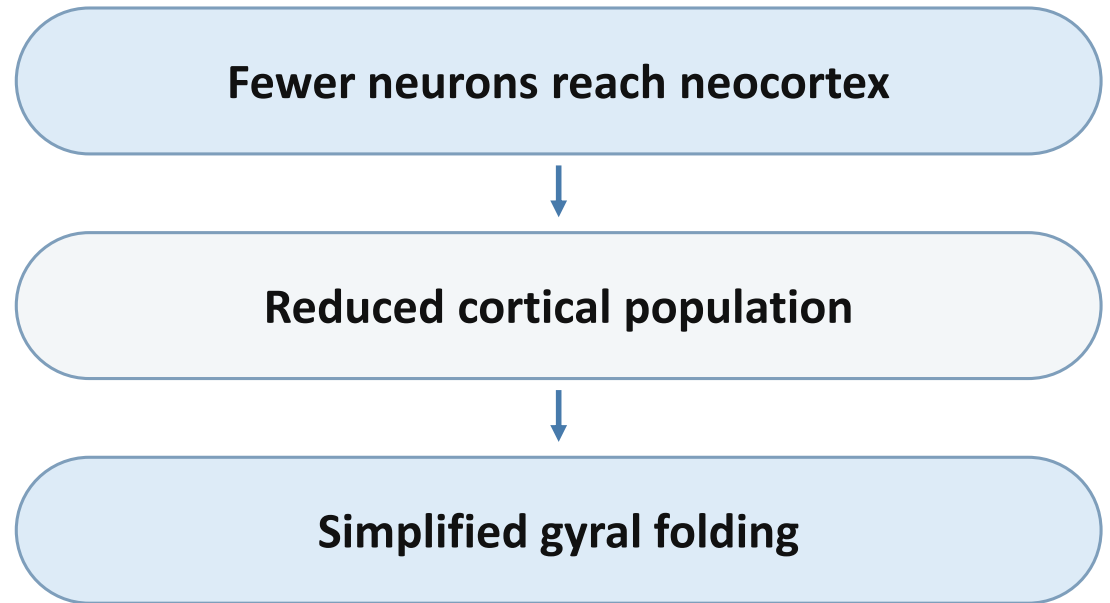
Congenital viral infection can affect brain growth

- The excerpt names in-utero HIV-1 and Zika virus infection as examples
- Both are associations with microencephaly in the supplied source
- No infection frequency or diagnostic testing threshold is specified here

Prenatal association	Source examples
Infectious	HIV-1; Zika virus
Noninfectious	Chromosomal abnormality; fetal alcohol syndrome

Proposed mechanism: Fewer neurons reach cortex

- Reduced delivery of neurons to the neocortex
- A smaller cortical neuronal population may simplify gyral folding
- Experimental mouse data support this model; It is presented as a postulated mechanism



Schematic: Conceptual sequence

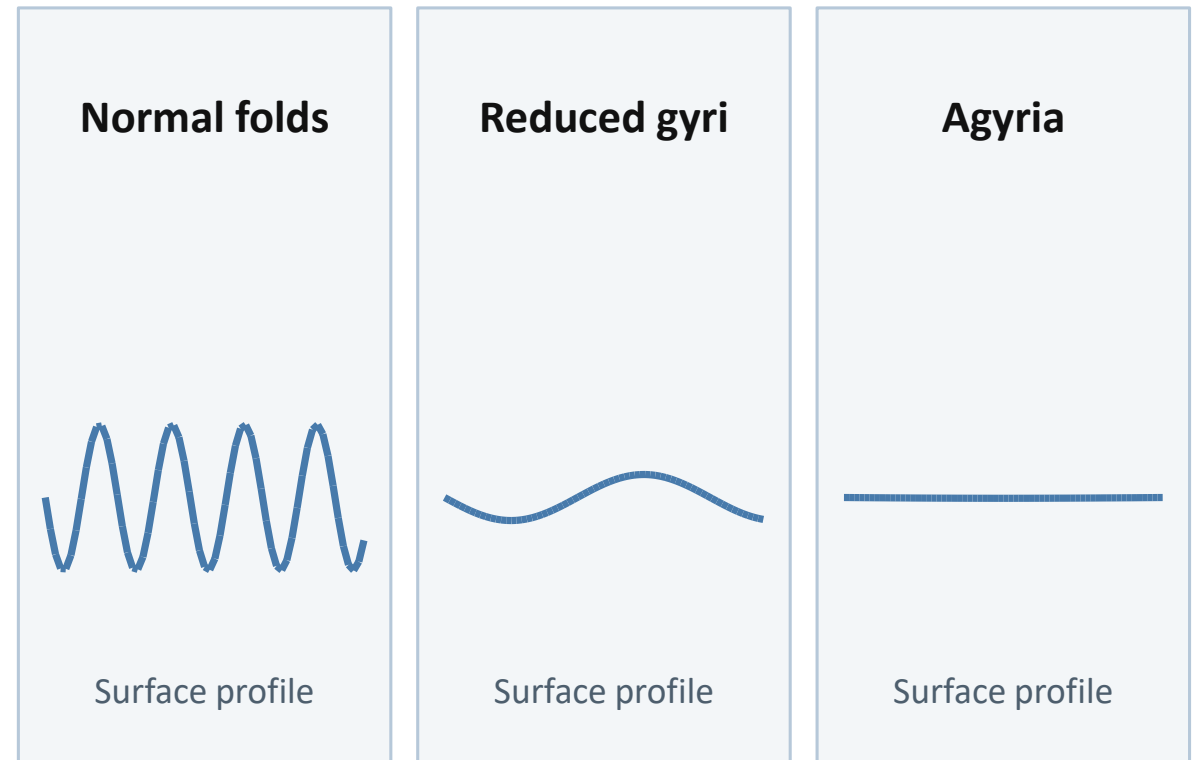
Microencephaly is not a synonym for agyria

- Microencephaly describes small brain volume
- Agyria describes an extreme loss of cerebral gyral pattern
- Reduced brain size and simplified gyration can coexist but are not identical definitions

Term	What is abnormal?
Microencephaly	Brain volume
Agyria	Surface gyration

Lissencephaly: Diminished gyration

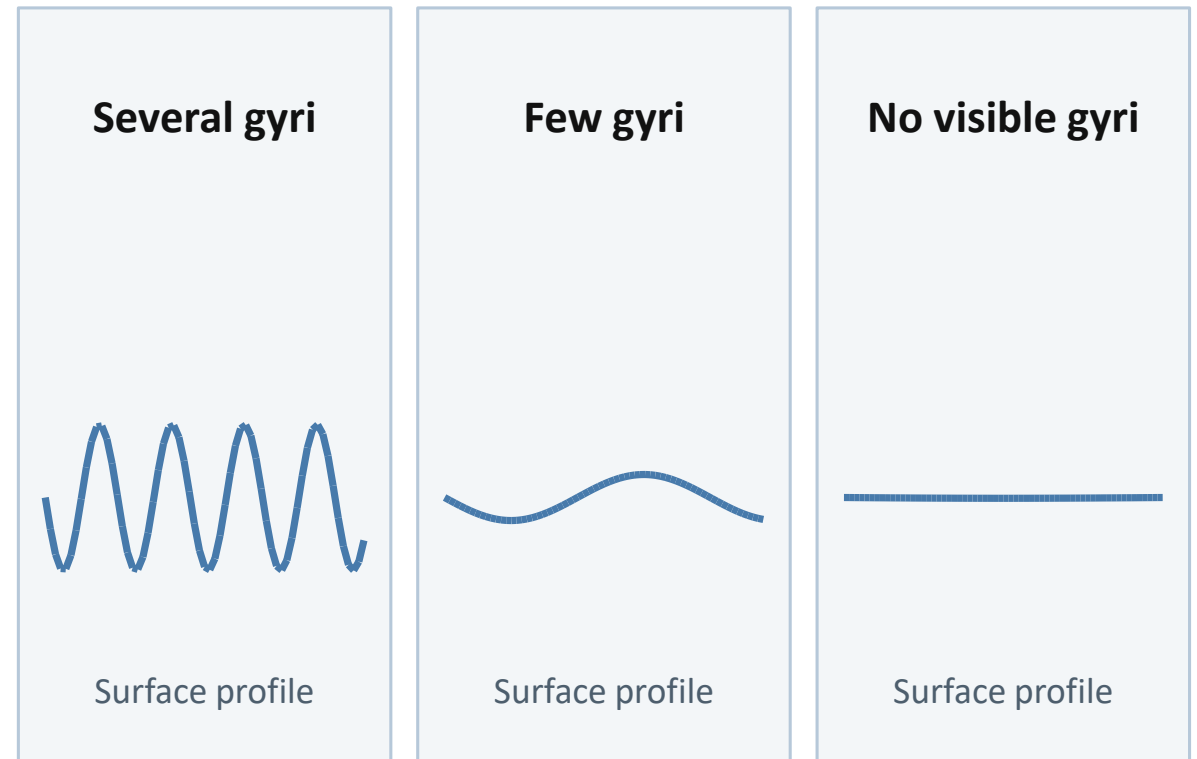
- The defining macroscopic feature is reduction in the number of gyri
- At the extreme, no discernible gyral pattern remains: Agyria
- This phenotype directs attention to disturbances in cortical development



Schematic profiles—not microscopic sections

Agyria represents a morphologic extreme

- Agyria is absence of the normal gyral pattern
- It falls within the severe end of reduced gyration described in lissencephaly
- Use anatomic terminology precisely: Not every lissencephalic brain is entirely agyric



Schematic profiles—not microscopic sections

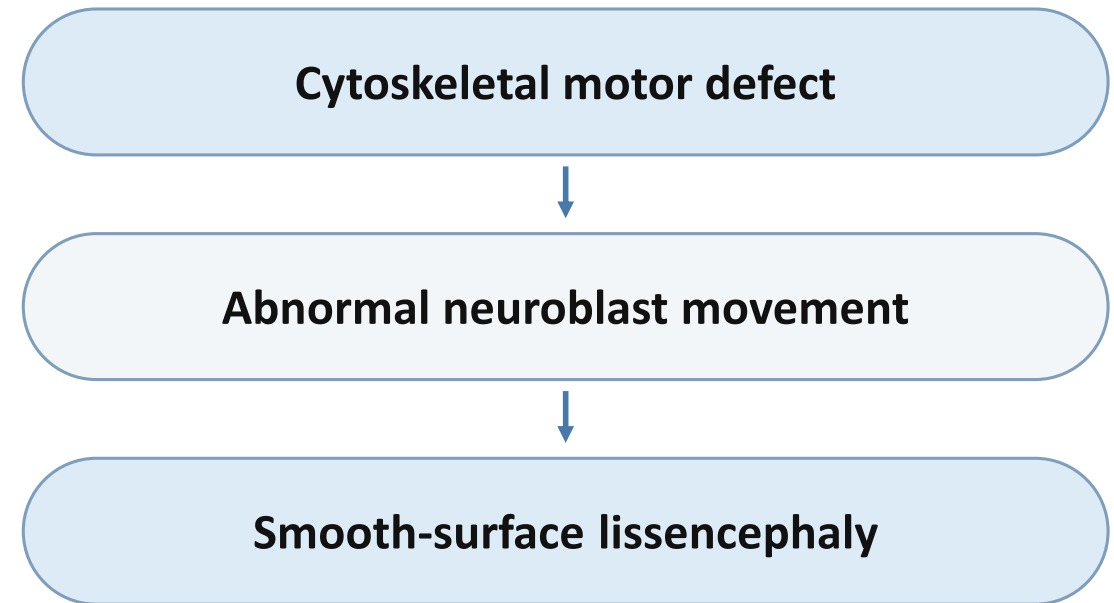
Two architectural patterns of lissencephaly

- Type I is the classic smooth-surface pattern
- Type II has a rough or cobblestone-like surface
- The visible differences align with different migration-related mechanisms

Pattern	Surface	Mechanism emphasized
Type I	Smooth	Defective cell migration
Type II	Cobblestone	Defective migration stop signal

Type I: Impaired migration machinery

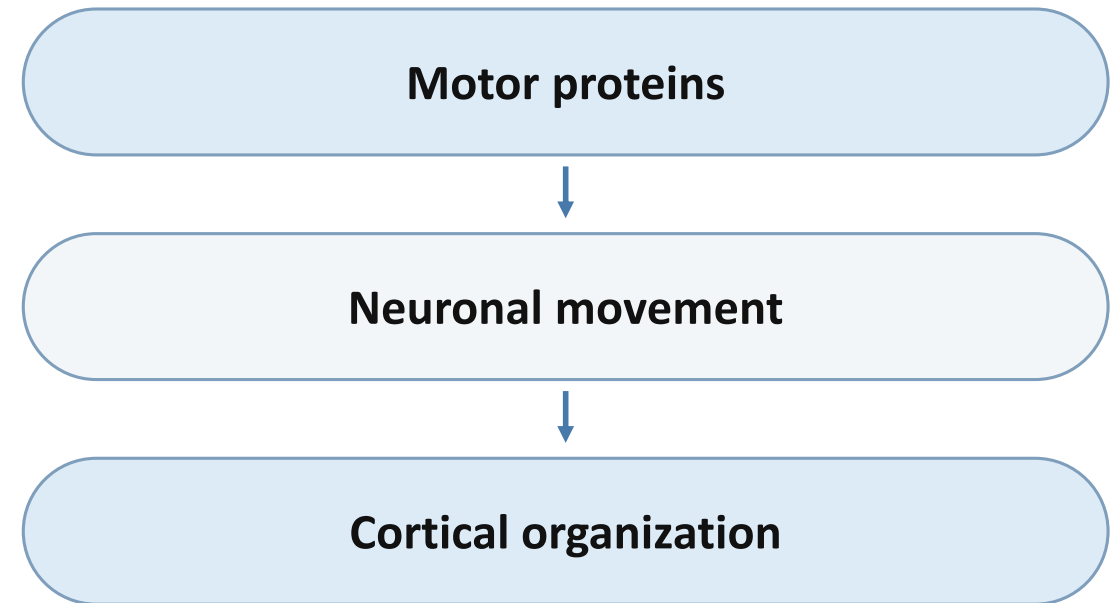
- Classic lissencephaly is commonly linked to disruption of neuronal movement
- Cytoskeletal motor proteins that drive neuroblast migration
- The mechanistic emphasis is failure to accomplish appropriately directed movement



Schematic: Conceptual sequence

The cytoskeleton is mechanistically relevant

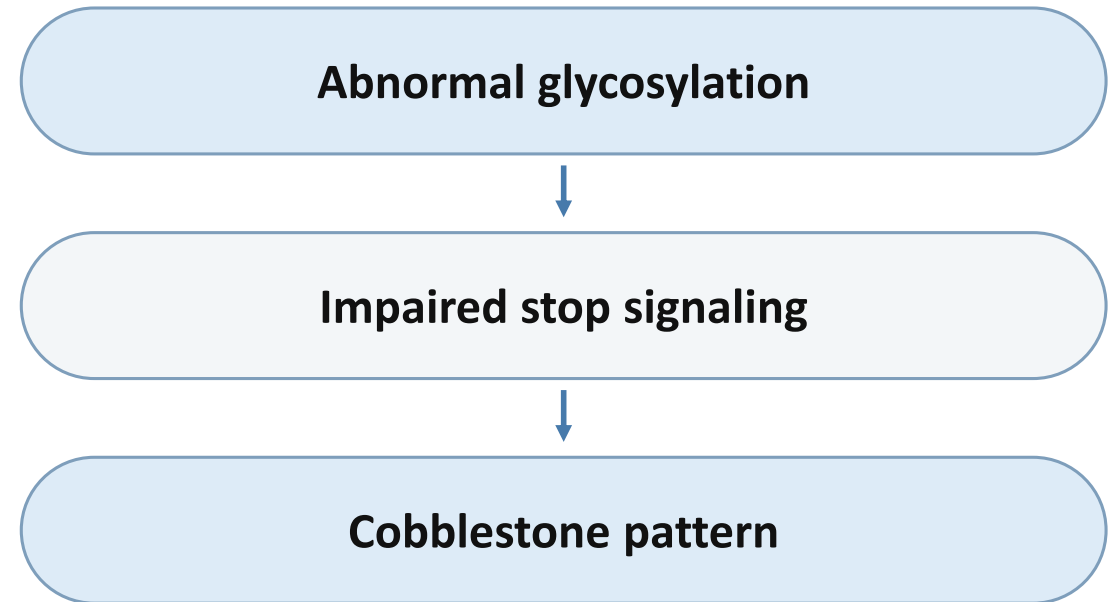
- Moving neuroblasts depend on cytoskeletal organization
- Disruption of the proteins controlling movement can affect cortical positioning
- This is an explanatory mechanism, not a morphologic diagnostic criterion by itself



Schematic: Conceptual sequence

Type II: Failure of migration termination

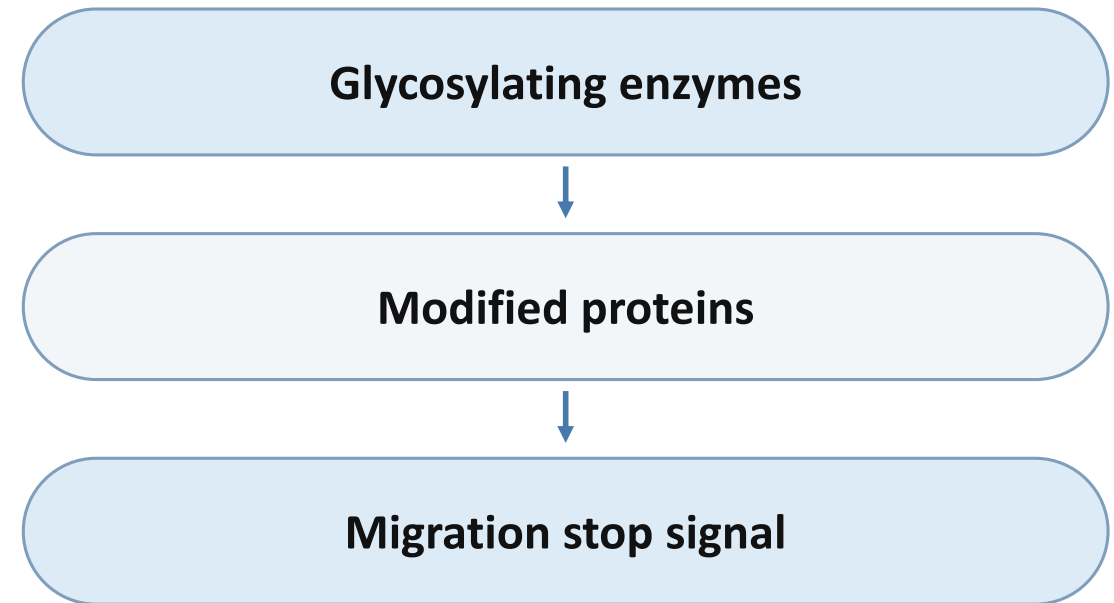
- Type II is often associated with alteration of the migration stop signal
- The signal requires proteins bearing particular glycosylation patterns
- The result is an abnormal rough or cobblestone cortical surface



Schematic: Conceptual sequence

Glycosylation is central to type II

- A group of specifically glycosylated proteins supports normal migration termination
- Mutations affecting enzymes that add sugars to these proteins are common causes in this pattern
- Defective protein modification can therefore alter brain architecture



Schematic: Conceptual sequence

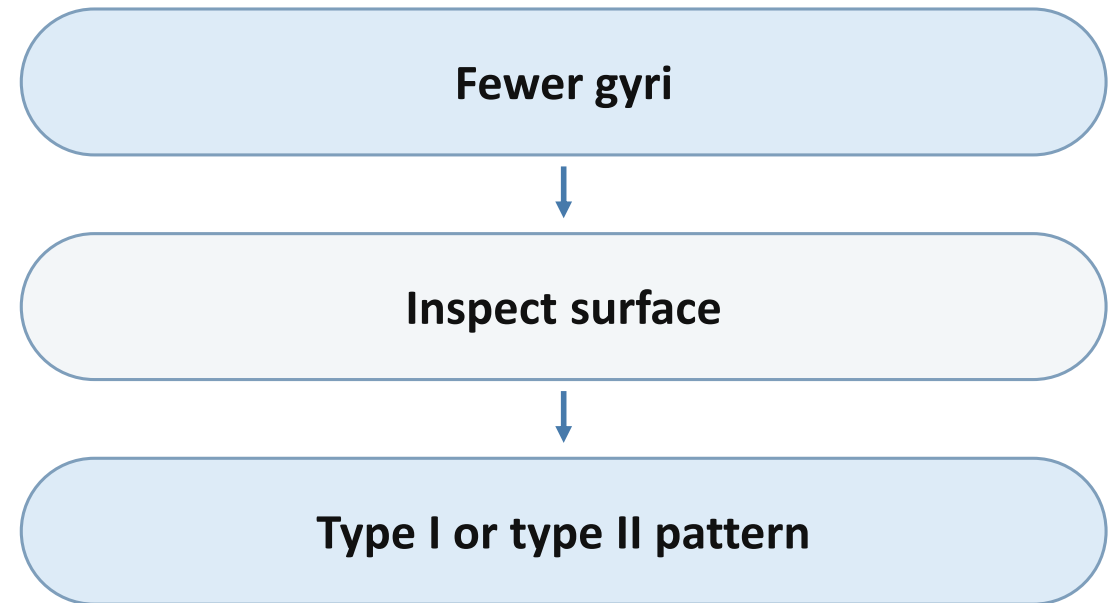
Compare moving versus stopping defects

- Type I emphasizes the machinery that moves migrating neuroblasts
- Type II emphasizes the mechanism that stops migration
- Both can impair normal cortical structure but should not be conflated

Question	Type I	Type II
Primary issue	Migration machinery	Migration termination
Robbins example	Motor proteins	Glycosylation enzymes
Surface	Smooth	Cobblestone

Pattern recognition: Too few gyri

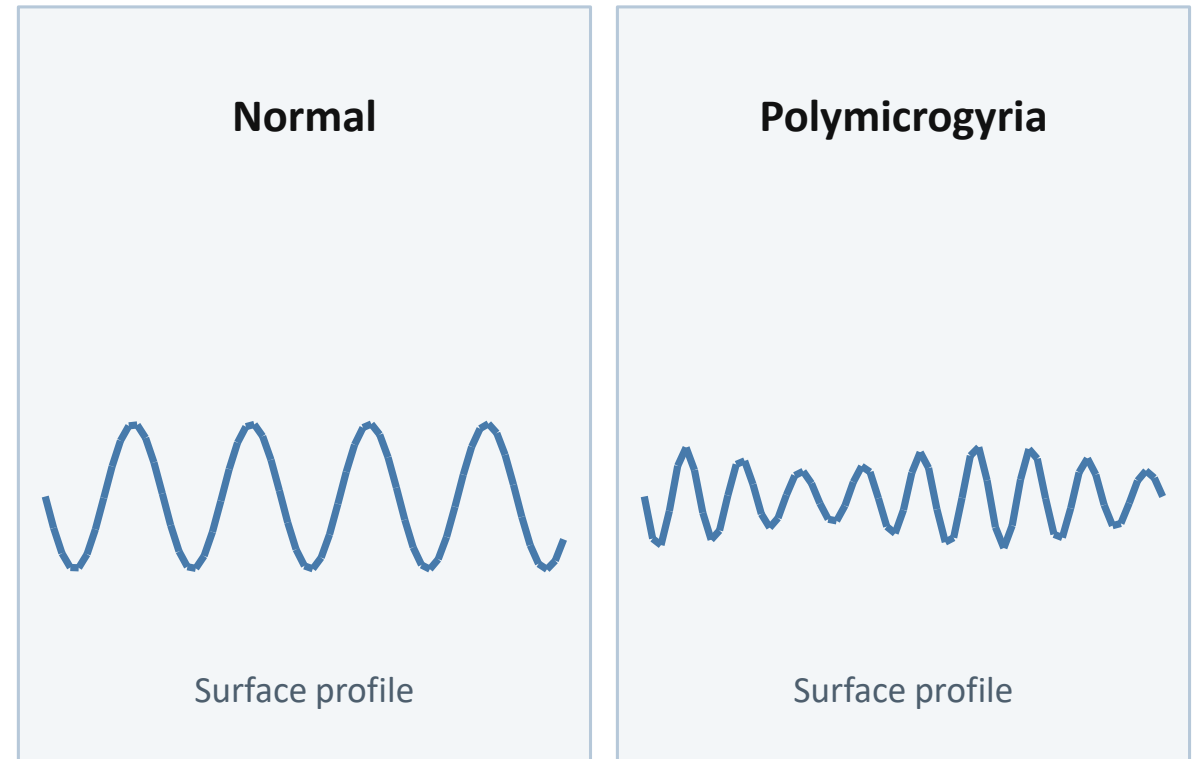
- First identify whether the number of gyri is reduced
- Then determine whether the surface appears smooth or cobblestone-like
- Only after the phenotype is defined should the relevant mechanistic class be considered



Schematic: Conceptual sequence

Polymicrogyria: Numerous small gyri

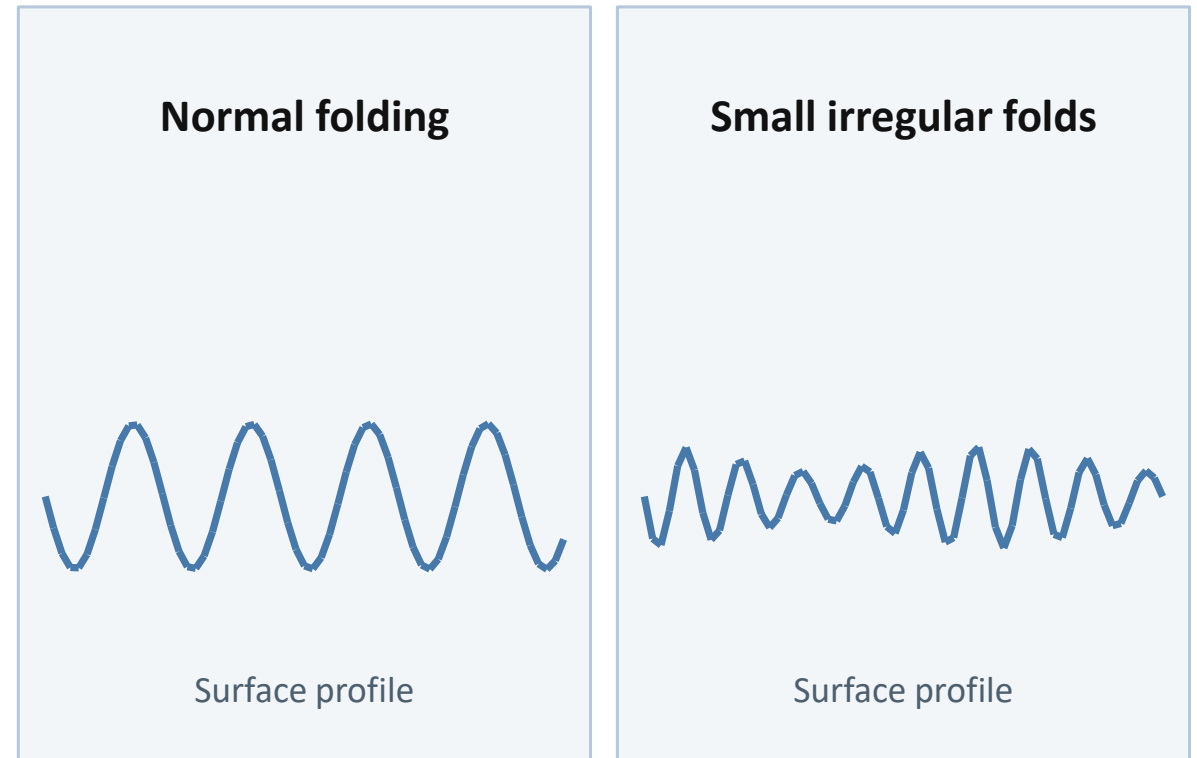
- The surface contains excessive small, irregularly formed convolutions
- Sulci are characteristically shallow
- This is morphologically distinct from the diminished gyration of lissencephaly



Schematic profiles—not microscopic sections

The cerebral surface is irregular

- Many small folds replace the expected gyral pattern
- The convolutions are malformed rather than simply more numerous normal gyri
- Visual interpretation requires assessment of fold size, irregularity, and sulcal depth



Schematic profiles—not microscopic sections

Polymicrogyria disrupts cortical lamination

- Normal cerebral cortex has six principal layers
- Polymicrogyric cortex has four or fewer layers in the Robbins description
- A surface malformation therefore also reflects abnormal cortical microarchitecture

Normal six layers



6 illustrated layers

Polymicrogyria ≤ 4 layers



4 illustrated layers

Schematic; Layer counts reflect only depicted concept

Molecular layers may fuse across gyri

- Fusion of molecular layers between adjacent small gyri
- The altered interface helps explain loss of ordinary sulcal and gyral architecture
- This is an architectural description, not an externally visible surface measurement

Adjacent small gyri



4 illustrated layers

Fused molecular layers

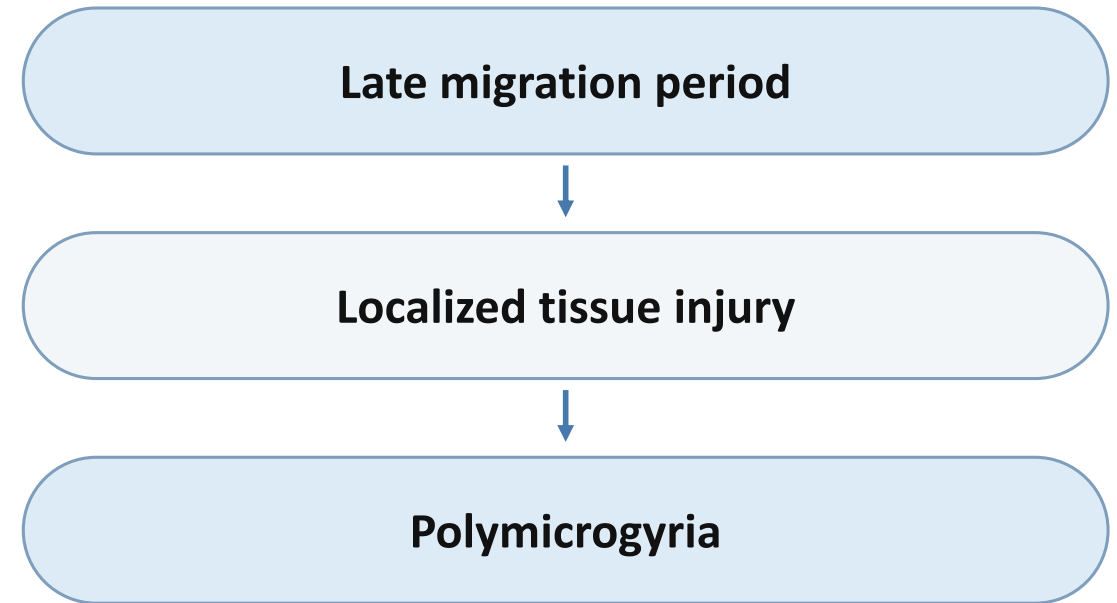


4 illustrated layers

Schematic; Layer counts reflect only depicted concept

Late migration injury can produce polymicrogyria

- Localized tissue injury toward the end of neuronal migration is one possible cause
- The timing of injury can influence the resulting cortical pattern
- Not every case is attributed to injury by the supplied source



Schematic: Conceptual sequence

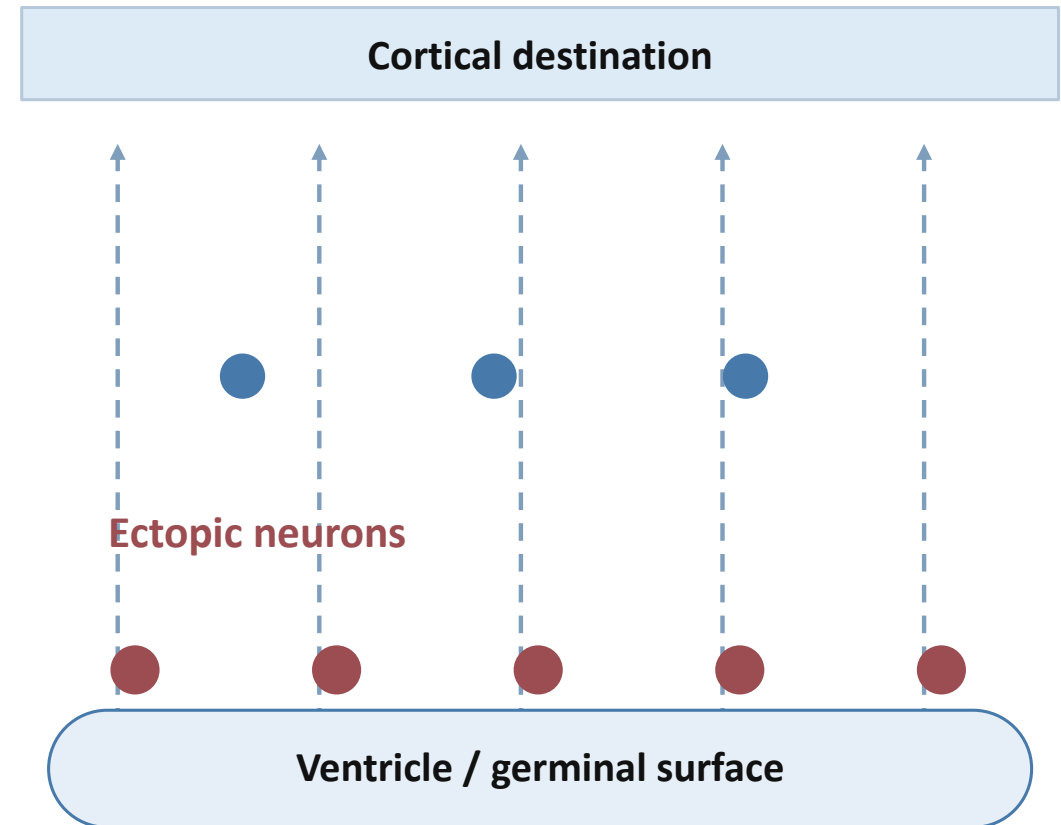
Lissencephaly versus polymicrogyria

- Lissencephaly: Diminished or absent gyri
- Polymicrogyria: Many small, abnormal gyri with shallow sulci
- Polymicrogyria additionally has a characteristic lamination abnormality

Feature	Lissencephaly	Polymicrogyria
Gyrations	Reduced	Excess small, irregular
Surface	Smooth or cobblestone	Many shallow folds
Layers	Mechanism-dependent	Four or fewer

Neuronal heterotopia: Misplaced cells

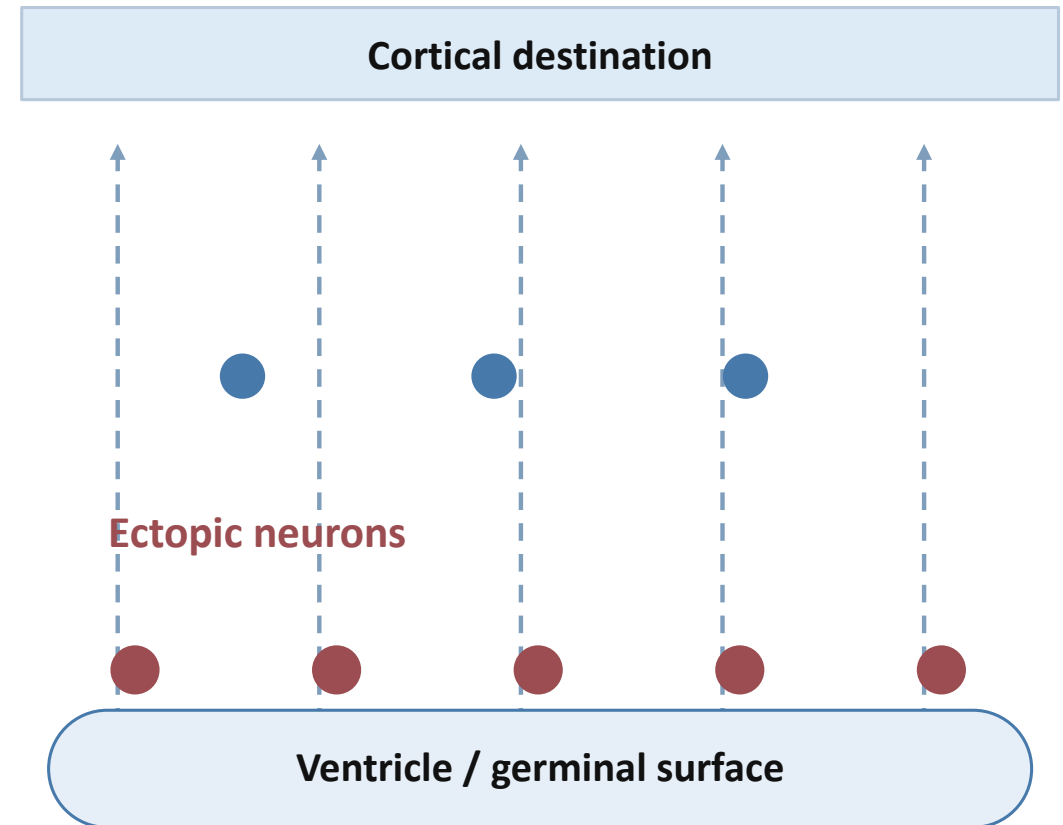
- Heterotopia denotes neurons collected at abnormal subcortical sites
- The ectopic location lies along the developmental route of migration
- The defining defect is neuronal position, not necessarily total brain size



Migration / heterotopia schematic

Migration can fail before neurons leave origin

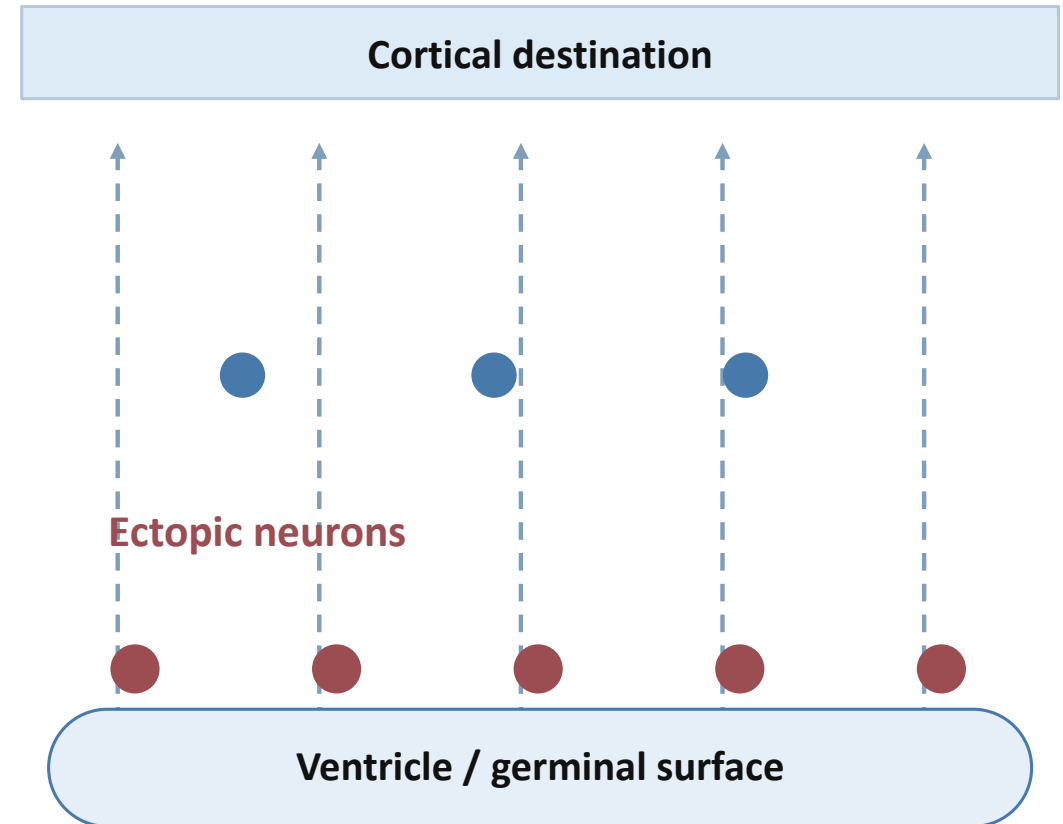
- A specific location for heterotopic neurons is the ventricular surface
- These cells as if they had never left their birthplace
- This explains the name periventricular nodular heterotopia



Migration / heterotopia schematic

Periventricular nodules are anatomically specific

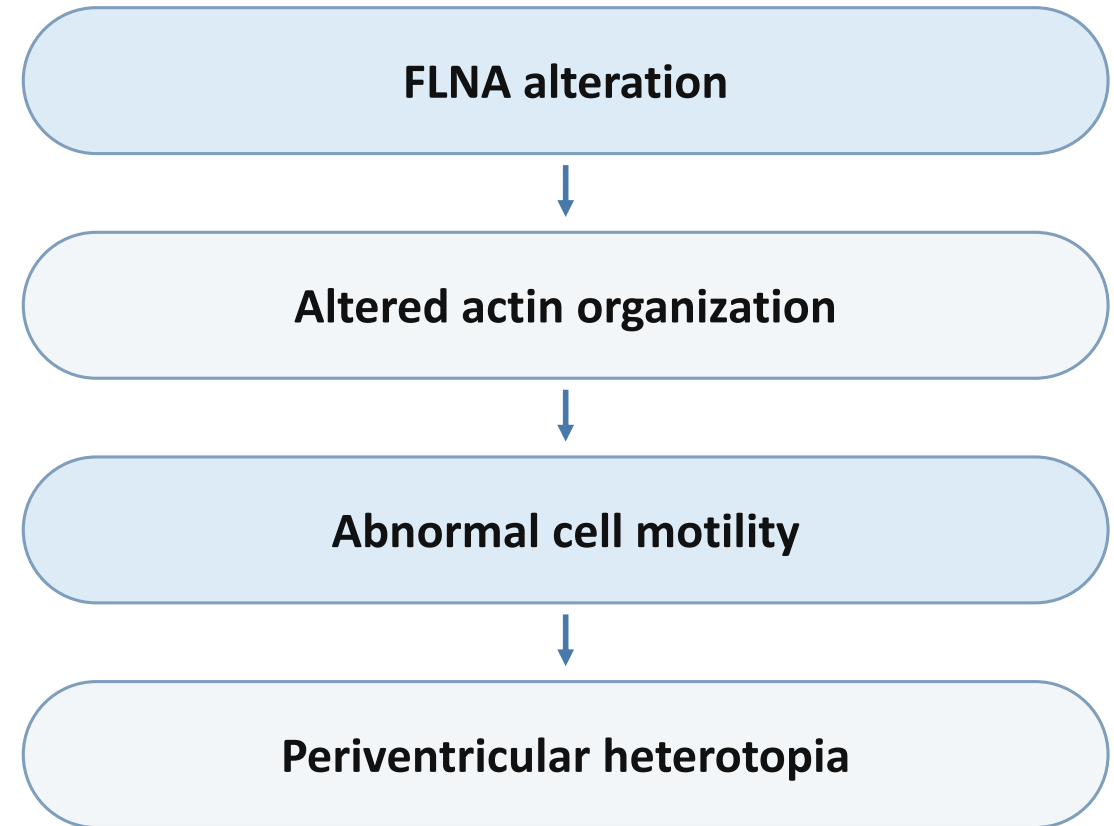
- Nodular aggregates reside along the lateral ventricular surface
- These represent misplaced neurons, not additional ventricular chambers
- Location provides a clue to defective departure or movement of neurons



Migration / heterotopia schematic

Filamin A links motility to periventricular heterotopia

- The FLNA gene encodes the actin-binding protein filamin A
- Filamin A contributes to cytoskeletal organization and cell motility
- Mutations can cause periventricular nodular heterotopia



Schematic: Conceptual sequence

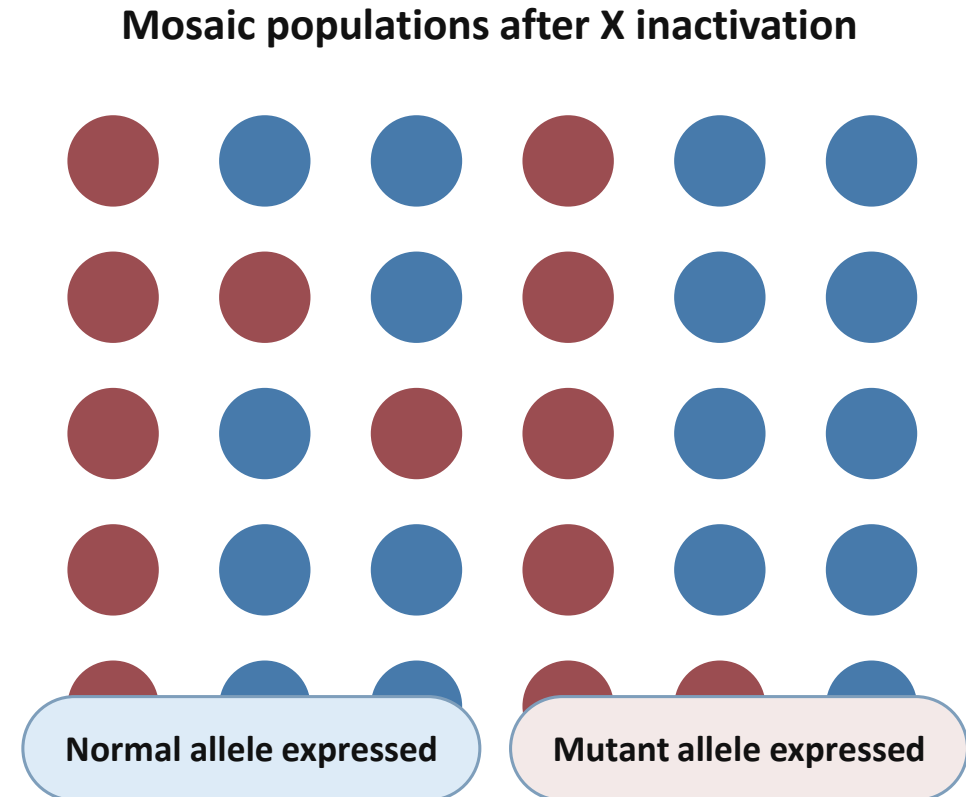
FLNA is located on the X chromosome

- The gene encoding filamin A is X-linked
- That the mutant allele can be lethal in individuals with a single X chromosome
- This source-specific pattern must not be generalized to all X-linked neural malformations

Genetic feature	Source description
Gene	FLNA
Chromosomal location	X chromosome
Single-X mutant allele	May be lethal in described pattern

X inactivation can create neuronal mosaicism

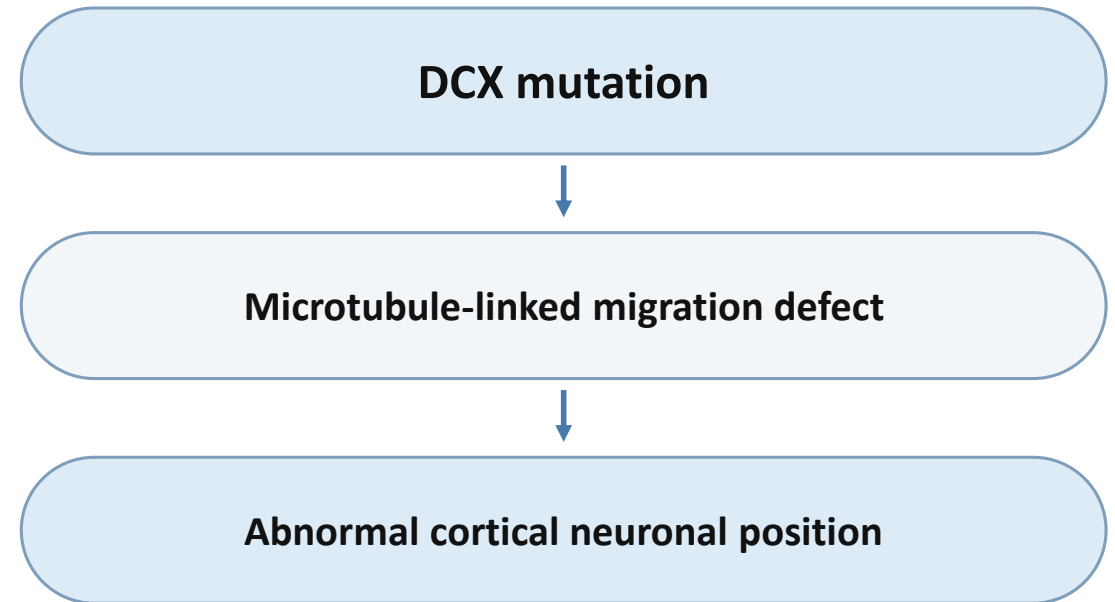
- In individuals with two X chromosomes, X inactivation creates distinct cell populations
- Cells expressing the normal allele may reach the correct location
- Cells expressing the mutant allele may remain in heterotopic locations



Cells shown for inheritance mechanism, not tissue evidence

Doublecortin participates in migration

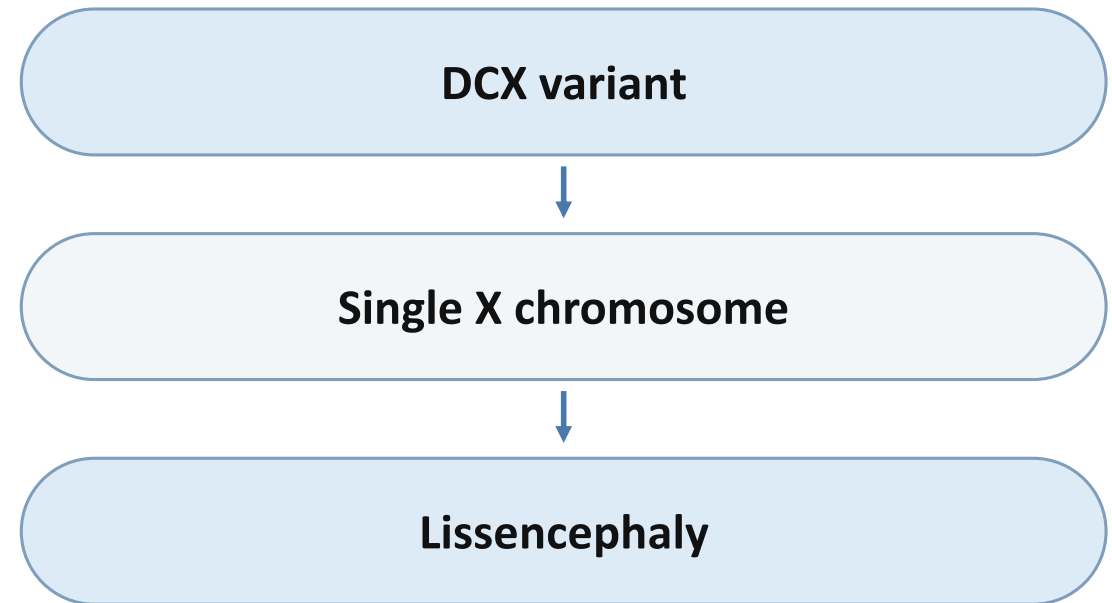
- DCX encodes doublecortin, a microtubule-associated protein
- The gene is X-linked in the Robbins account
- Its disruption gives sex-chromosome-dependent neuronal migration phenotypes



Schematic: Conceptual sequence

DCX: Phenotype with a single X chromosome

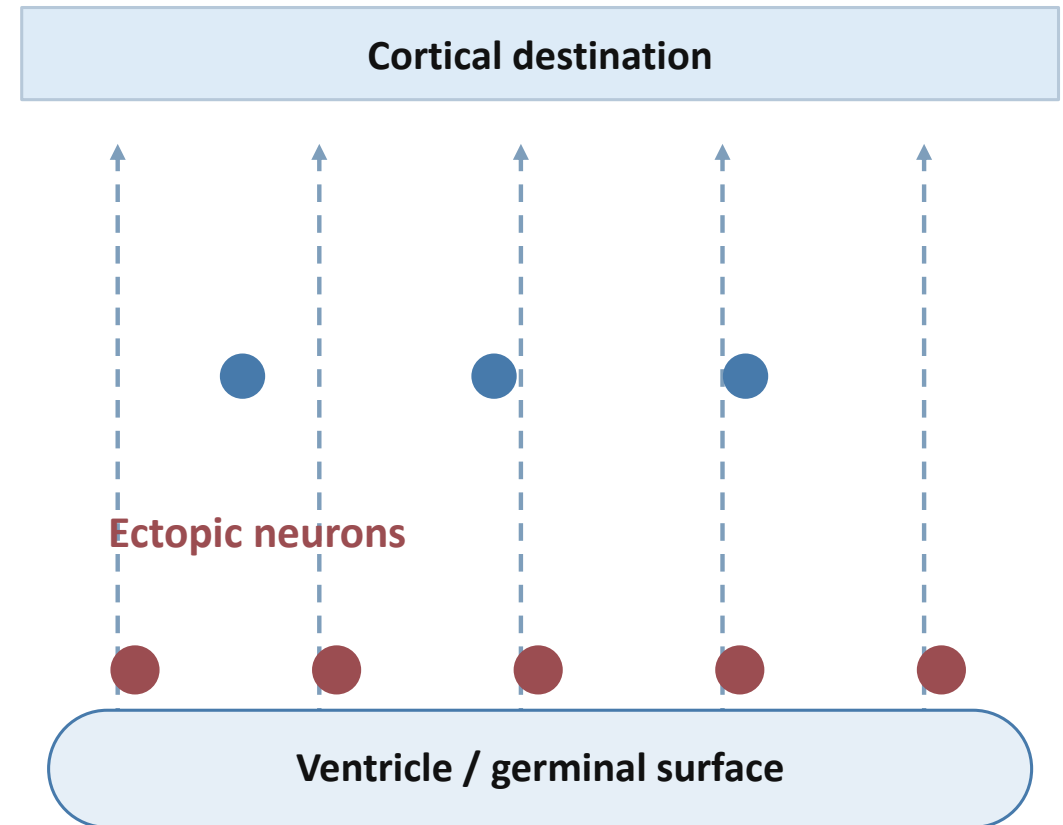
- DCX mutation with lissencephaly in individuals having a single X chromosome
- This phenotype belongs to the migration-defect spectrum
- It differs from the bandlike heterotopia seen in many individuals with two X chromosomes



Schematic: Conceptual sequence

DCX: Phenotype with two X chromosomes

- DCX mutation with subcortical bandlike heterotopia in individuals with two X chromosomes
- An extra band of gray matter appears beneath the ordinary cortex
- The pattern is described as a double cortex



Migration / heterotopia schematic

Why a double cortex is not a second hemisphere

- The phrase describes two vertically separated bands of cortical gray matter
- The deeper band is formed by heterotopic neurons
- It does not imply duplicated cerebral hemispheres or normal cortical anatomy

Depth	Anatomic element
Superficial	Cortical gray matter
Intermediate	White matter
Deeper	Heterotopic gray band

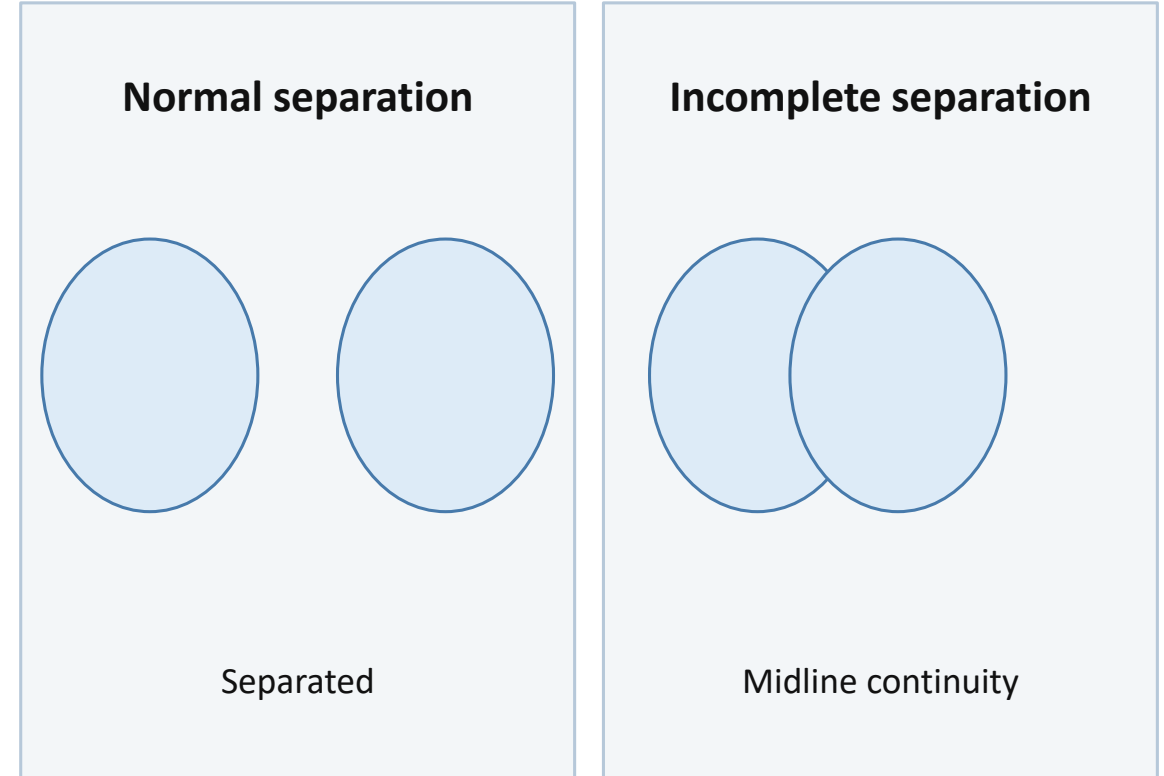
FLNA and DCX produce distinct migration phenotypes

- FLNA is linked to periventricular nodular heterotopia
- DCX is linked to lissencephaly or subcortical band heterotopia depending on X-chromosome context
- The protein roles differ: Actin binding versus microtubule association

Feature	FLNA	DCX
Protein	Filamin A	Doublecortin
Cytoskeletal link	Actin	Microtubules
Phenotype example	Periventricular nodules	Lissencephaly / band

Holoprosencephaly: Incomplete separation

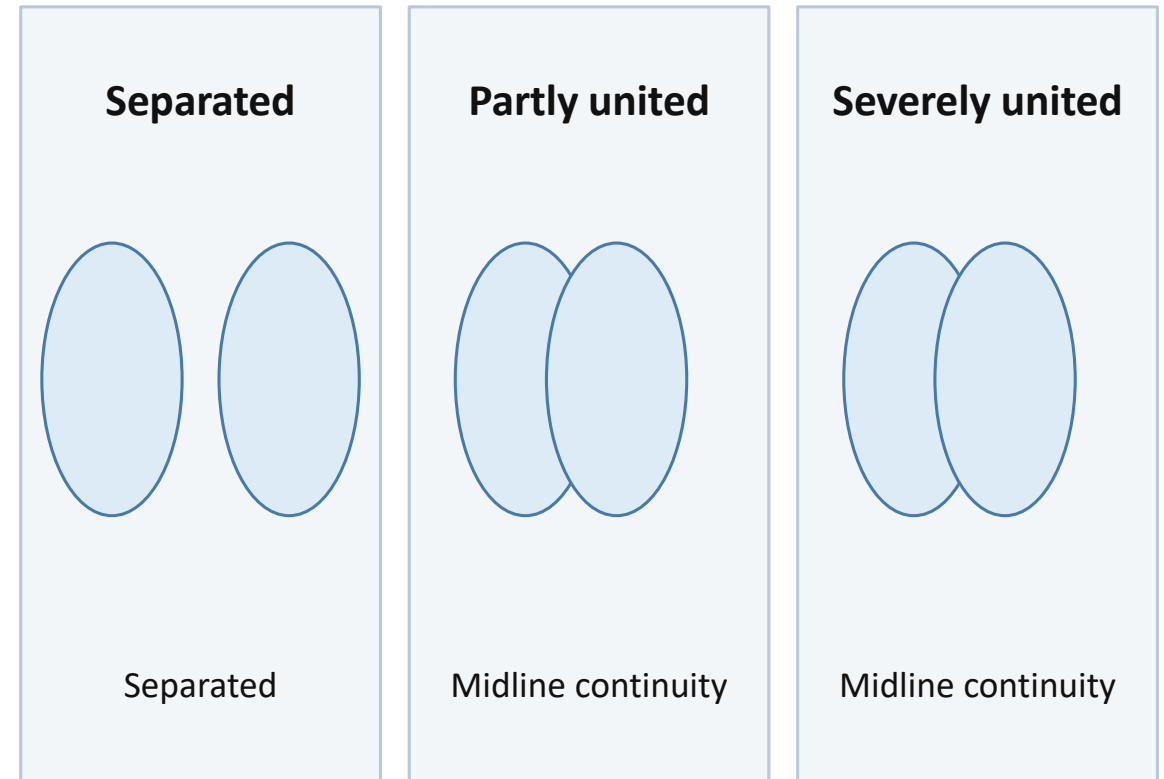
- The defining abnormality is incomplete midline separation of the cerebral hemispheres
- It represents a spectrum rather than a single uniform gross pattern
- Severity may be reflected in associated craniofacial abnormalities



Conceptual dorsal shapes; Not clinical imaging

The midline is a developmental boundary

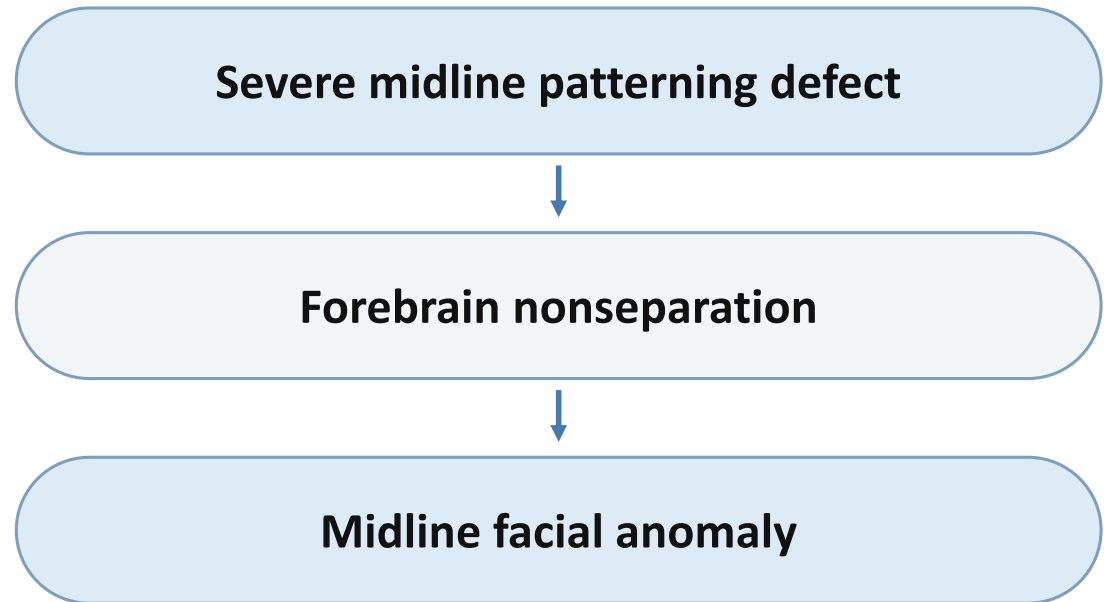
- Normal hemispheres develop as distinct left and right compartments
- Holoprosencephaly disrupts the formation of this separation
- The principal diagnostic question is extent of hemispheric nonseparation



Conceptual dorsal shapes; Not clinical imaging

Severe forms may have major facial anomalies

- Midline facial abnormalities with severe holoprosencephaly
- Cyclopia is an extreme example mentioned in the source
- Facial findings are associated clues, not a substitute for defining forebrain anatomy



Schematic: Conceptual sequence

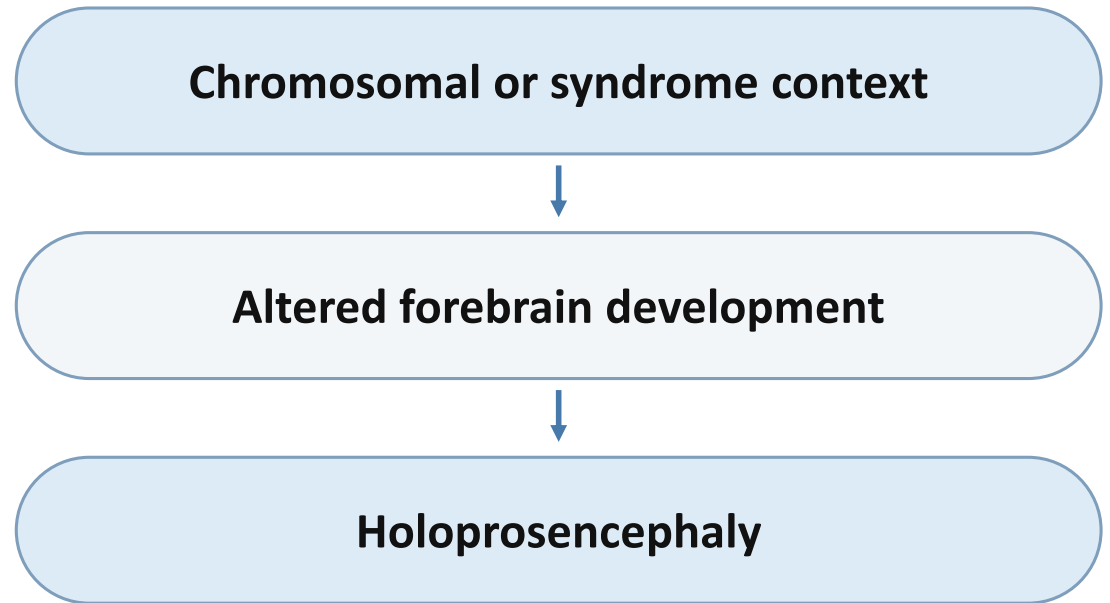
Arrhinencephaly illustrates milder variants

- Arrhinencephaly for less severe variants of this spectrum
- The olfactory cranial nerves and associated structures may be absent
- The key morphological clue here is loss of olfactory-related anatomy

Severe spectrum	Less severe example
Marked nonseparation	Arrhinencephaly
May include cyclopia	Olfactory system absent

Trisomy 13 is a documented association

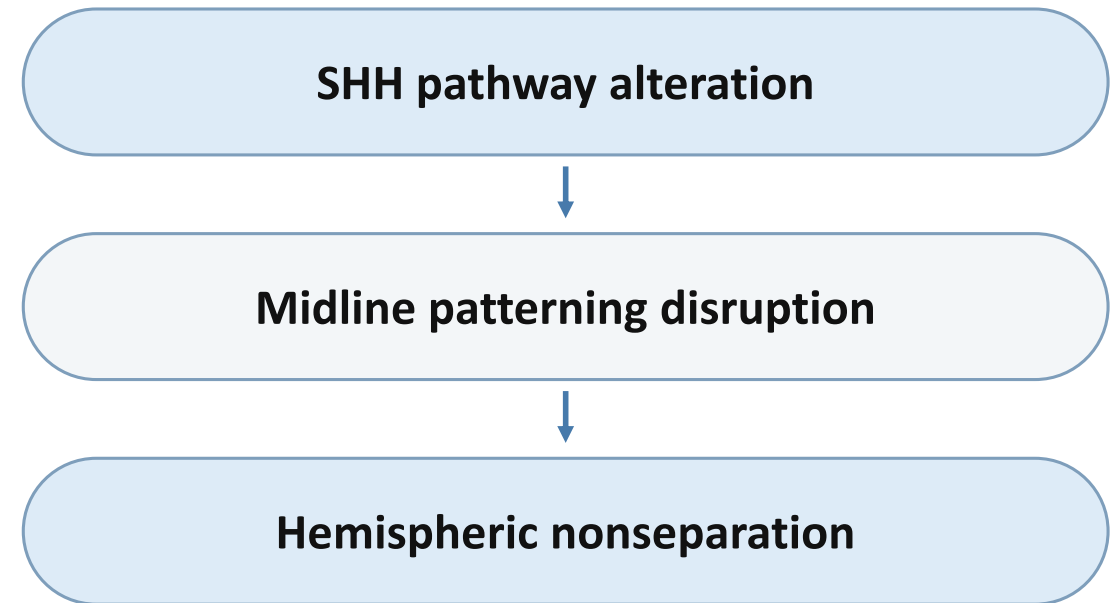
- Holoprosencephaly can accompany trisomy 13
- The excerpt also mentions other genetic syndromes
- A syndromic association does not mean all cases share the same karyotype



Schematic: Conceptual sequence

Sonic hedgehog signaling is implicated

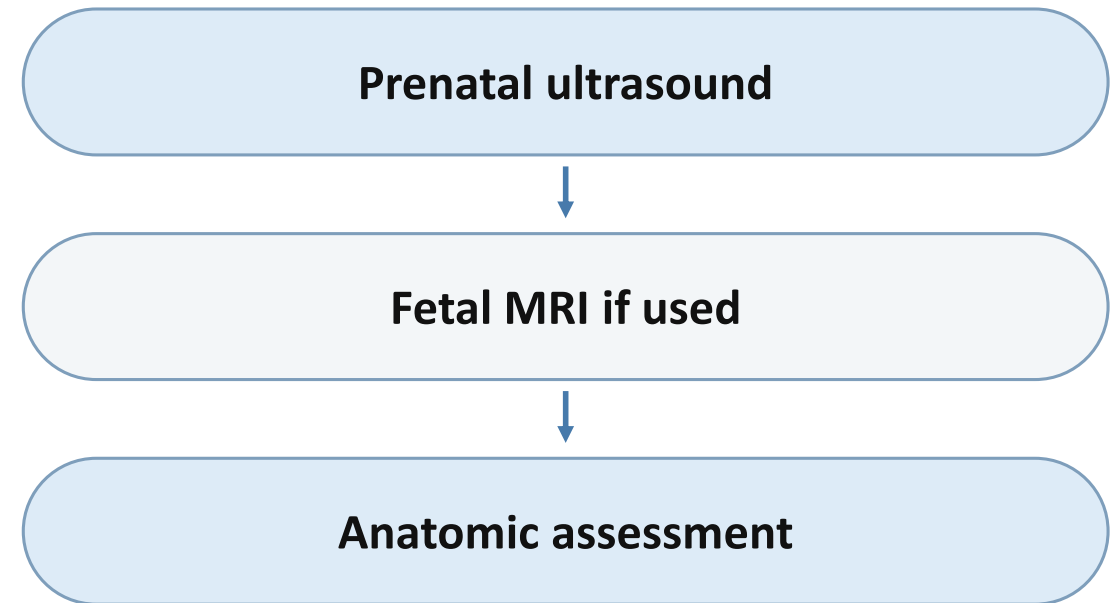
- Mutations in genes encoding sonic hedgehog pathway components may cause holoprosencephaly
- This links molecular patterning to the anatomy of hemispheric division
- The supplied source does not provide a complete gene-level testing algorithm



Schematic: Conceptual sequence

Severe cases may be recognized prenatally

- Ultrasonography can identify severe holoprosencephaly in utero
- Fetal MRI is another imaging modality
- The excerpt gives no sensitivity estimates or gestational-age thresholds



Schematic: Conceptual sequence

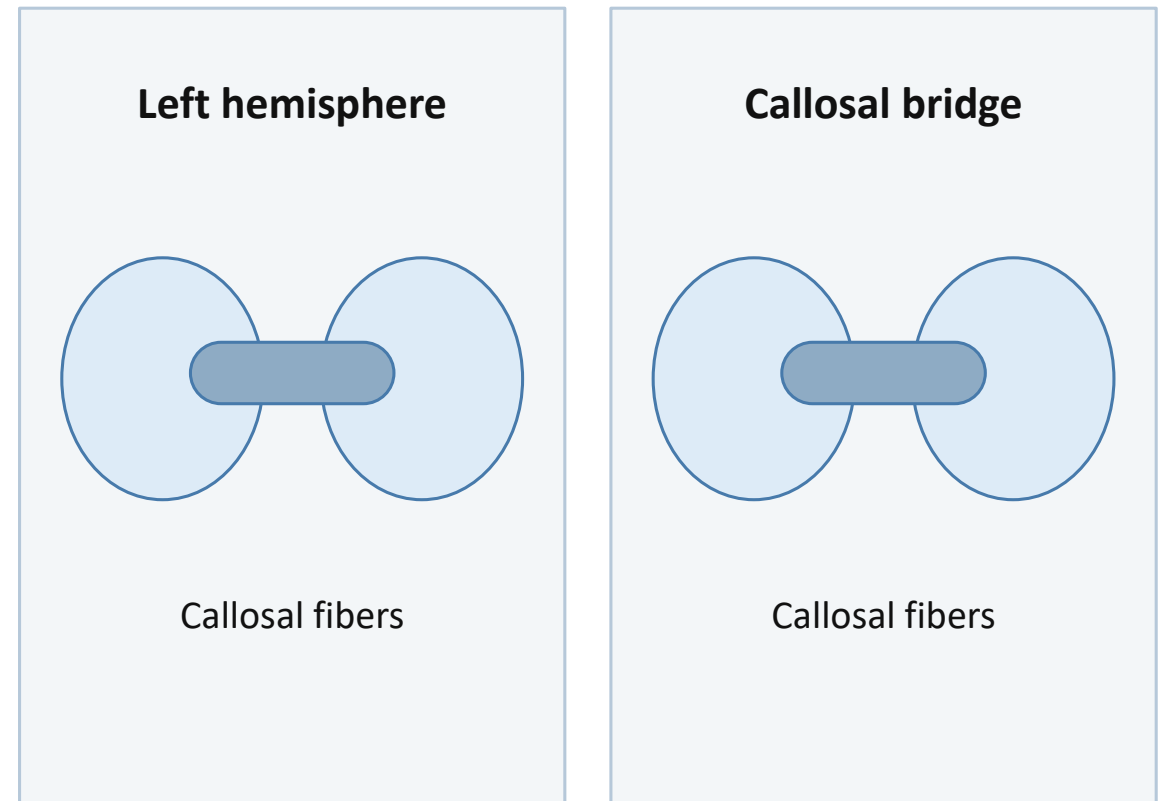
Holoprosencephaly is not callosal agenesis

- Holoprosencephaly concerns incomplete separation of two hemispheres
- Callosal agenesis concerns absence of interhemispheric commissural white matter
- These entities have fundamentally different anatomic definitions

Malformation	Primary structural defect
Holoprosencephaly	Failure of hemispheric separation
Callosal agenesis	Absence of callosal white matter

The corpus callosum links both hemispheres

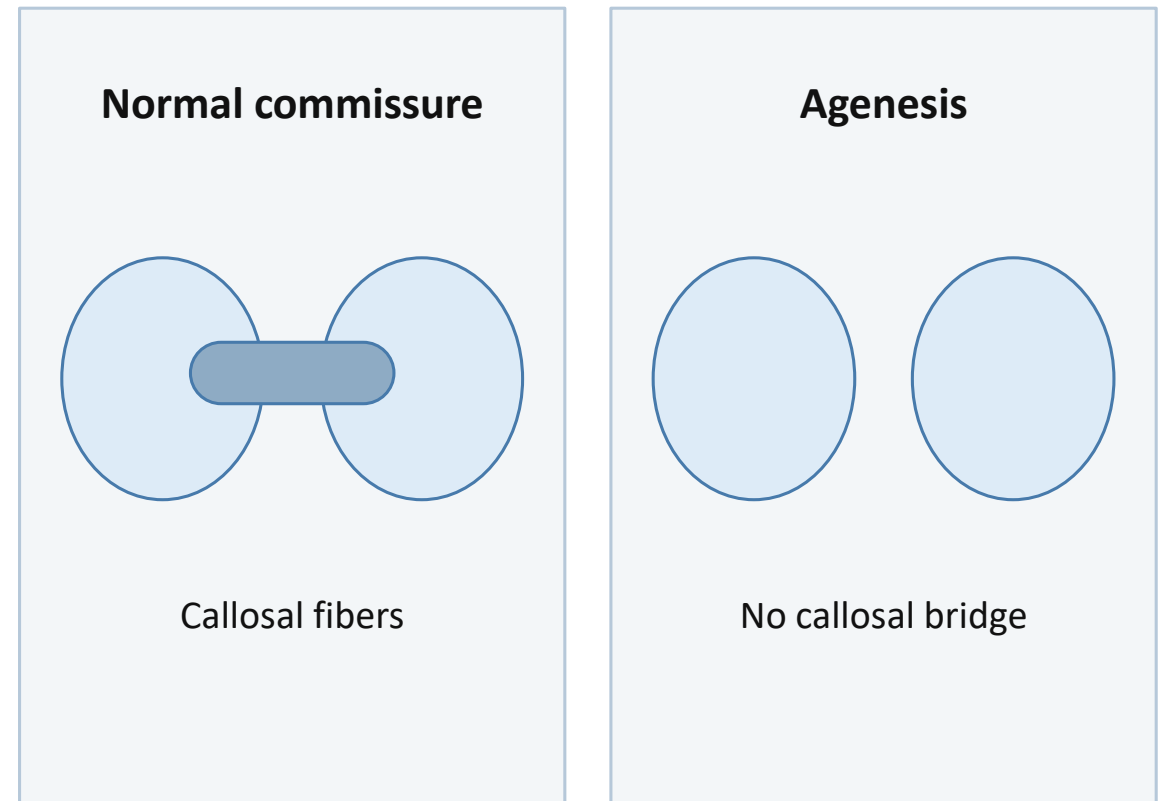
- The corpus callosum consists of white matter commissural bundles
- Its fibers carry cortical projections from one hemisphere to the other
- The normal structure presupposes distinct cerebral hemispheres



Schematic commissural connection

Agensis means absence of those bundles

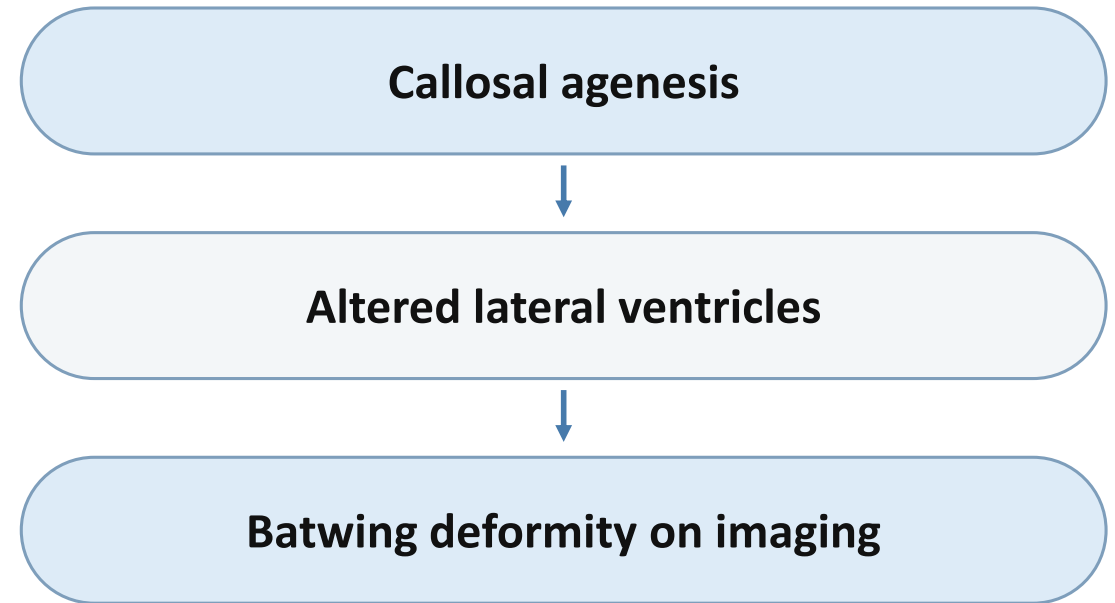
- Agensis of the corpus callosum is absence of normal interhemispheric callosal fibers
- It is described as a relatively common forebrain malformation
- The anatomic definition is not dependent on a particular cognitive phenotype



Schematic commissural connection

Lateral ventricular morphology can provide a clue

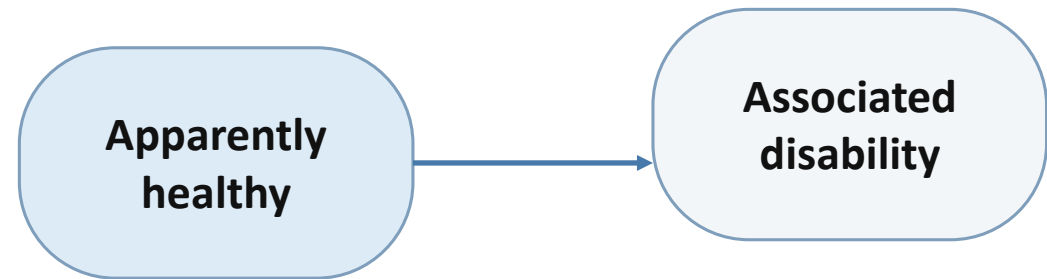
- Misshapen lateral ventricles on radiologic studies
- The stated imaging appearance is a batwing deformity
- The ventricular pattern supports recognition but should be correlated with callosal anatomy



Schematic: Conceptual sequence

Clinical expression may vary widely

- Callosal agenesis can occur in healthy individuals
- In other cases, it may accompany intellectual disability
- Imaging morphology alone does not establish a uniform developmental prognosis



Phenotype spectrum / alternatives (schematic)

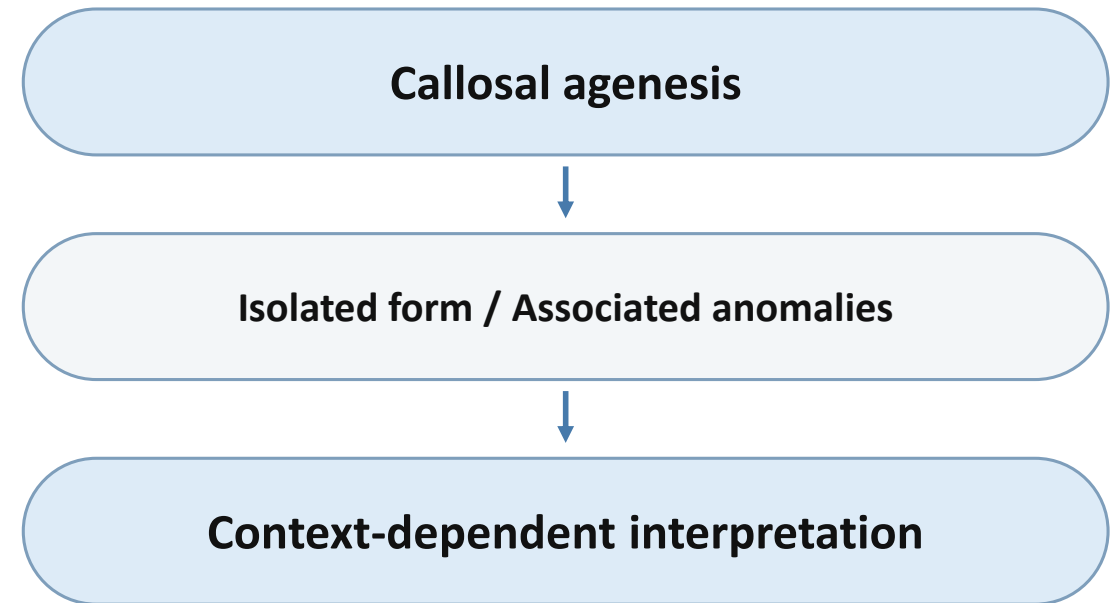
Callosal agenesis can be sporadic or familial

- The supplied source describes both sporadic and familial occurrence
- Genetic context varies across affected individuals
- No particular Mendelian inheritance frequency is specified

Occurrence	Source-defined possibilities
Family history	Sporadic or familial
Additional anomalies	Isolated or associated

Isolated and syndromic patterns differ

- Some patients have callosal agenesis without another recognized anomaly
- Others have additional malformations
- Associated anatomy is essential context when interpreting clinical significance



Schematic: Conceptual sequence

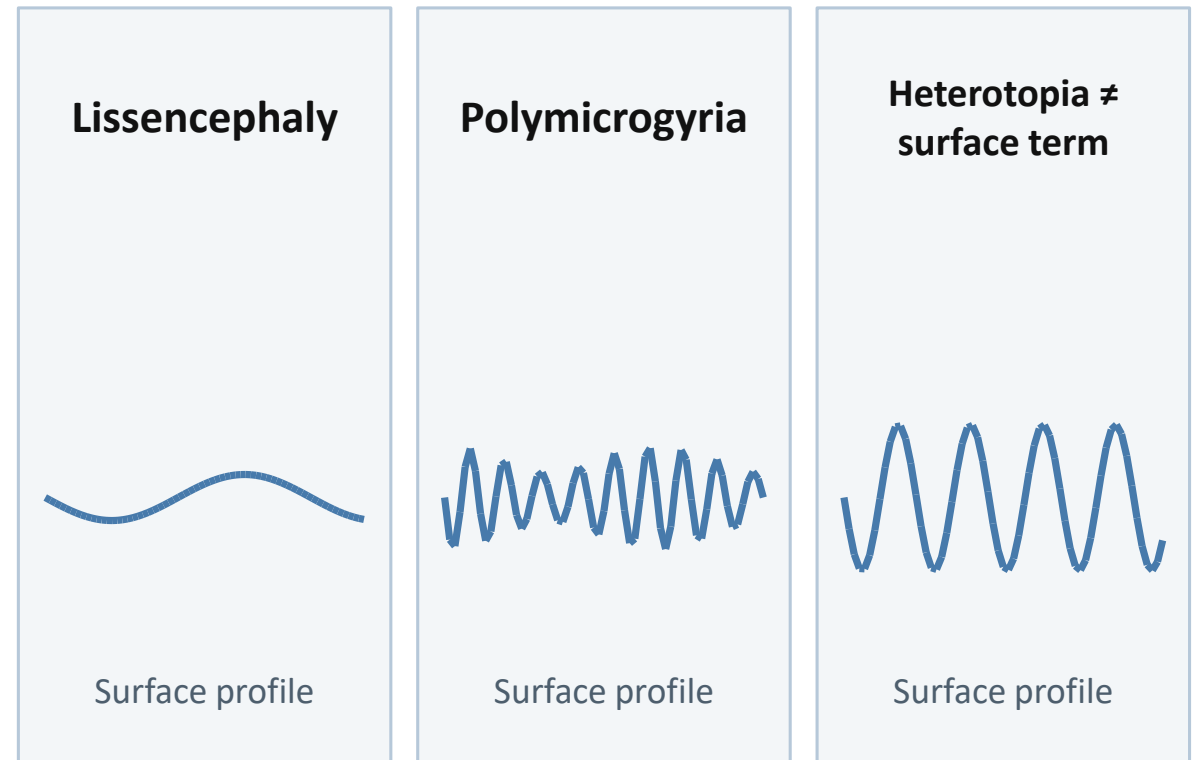
Map morphology to developmental process

- Small volume points toward a disturbance in neuronal population size
- Reduced gyration and abnormal folding point toward cortical construction defects
- Ectopic neuronal bands or nodules point toward migration abnormalities
- Unseparated hemispheres and absent commissure are distinct midline-related defects

Observed feature	First developmental question
Small brain	Were adequate neurons produced/recruited?
Abnormal folds	Was cortical construction organized?
Ectopic neurons	Did neurons migrate correctly?
Midline defect	Did division or commissure form?

Do not interchange the surface phenotypes

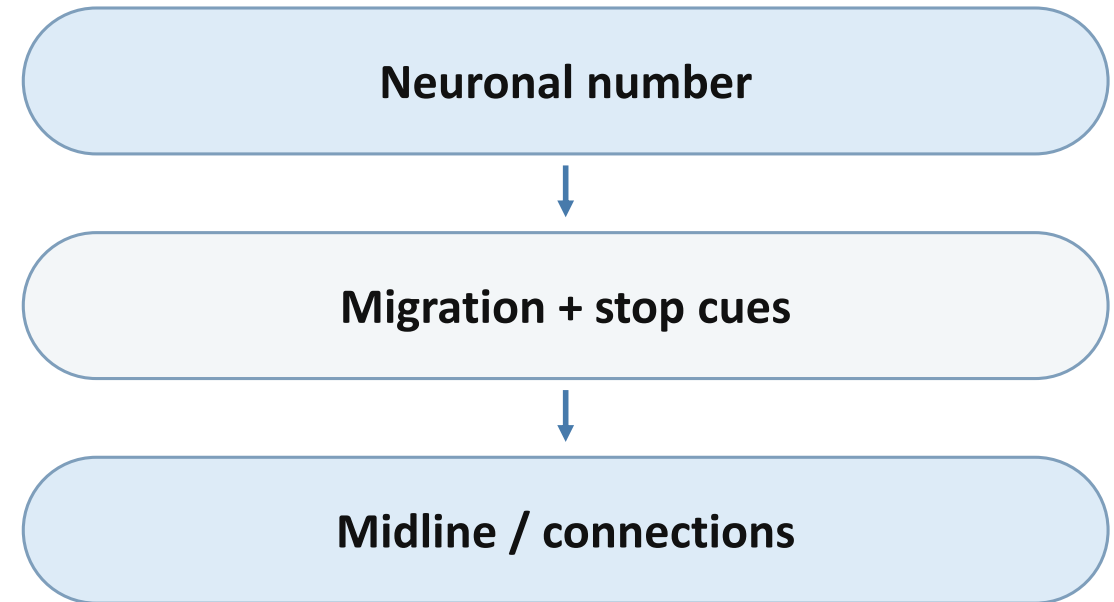
- Lissencephaly features abnormally few gyri
- Polymicrogyria features many small and malformed gyri
- Heterotopia describes ectopic neurons and need not be named by surface folding



Schematic profiles—not microscopic sections

A mechanistic classification sharpens the differential

- Precursor proliferation and cell-cycle exit influence neuronal number
- Motility and stopping cues influence neuronal position and cortical architecture
- Midline patterning and commissural development govern different gross structures



Schematic: Conceptual sequence

Genes are examples, not one-to-one labels

- FLNA and DCX illustrate distinct cytoskeletal routes to migration anomalies
- SHH pathway components illustrate a midline patterning mechanism
- Phenotype is necessary context when evaluating a proposed molecular cause

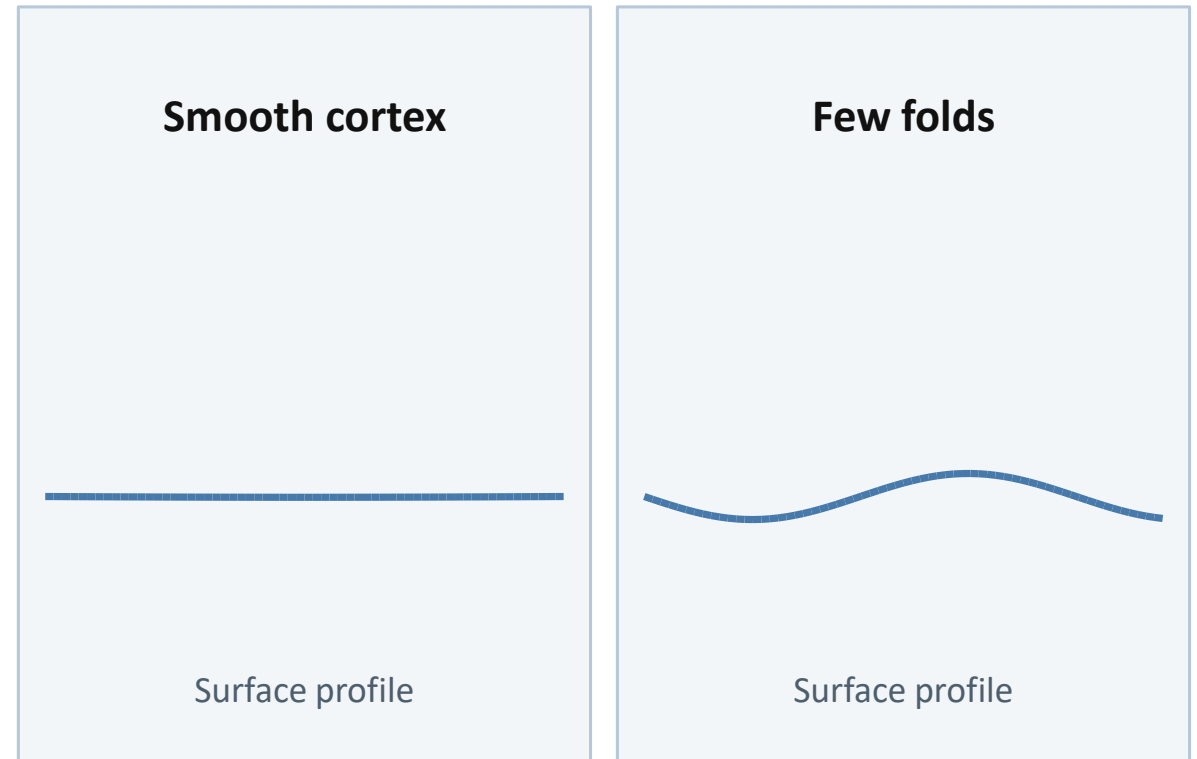
FLNA → nodules

**DCX → band /
lissencephaly**

SHH → midline

Morphology exercise: A smooth cortex

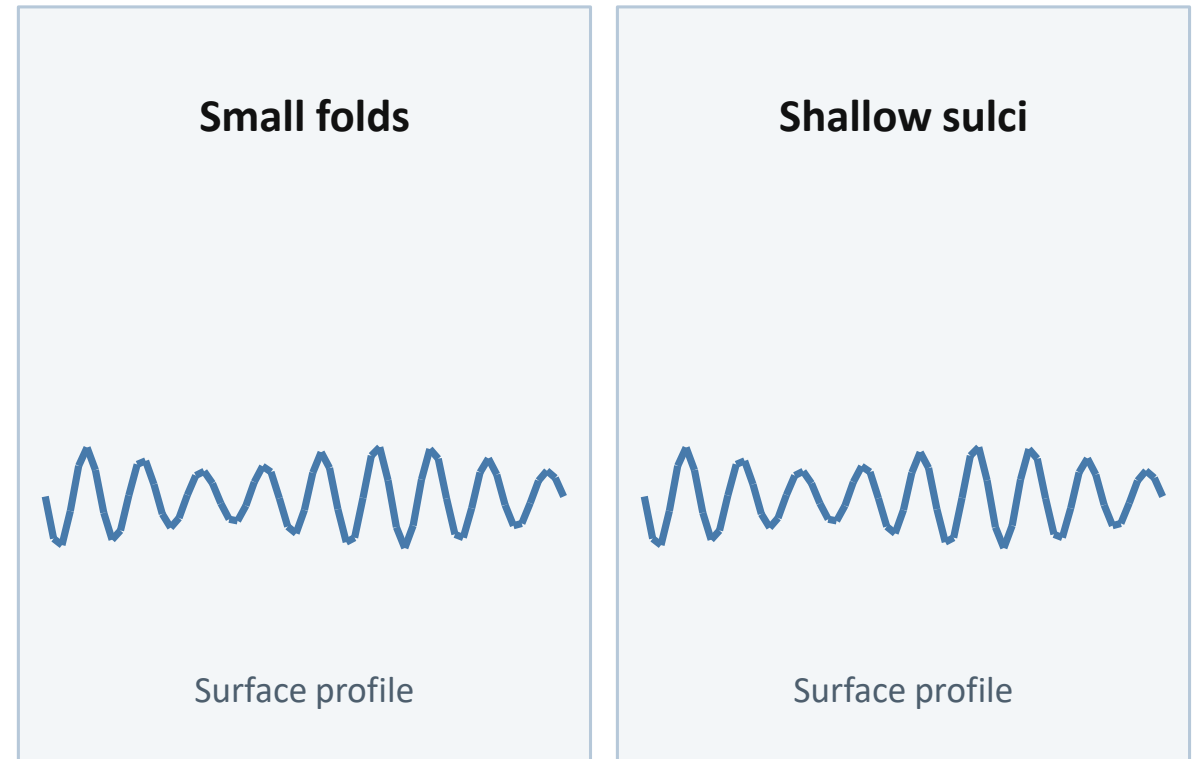
- Observed: Markedly reduced cortical convolutions
- Classify the primary morphologic dimension before suggesting a gene
- Ask whether the surface is smoothly reduced or cobblestone-like



Schematic profiles—not microscopic sections

Morphology exercise: Many shallow sulci

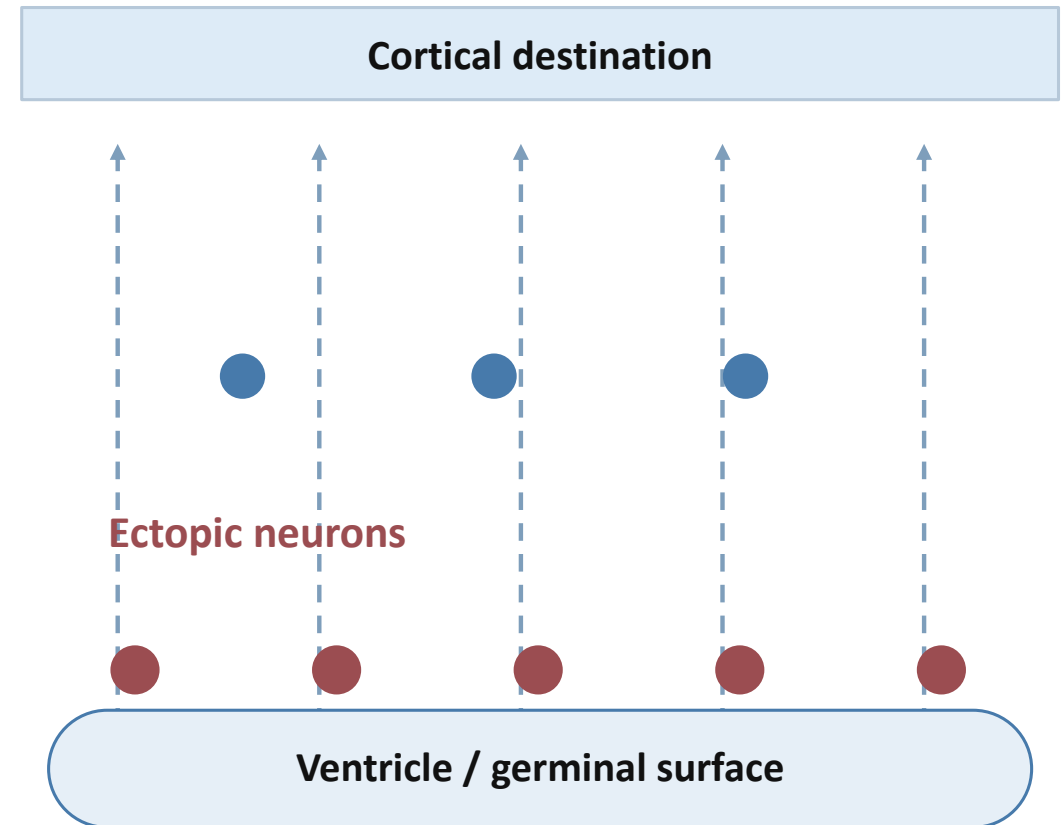
- Observed: Numerous small irregular cerebral convolutions
- The corresponding Robbins entity is polymicrogyria
- Histologic context: Simplified cortical lamination and fused molecular layers



Schematic profiles—not microscopic sections

Migration exercise: Nodules beside ventricles

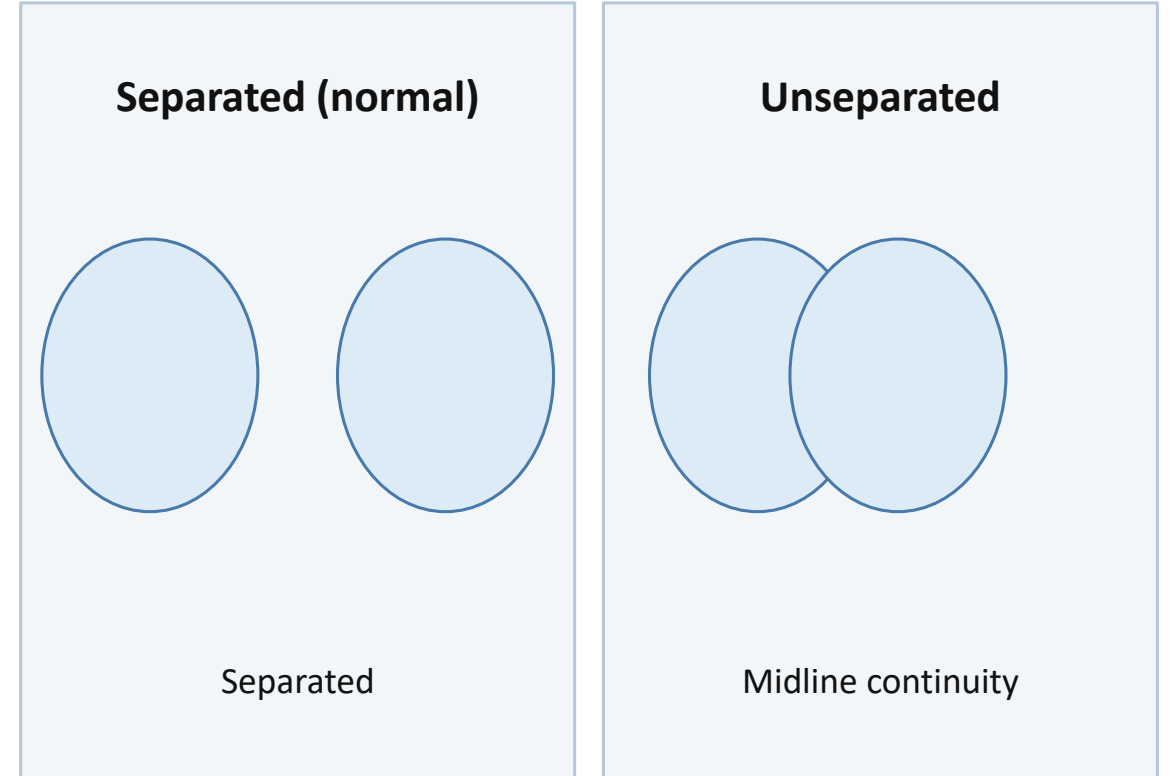
- Observed: Subcortical neuronal collections along the ventricular surface
- This corresponds to periventricular nodular heterotopia
- FLNA illustrates a relevant actin-associated migration pathway



Migration / heterotopia schematic

Midline exercise: Unseparated hemispheres

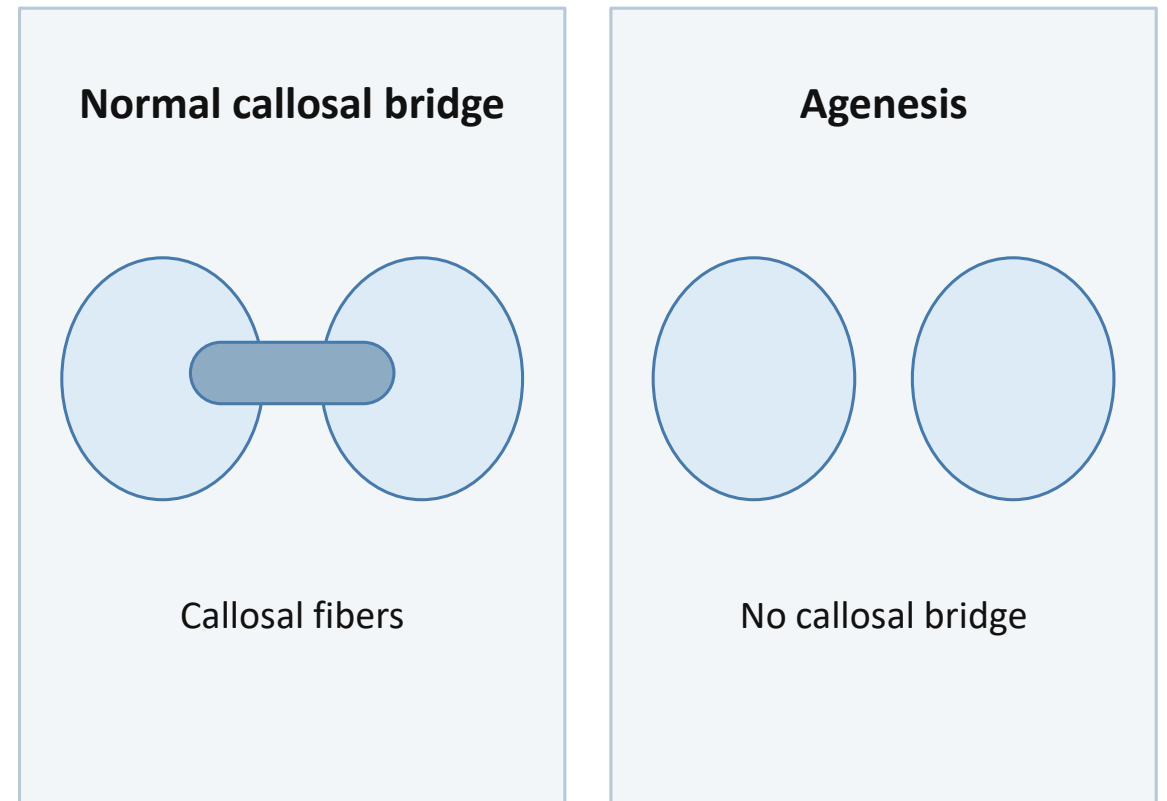
- Observed: The cerebral hemispheres remain joined across the midline
- This is the defining feature of holoprosencephaly
- Trisomy 13 and sonic hedgehog pathway changes are documented associations



Conceptual dorsal shapes; Not clinical imaging

Imaging exercise: Absent commissural bridge

- Observed: Absence of callosal white matter bundles
- Lateral ventricles may show the characteristic batwing deformity
- Interpretation must account for possible isolated or associated malformations



Schematic commissural connection

Distinct entities; Distinct anatomic questions

- Microencephaly: Is the brain abnormally small?
- Lissencephaly / polymicrogyria: How is the cerebral surface organized?
- Heterotopia: Are neurons located where they belong?
- Holoprosencephaly / callosal agenesis: Are midline structures properly formed?

Volume

Folding

Location

Midline

Classification schematic

References and source boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026), Chapter 28, pp. 1134–1135
- Section: Forebrain Anomalies; nearby material used only to establish topic boundaries
- Mechanism diagrams are original editable teaching schematics, not clinical images
- No source figures or authentic MRI scans have been reproduced

Scope: source-based teaching

No independent diagnostic thresholds or outcome rates are asserted