Pediatric Neuropathology: Malformations

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I have no relevant financial relationships to disclose

Learning Objectives

- Describe the basic steps of cortical development and how disruptions in each step may result in different types of cortical malformations.
- Compare and contrast the gross findings, microscopic features and etiologies of lissencephaly type I (classic) and lissencephaly type II (cobblestone).
- List the most common genetic and non-genetic etiologies associated with holoprosencephaly.
- Cite an example of how mutations in one gene may result in different phenotypes/malformations.

Outline

- Disorders of forebrain induction
  - Alobar holoprosencephaly
  - Semilobar holoprosencephaly
  - Lobar holoprosencephaly
  - Agenesis of the corpus callosum
- Malformations of cortical development
  - Lissencephaly
  - Heterotopias
  - Cortical dysplasia with cytomegaly
    - Focal cortical dysplasia
    - Tuberous Sclerosis
- Virtual Slides

Malformations

- Genetic and environmental factors have been implicated in the etiology of CNS malformations
- Most birth defects are likely multifactorial (combination of genetic, epigenetic and environmental)

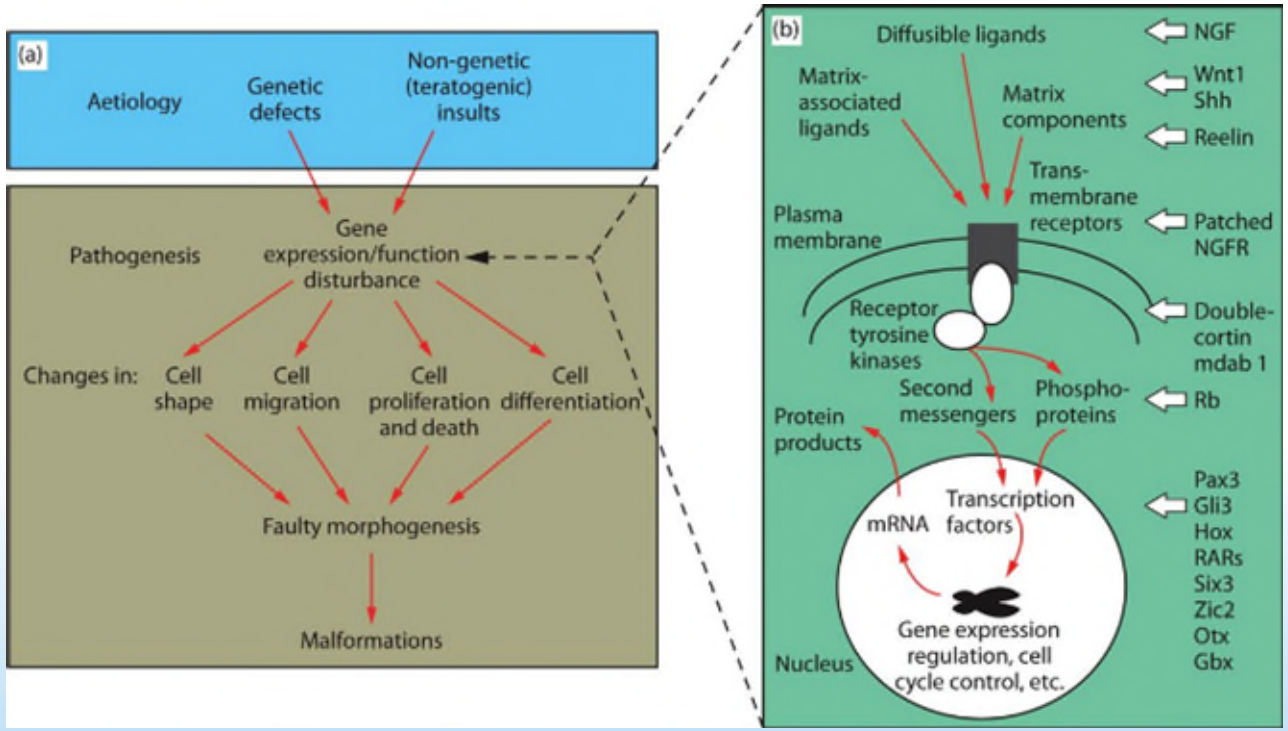


Figure 4.4: Greenfield's Neuropathology, 9th Edition

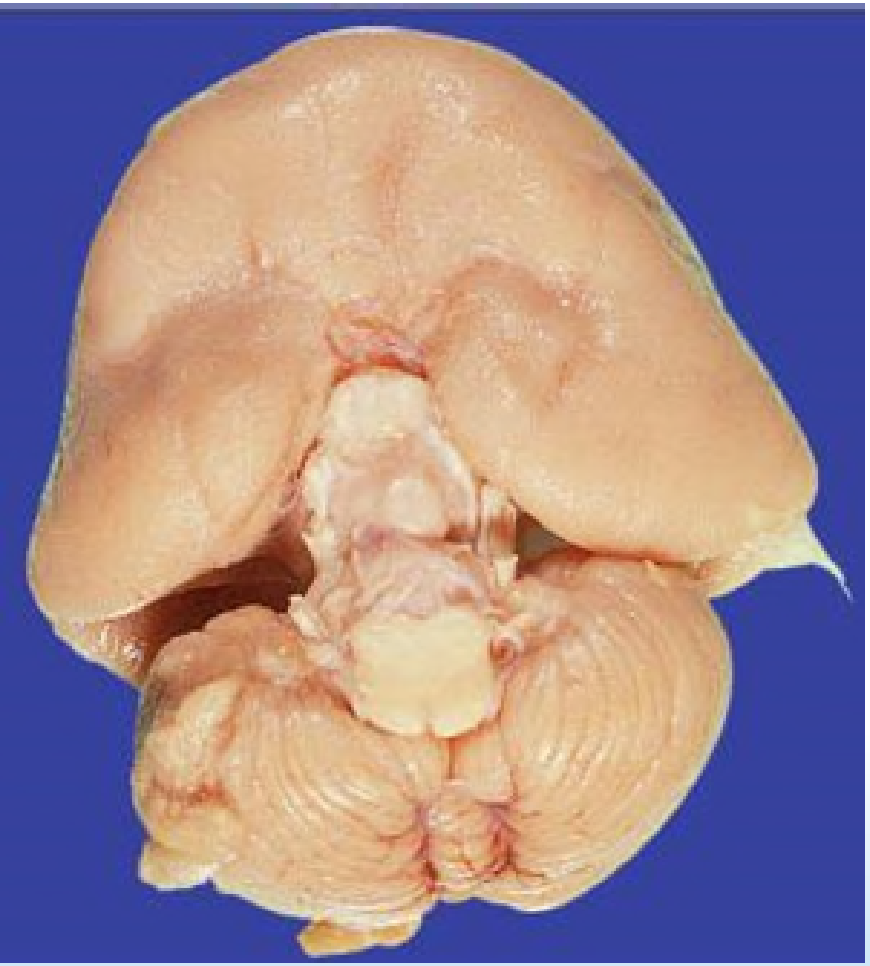
Disorders of Forebrain Induction

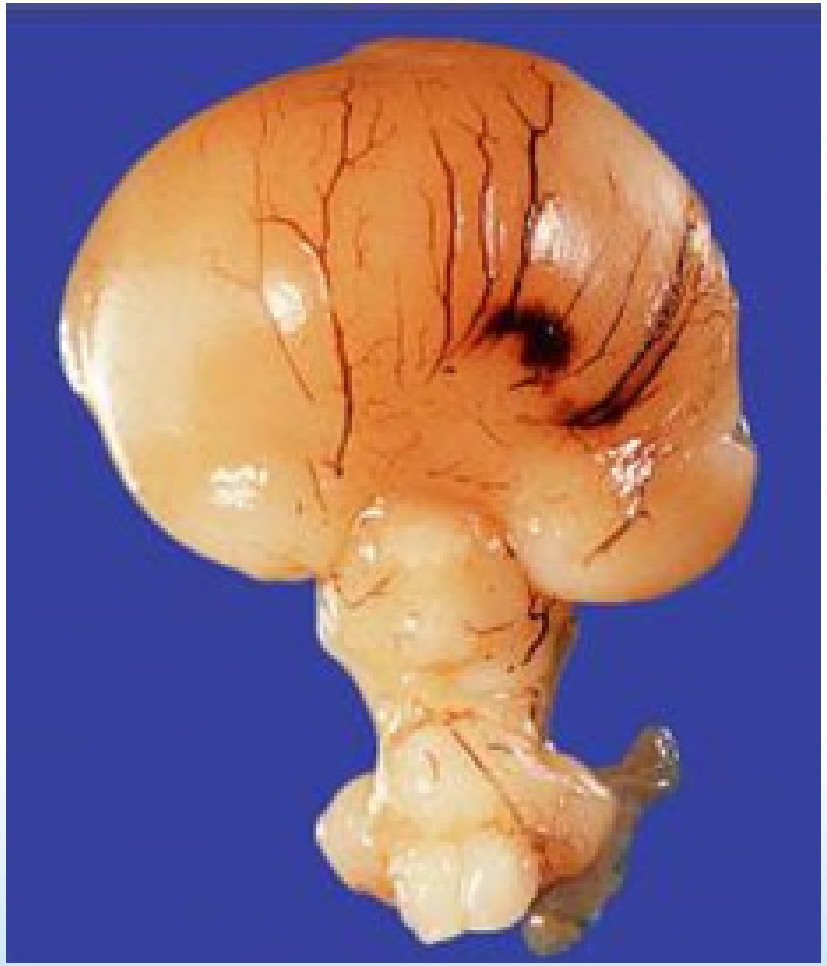
- Alobar holoprosencephaly
- Semilobar holoprosencephaly
- Lobar holoprosencephaly
- Agenesis of the corpus callosum

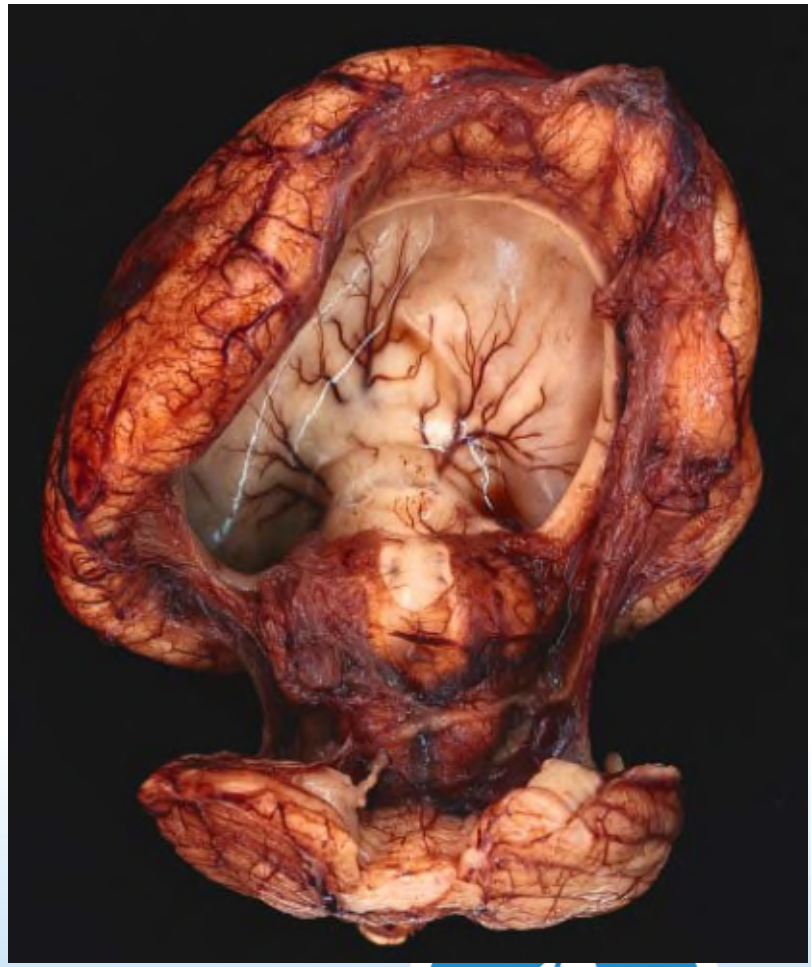
Holoprosencephaly

- Developmental defect of the forebrain (prosencephalon)
- Incomplete separation of the cerebral hemispheres into distinct right and left halves
- Mostly sporadic (occasional familial cases)
- Prevalence:
  - 1:16,000 live births
  - 1:250 conceptuses
- Three types:
  - Alobar (complete): no separation of the telencephalon, single ventricle in a small brain
  - Semilobar (incomplete): variable degrees of separation of the posterior cerebrum
  - Lobar: a small focal fusion of the midline with T-shaped or Y-shaped lateral and third ventricles

Alobar Holoprosencephaly

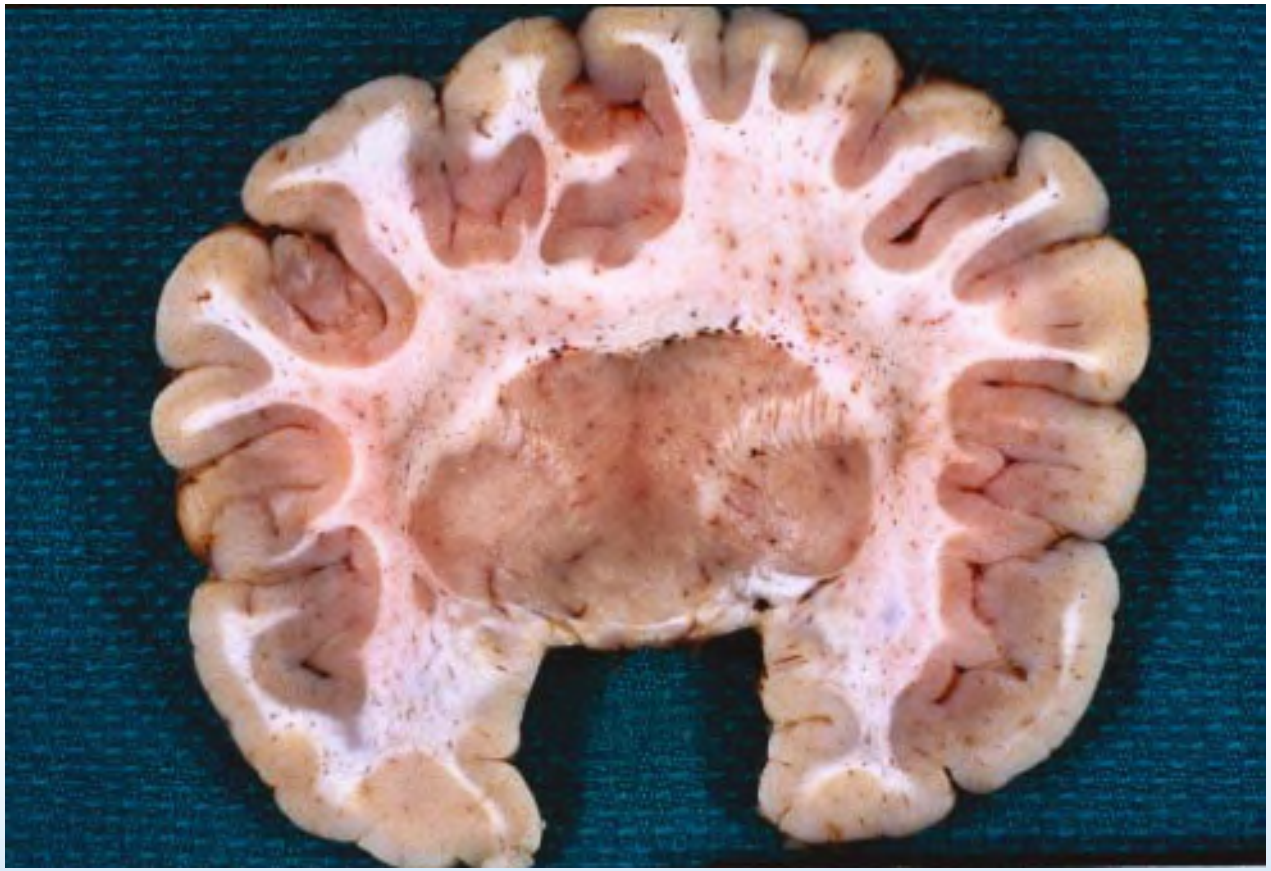


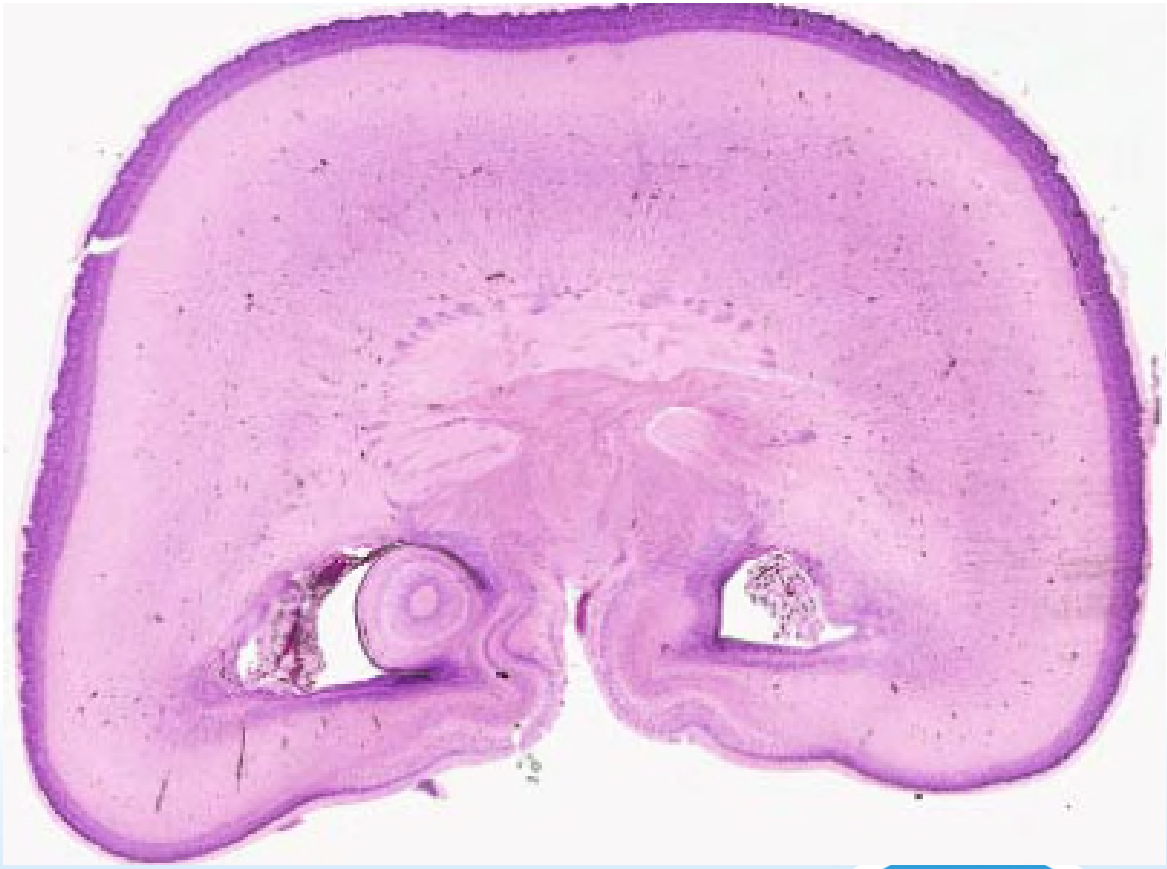




Images courtesy of Brian Harding, DPhil FRCPath; Figure 2.7-1, Pediatric Neuropathology: A Text-Atlas

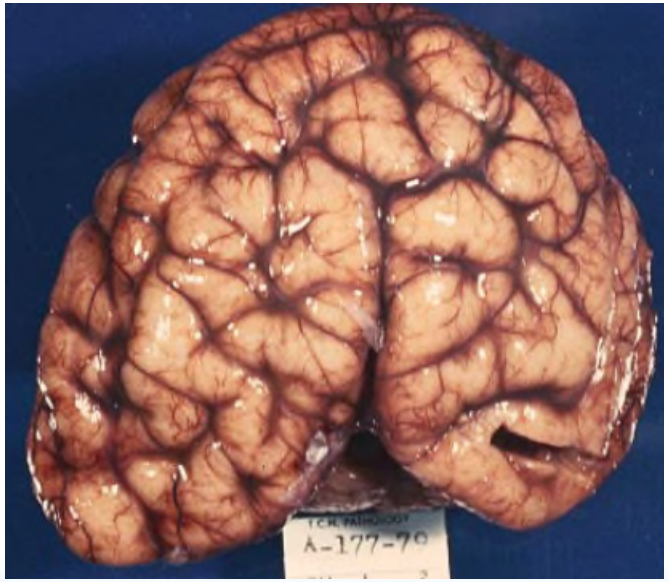
Alobar Holoprosencephaly

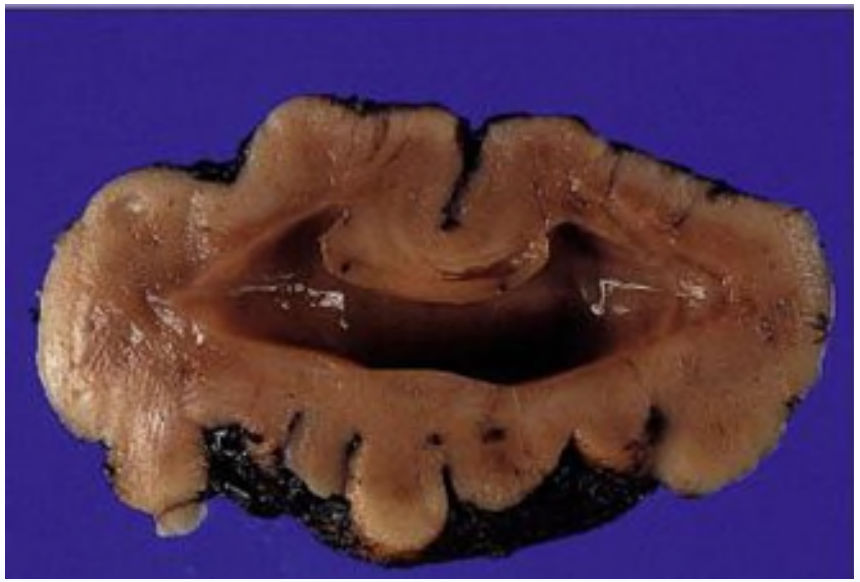




Figures 2.7-3 and 2.7-5, Pediatric Neuropathology: A Text-Atlas

Semilobar Holoprosencephaly





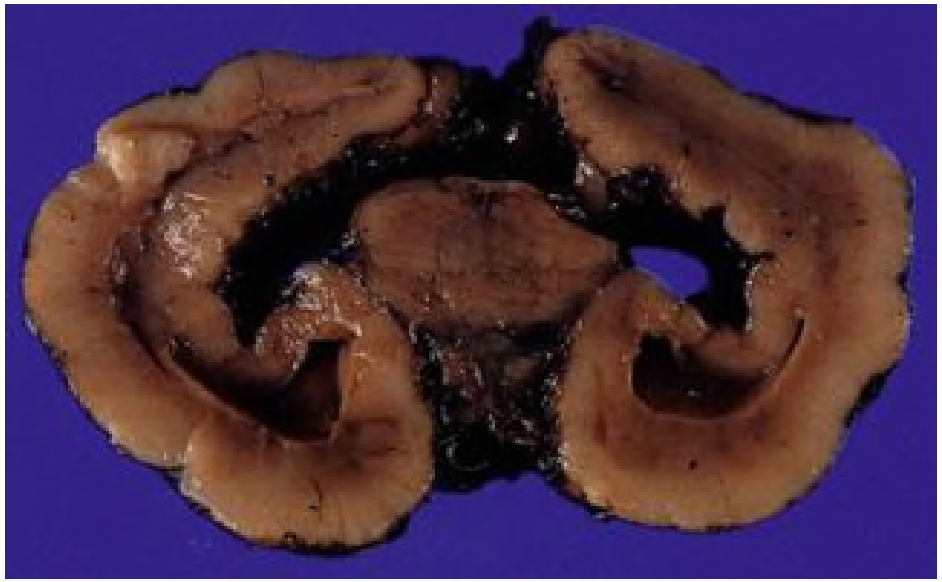
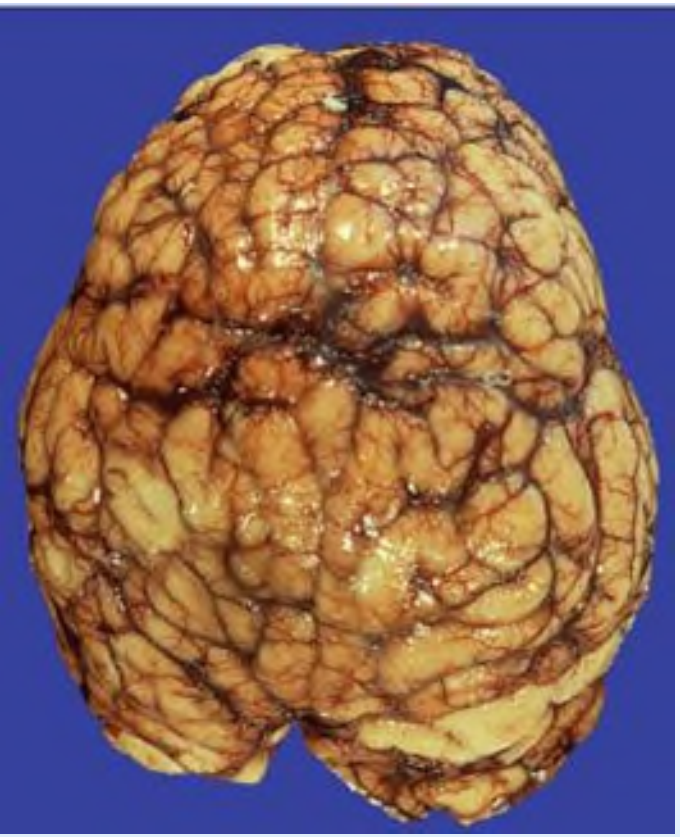
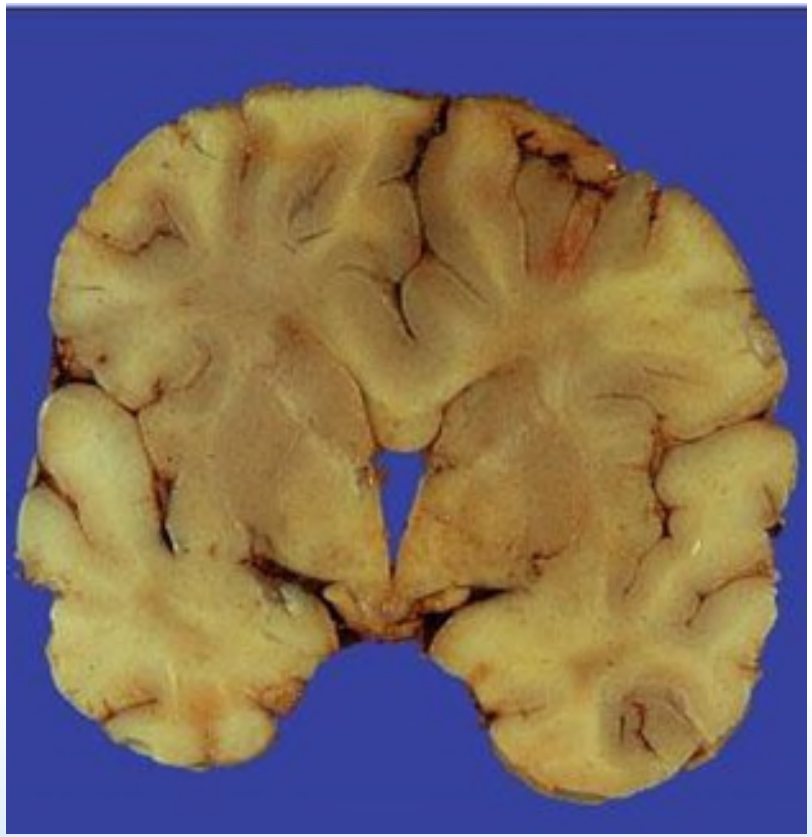
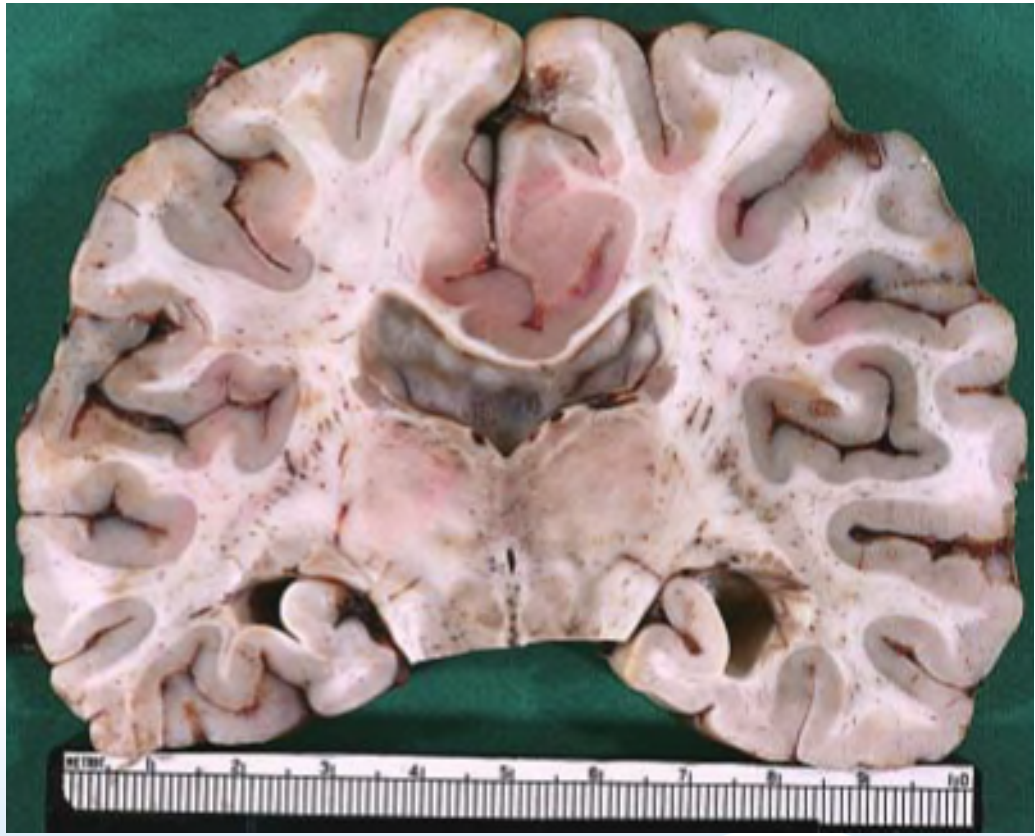


Figure 2.8-3, Pediatric Neuropathology: A Text-Atlas; Images courtesy of Brian Harding, DPhil FRCPath

Lobar Holoprosencephaly

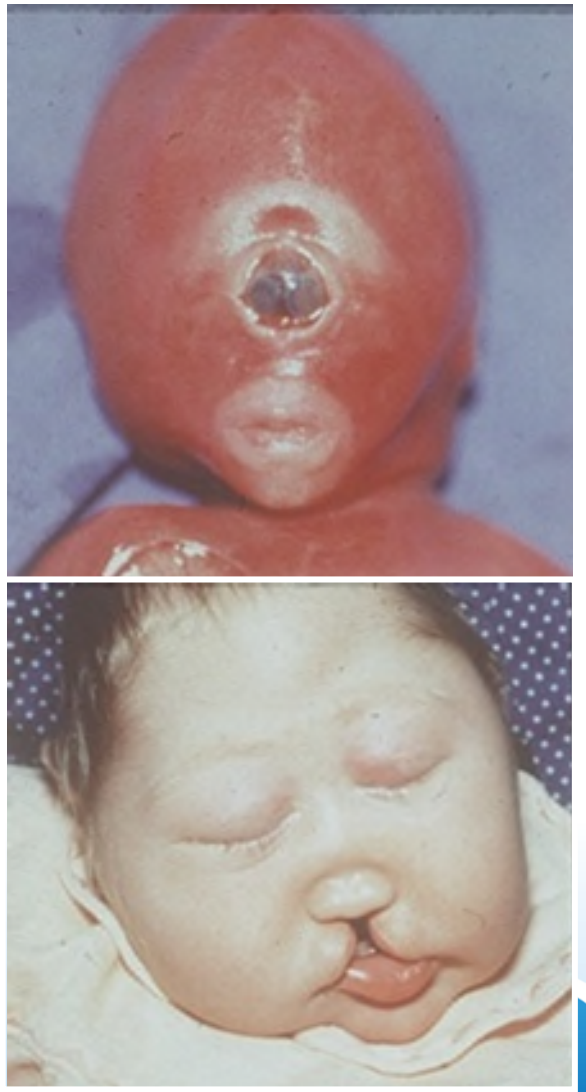






Holoprosencephaly Clinical Features

- Cleft lip/palate
- Eye anomalies (cyclopia)
- Anosmia
- Congenital nasal pyriform aperture stenosis
- Single central maxillary incisor
- Pituitary dysfunction (including SIADH)
- Seizures
- Hypotonia



Images courtesy of Brian Harding, DPhil FRCPath

Holoprosencephaly Etiology

- Material diabetes mellitus
- Infections: toxoplasmosis, syphilis, rubella
- Teratogens: ethanol, retinoic acid, cholesterol synthesis inhibitors
- Genetic factors:
  - Cytogenetic abnormalities seen in 50% of cases
    - Trisomy 13 most frequent
  - Smith-Lemli-Opitz syndrome (*DHCR7*)
  - Mutations (see next slide)

Holoprosencephaly genes

Disease or locus name	CNS malformations involved	Gene	Function of gene product	Chromosome location	OMIM number*	Mouse model or homologue
Holoprosencephaly (HPE1)	Alobar holoprosencephaly	ND	ND	21q22.3	236100	ND
Holoprosencephaly (HPE2)	Alobar or semi-lobar holoprosencephaly	*SIX3*[1064]	Homologue of sine oculis gene of *Drosophila:* homeobox-containing transcription factor	2p21	157170	Targeted mutation of *Six3* gene has truncation of forebrain[579]
Holoprosencephaly (HPE3)	Holoprosencephaly	*SHH* (Sonic hedgehog)[875]	Secreted signalling molecule; neural inducer	7q36	142945	Targeted mutation of *Shh* gene has holoprosencephaly in addition to many other defects[151]
Holoprosencephaly (HPE4)	Holoprosencephaly	*TGIF*[405]	Homeodomain protein functioning as repressor of TGF-β	18p11.3	142946	Targeted mutation of *Tgif* gene produces no visible phenotype[524]
Holoprosencephaly (HPE5; 13q32 deletion syndrome)	Holoprosencephaly, exencephaly	*ZIC2*[124]	Transcription factor encoded by homologue of odd paired gene of *Drosophila*	13q32	609637	Targeted mutation of *Zic2* gene has holoprosencehaly[734]
Holoprosencephaly (HPE6)	Holoprosencephaly	ND	ND	2q37.1	605934	ND
Holoprosencephaly (HPE7)	Holoprosencephaly	*PTCH1*[703]	Patched: membrane receptor for Sonic hedgehog protein	9q22.3	601309	Targeted mutation of *Ptch1* causes medulloblastoma in heterozygotes and neural tube defects in homozygotes[390]
Holoprosencephaly (HPE8)	Holoprosencephaly	ND	ND	14q13	609408	ND

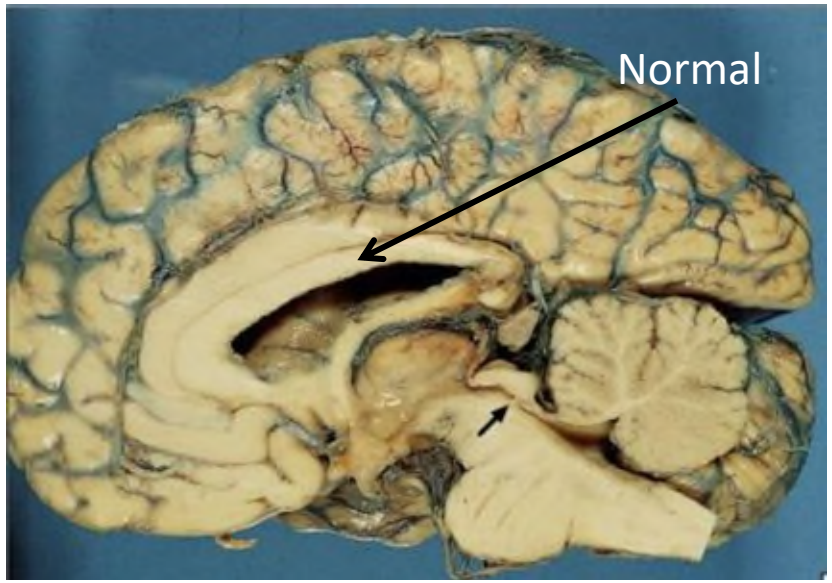
ND = not determined

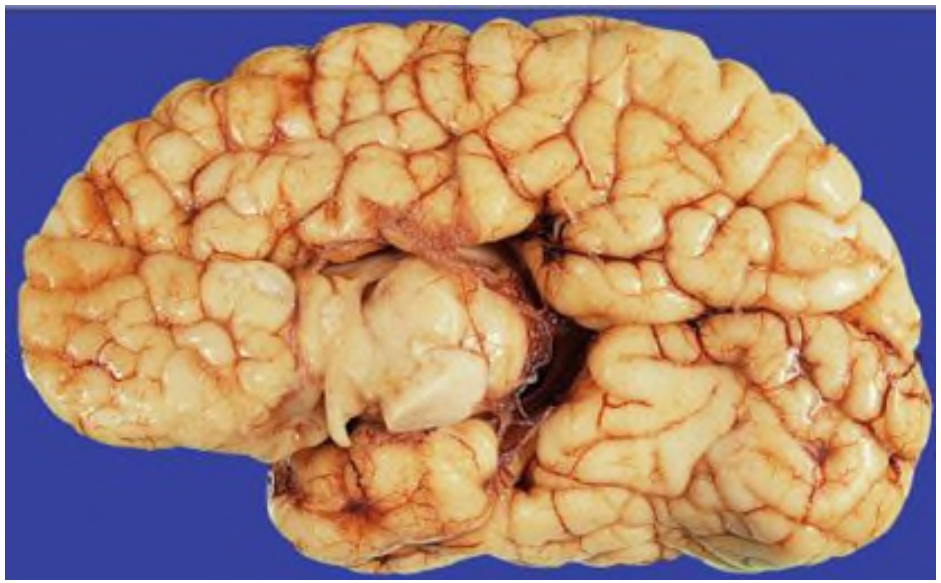
From Table 4.1: Greenfield's Neuropathology, 9th Edition

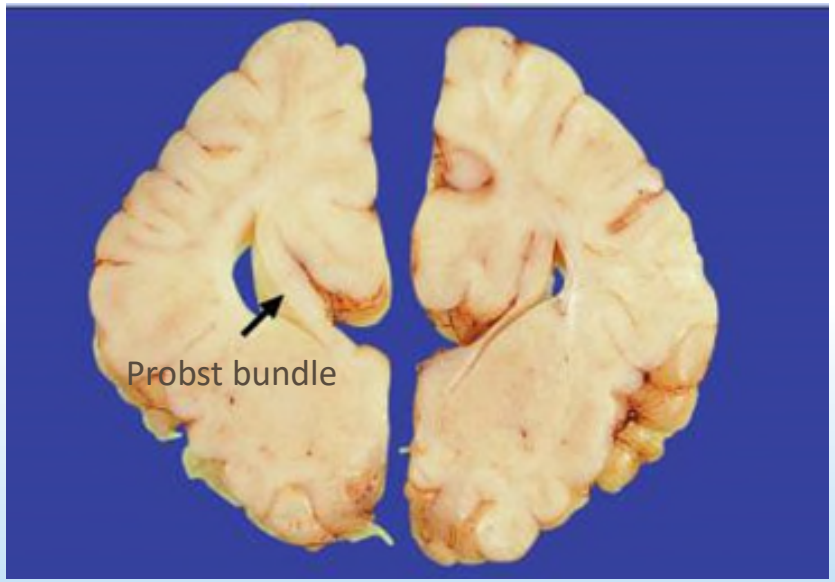
Agenesis of the Corpus Callosum

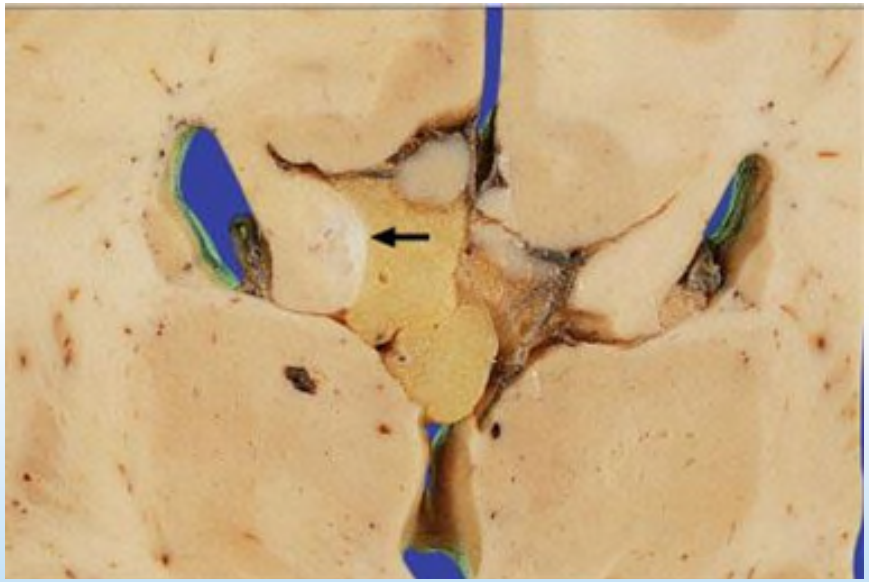
- Complete (total) and incomplete (partial) types
  - Partial is usually only missing the splenium
- Isolated (silent clinically or subtle) or seen in association with other malformations (ex. holoprosencephaly)
- May be sporadic but typically associated with syndromes: Aicardi, Andermann, Meckel
- Possible pathogenetic mechanisms:
  - Probst bundle of misdirected fibers
  - Mechanical defect suggested by hamartoma/ lipoma

Agenesis of the Corpus Callosum









Images courtesy of Brian Harding, DPhil FRCPath

Outline

- Disorders of forebrain induction
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  - Heterotopias
  - Cortical dysplasia with cytomegaly
    - Focal cortical dysplasia
    - Tuberous Sclerosis

Development of the Cerebral Cortex

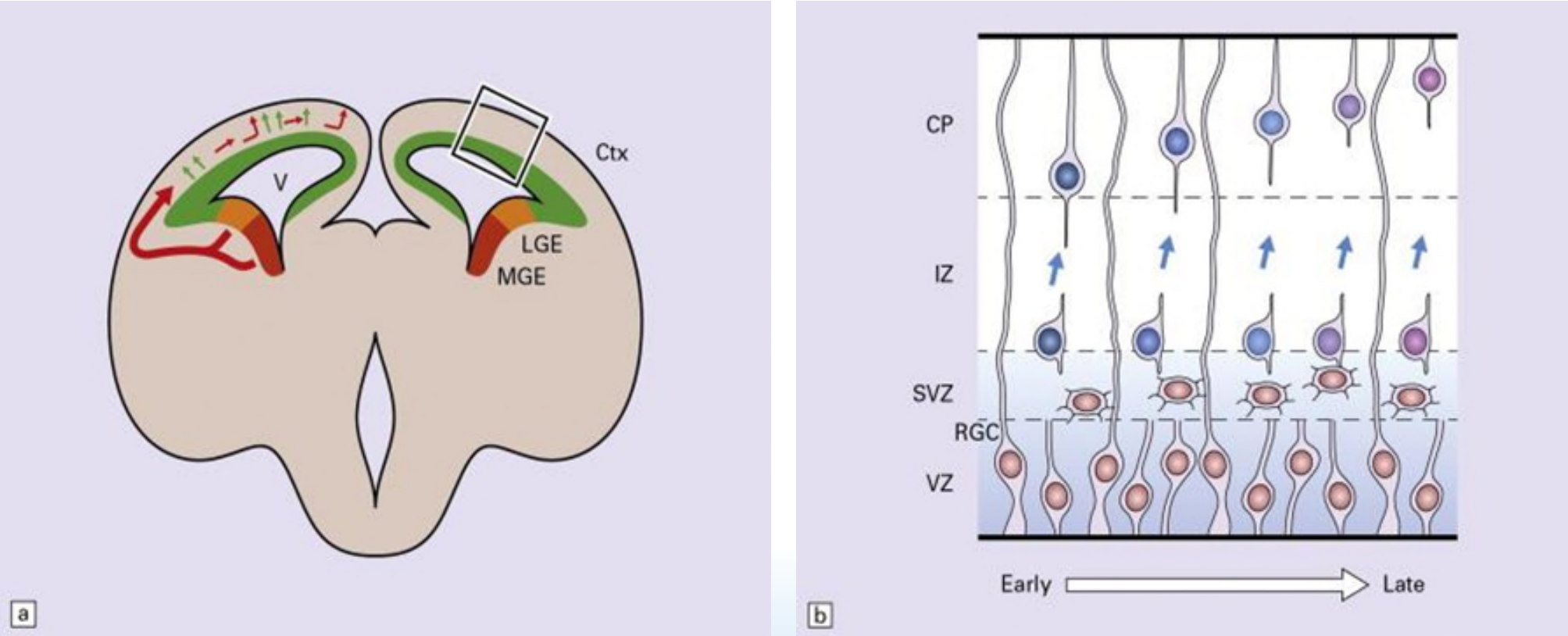


Figure 3.50: Neuropathology: A reference text of CNS pathology, 3rd edition

Malformations of cortical development with associated genes and clinical features

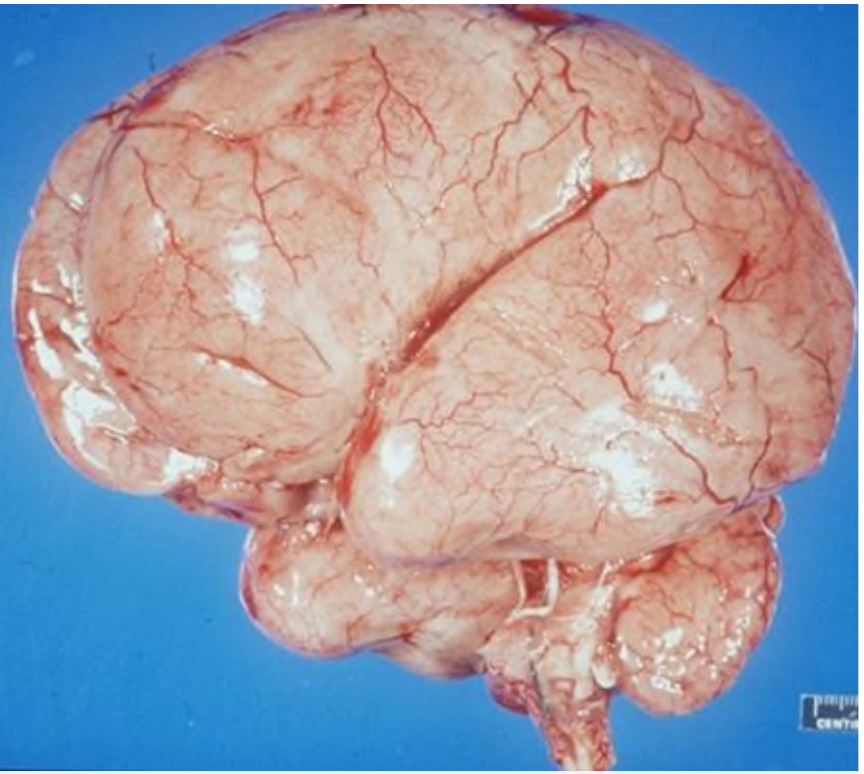
Developmental stage	Cortical malformation	Genetic cause	Clinical features
Abnormal neurogenesis			
	Microcephaly	*ASPM*	Mental retardation, not generally associated with epilepsy, autosomal recessive inheritance
		Microcephalin	
		CDK5RAP2	
		CENPJ	
	Hemimegalencephaly	Unknown	Mental retardation, early onset seizures (frequently intractable epilepsy), +/- neurocutaneous syndrome
	Focal cortical dysplasia	Unknown	Most common, focal and generalized Seizures
Abnormal neuronal migration			
	Periventricular heterotopia	*FLNA*	Normal intelligence, adolescent onset seizures, X-linked disorder with male lethality
		ARFGEF2	Mental retardation, microcephaly, autosomal recessive inheritance, rare
	Subcortical band heterotopia	*DCX*	Subcortical band heterotopia in females, mental retardation, epilepsy, X-linked disorder
	Lissencephaly	*LIS1*	Miller-Dieker syndrome (characteristic facial features), autosomal dominant inheritance
		DCX	Lissencephaly in males, X-linked
		TUBA1A	Lissencephaly, clinical features similar those caused by *LIS1* and *DCX*, de novo mutations
		ARX	Associated with ambiguous genitalia, hypothalamic dysfunction, neonatal epilepsy, X-linked disorder
		RELN	Associated with cerebellar hypoplasia, epilepsy, autosomal recessive inheritance
Abnormal arrest in neuronal migration			
	Cobblestone lissencephaly	*Fukutin*	Fukuyama congenital muscular dystrophy
		POMGnT1	Muscle-eye-brain disease
		POMT1	Walker-Warburg Syndrome

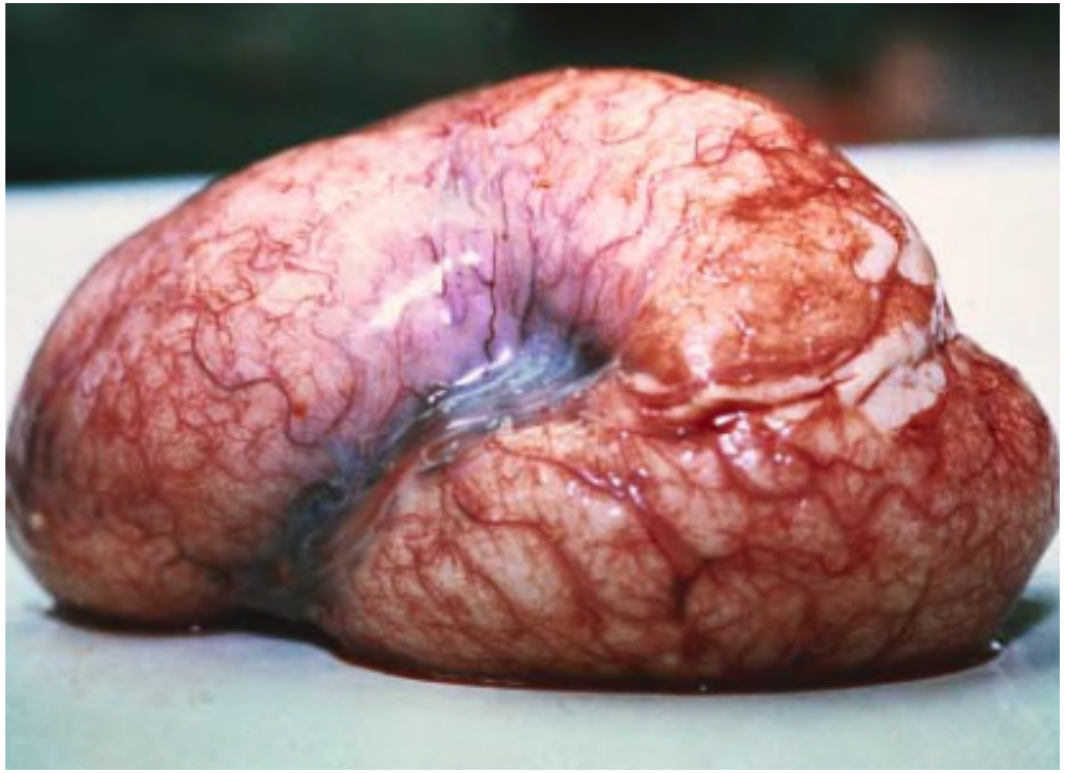
Adapted from Pang T, Atefy R, Sheen V. Malformations of cortical development. *Neurologist*. 2008;14(3):181–191.

Lissencephaly type I (Classic)

- Neuronal migration disorder characterized by abnormal gyri
- Varies from agyria to pachygyria
- Severe mental retardation, hypotonia, intractable seizures
- Several genetic types are recognized

Lissencephaly type I





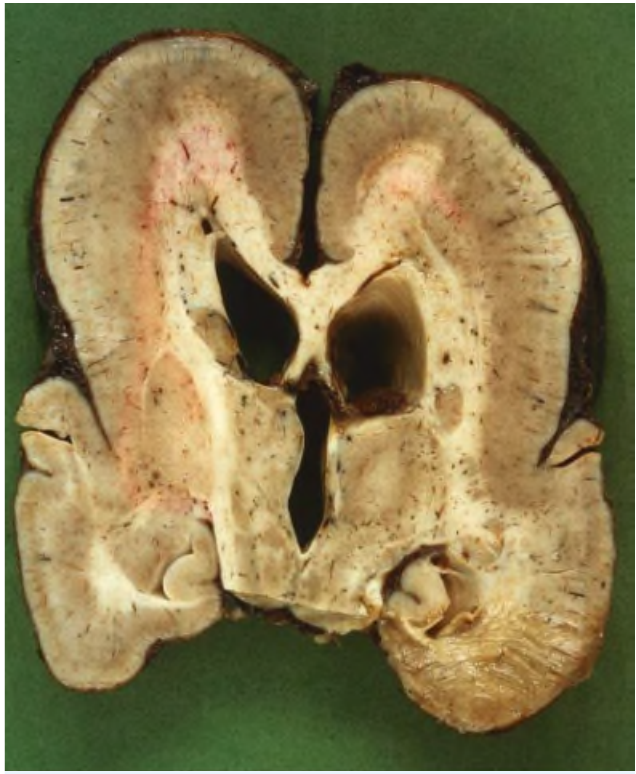
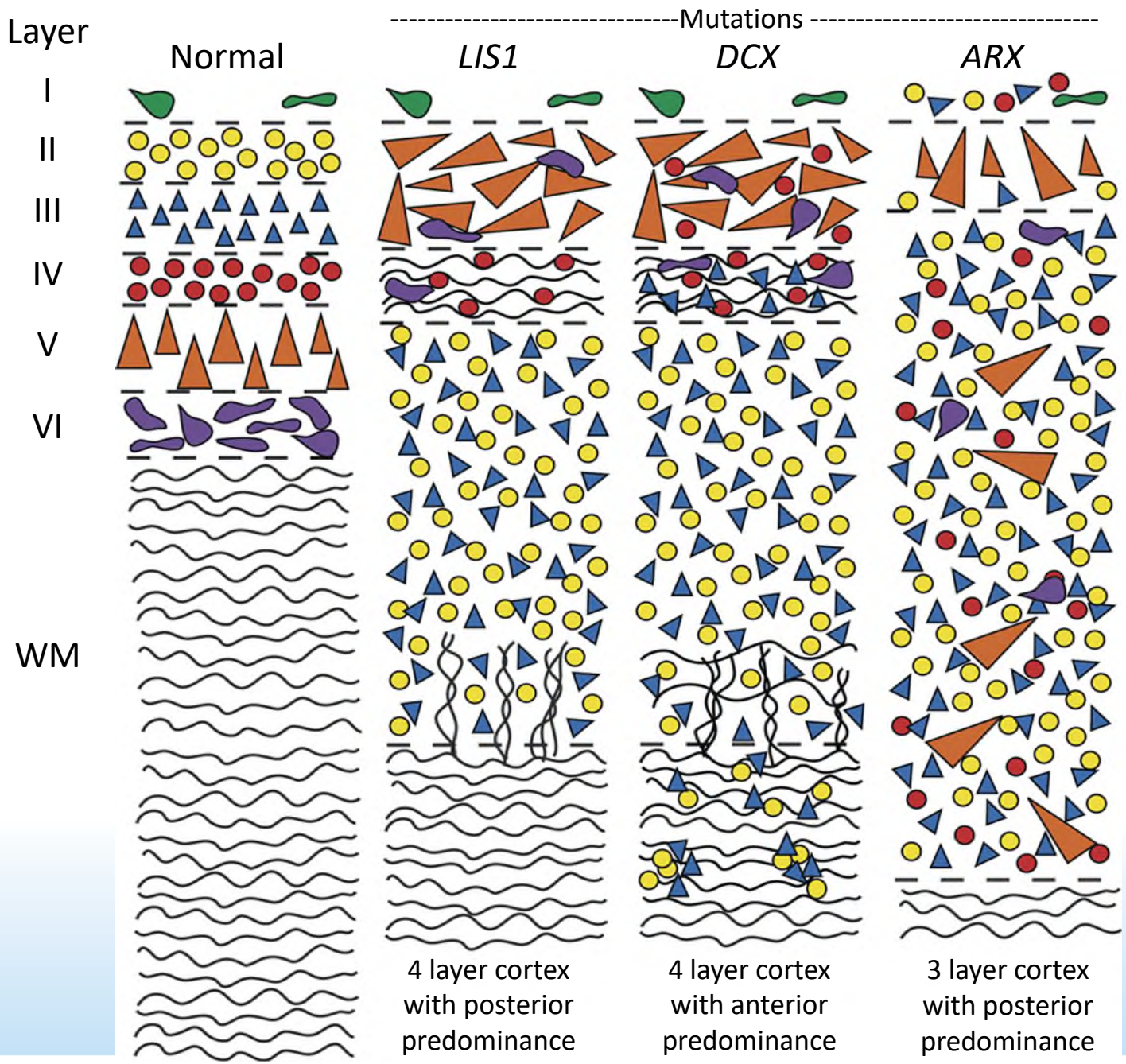
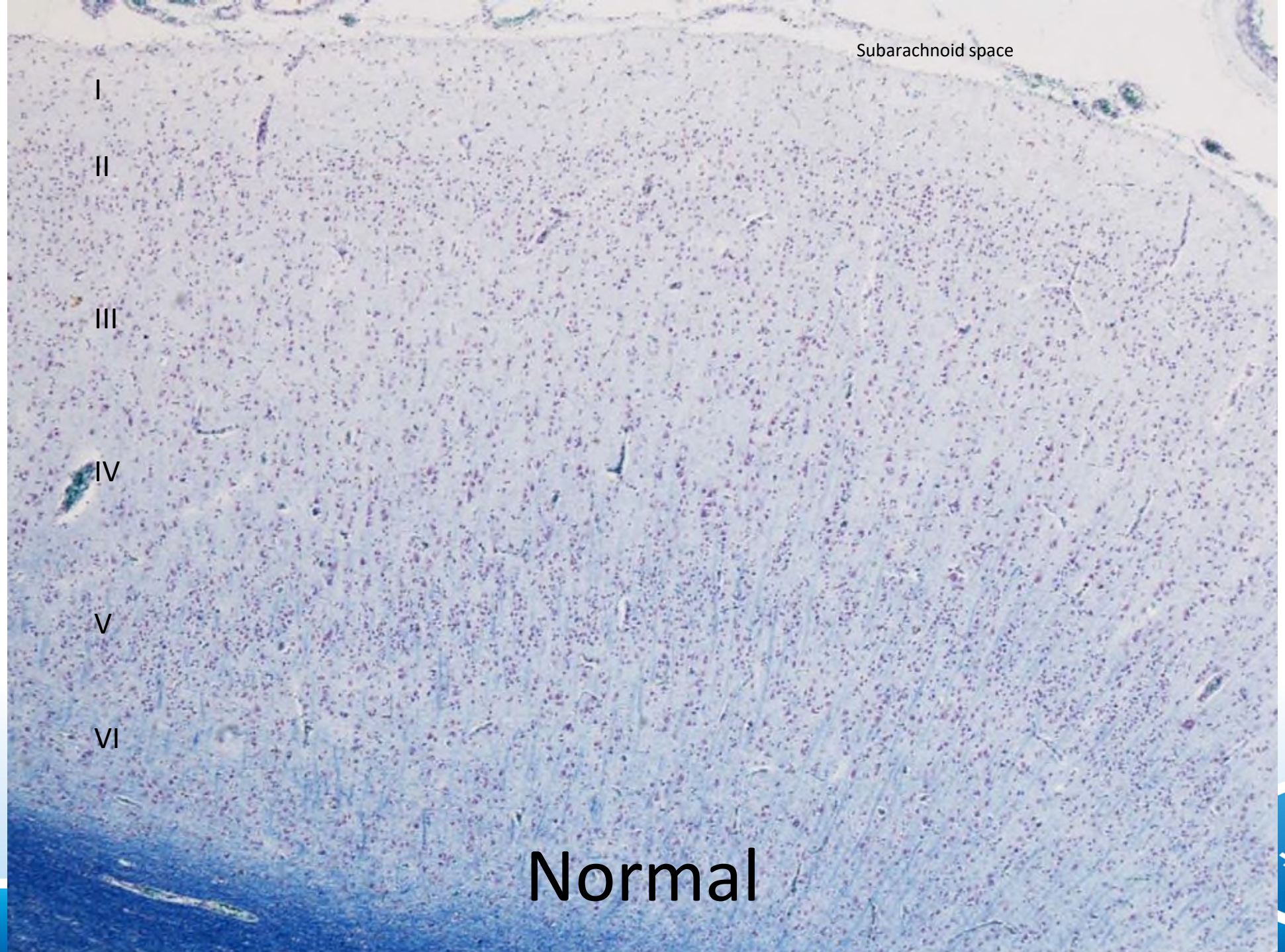


Image courtesy of Brian Harding, DPhil FRCPath; Figures 2.11-1 and 2.11-2, Pediatric Neuropathology: A Text-Atlas

Disease	CNS	Gene	Function of product	Chromosome	Mouse model
Lissencephaly (type I): autosomal recessive (Norman-Roberts type)	Lissencephaly with low sloping forehead and prominent nasal bridge	*RELN*	Reelin: extracellular matrix protein produced by Cajal-Retzius cells required for neuronal migration	7q22	*reeler* mutant mouse causes cerebellar and cerebral cortical lamination anomalies
Lissencephaly (type I): Miller-Dieker syndrome, autosomal dominant (haploinsufficiency)	Lissencephaly, cerebral heterotopias, facial dysmorphism	*LIS1* and *14-3-3$^{\varepsilon}$ YWHAE ;* (contiguous gene deletion)	LIS1: Non-catalytic subunit of brain platelet-activating factor acetyl hydrolase (PAFAH)	17p13.3	Targeted loss of function alleles of *Pafah1b1* gene and *14-3-3$^{\varepsilon}$*
Lissencephaly (type I): isolated lissencephaly sequence (ILS), autosomal dominant	Lissencephaly	*LIS1* deletion alone	LIS1: as above	17p13.3	Targeted loss of function alleles of *Pafah1b1* gene causes neuronal migration disorders
Lissencephaly (type I): X-linked	Lissencephaly with agenesis of corpus callosum in males; subcortical band heterotopia in females	*DCX*	Doublecortin: microtubule-associated protein that interacts with non-receptor tyrosine kinases, including Abl	Xq22.3-q23	suppression of doublecortin expression by RNAi inhibits neuronal migration in rat neocortex
Lissencephaly (type I): X-linked (XLAG)	Lissencephaly with ambiguous genitalia	*ARX*	Aristaless-related homeodomain transcription factor	Xp22.13	Targeted mutation of *Arx*



Adapted from Forman MS et al. *J Neuropathol Exp Neurol* 2005



Normal

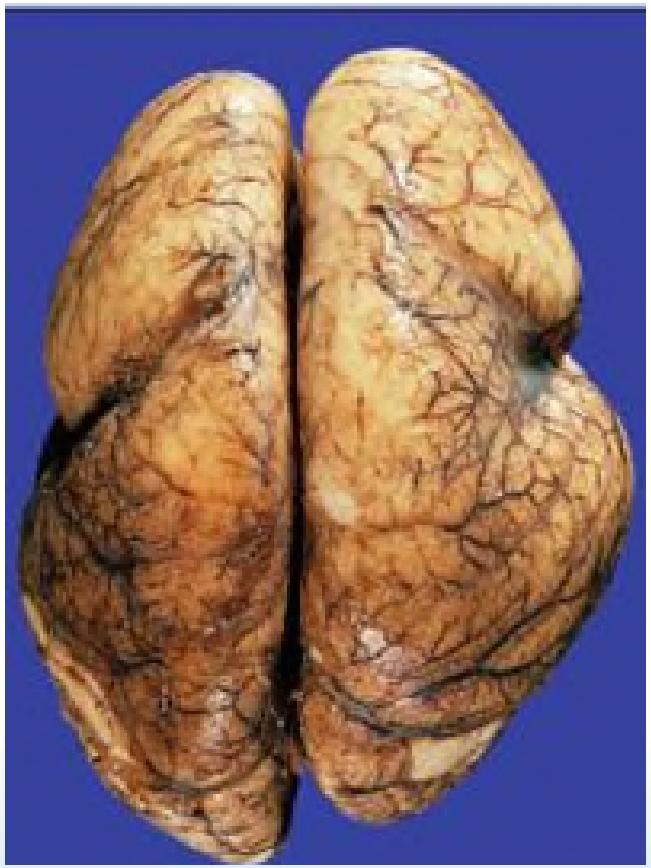
Lissencephaly type I: Isolated Lissencephaly

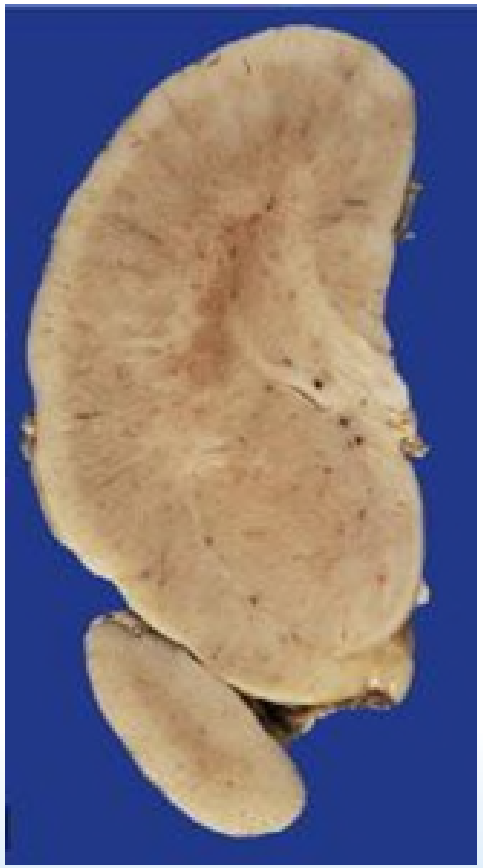
- Isolated lissencephaly sequence occurs in patients with deletions of the *LIS1* gene
- Autosomal dominant
- *LIS1* encodes the non-catalytic subunit of platelet activating factor acetyl hydrolase
  - Involved in the regulatory pathway for dynein
  - Important for neuronal migration
- More severe occipital/posterior parietal

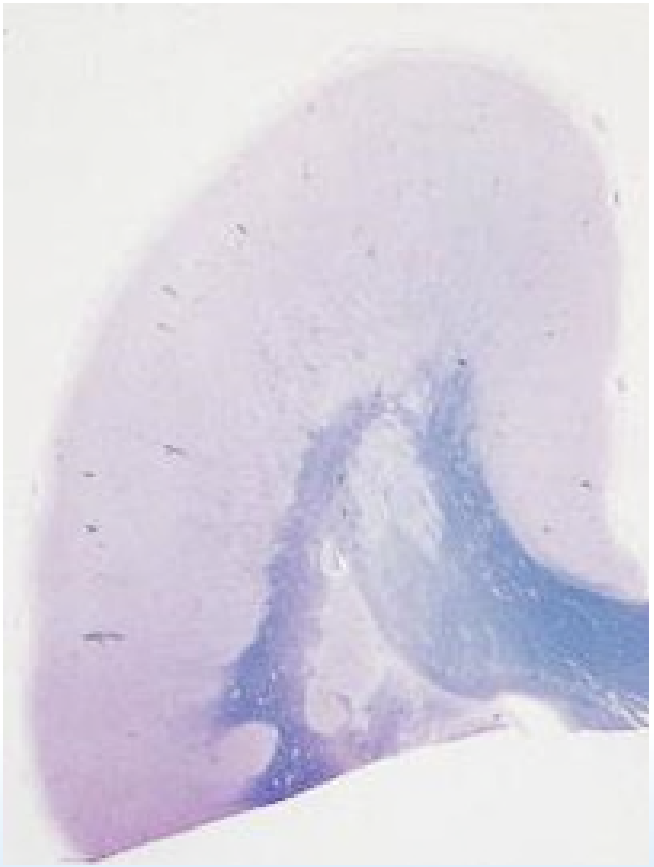
Lissencephaly type I: Miller-Dieker syndrome

- Clinical features:
  - Microcephaly, bitemporal narrowing, vertical ridging in forehead, micrognathia
  - Cryptorchidism, heart and kidney anomalies may be seen
- Due to codeletion of *LIS1* and *14-3-3* genes (both on the short arm of chromosome 17)
- Lissencephaly due to deletion of *LIS1*
- Facial features due to other genes on 17p

Miller-Dieker syndrome







Images courtesy of Brian Harding, DPhil FRCPath

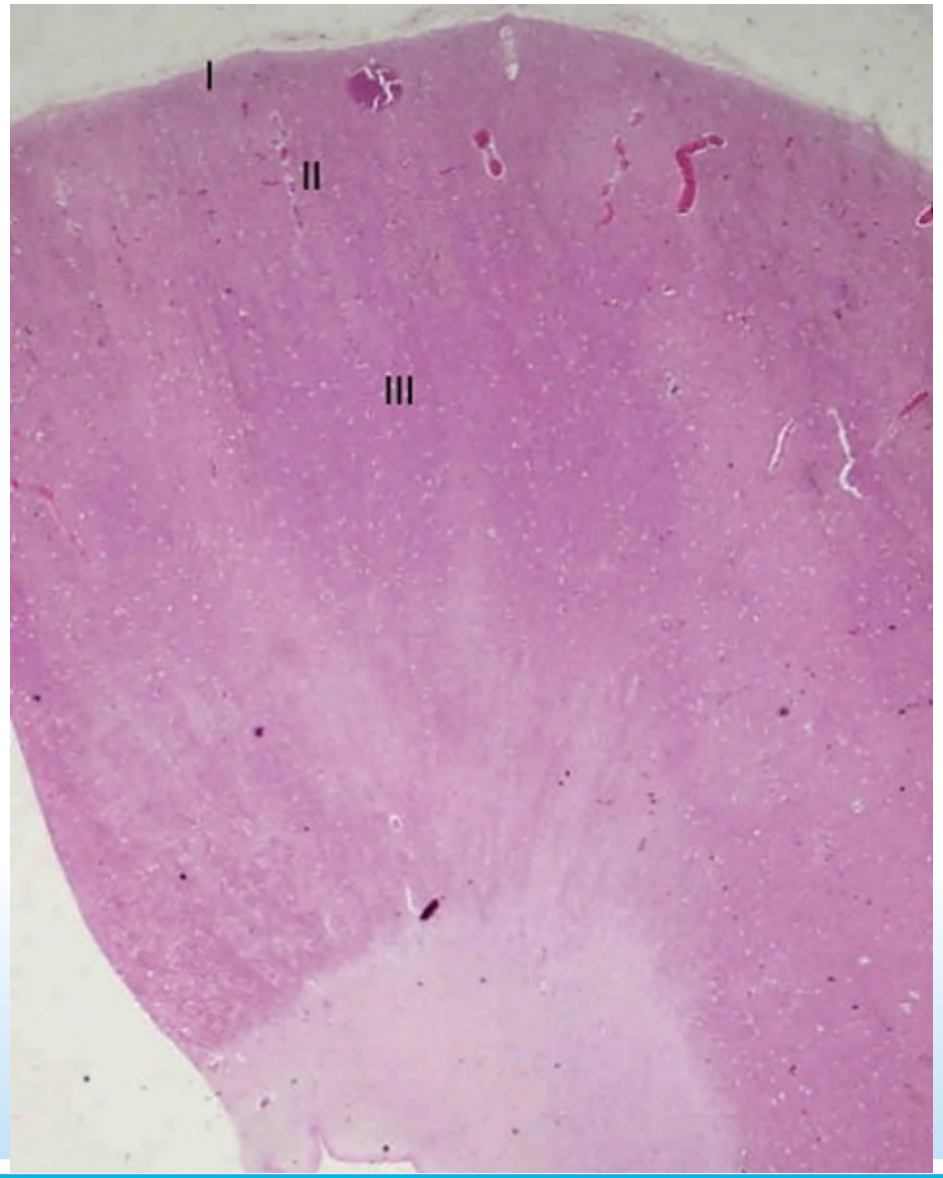
Lissencephaly type I: doublecortin (*DCX*) gene mutation

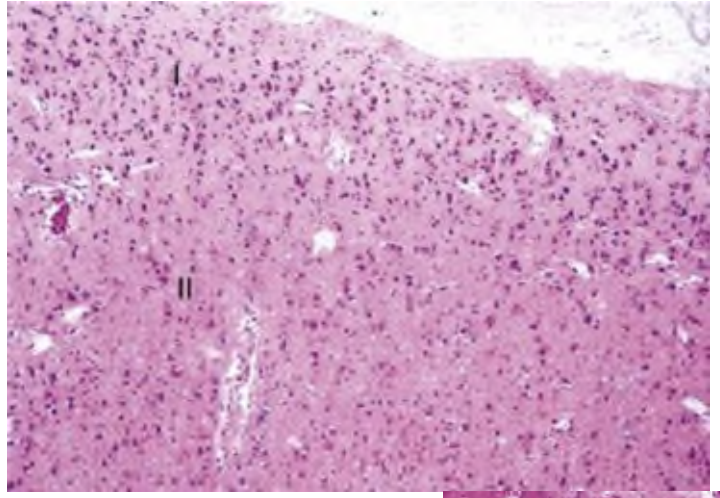
- Located on Xq22
- X-linked dominant
- In males, isolated lissencephaly
- More severe anteriorly

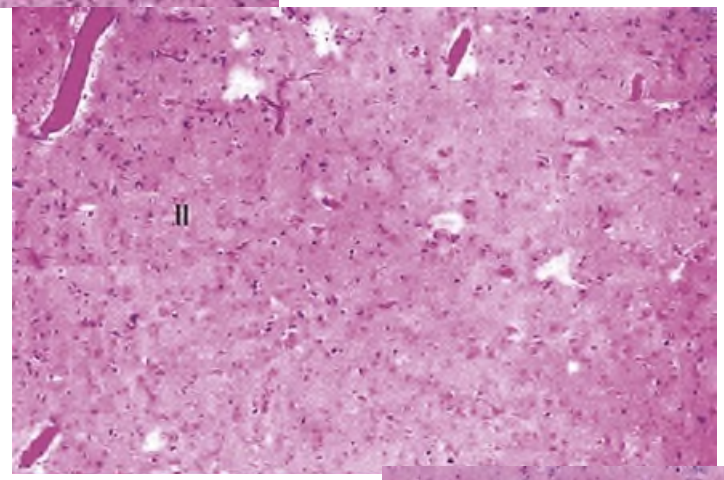
Lissencephaly type I: XLAG

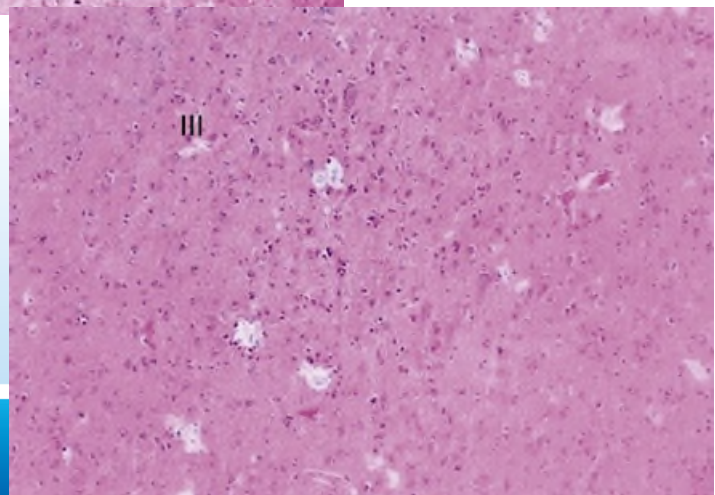
- X-linked lissencephaly with ambiguous genitalia (XLAG)
  - Due to *ARX* mutations
  - X-linked recessive
  - Agenesis of the corpus callosum, severe seizures, temperature dysregulation, microcephaly
  - Posterior-anterior gradient
  - 3-layer cortex

XLAG







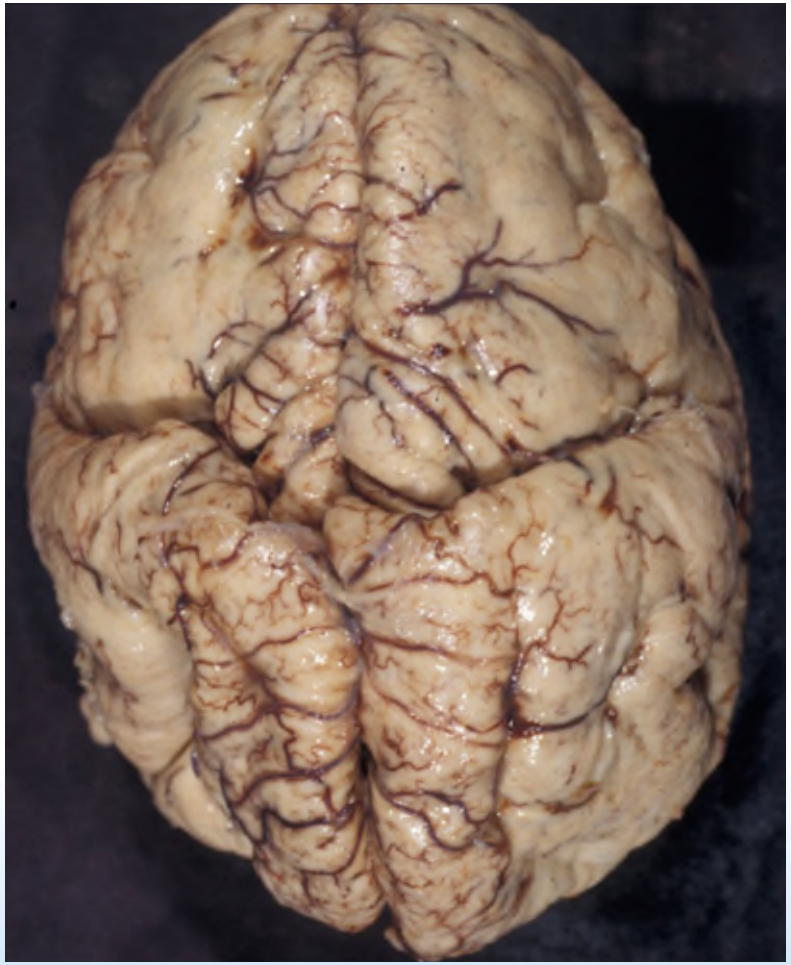


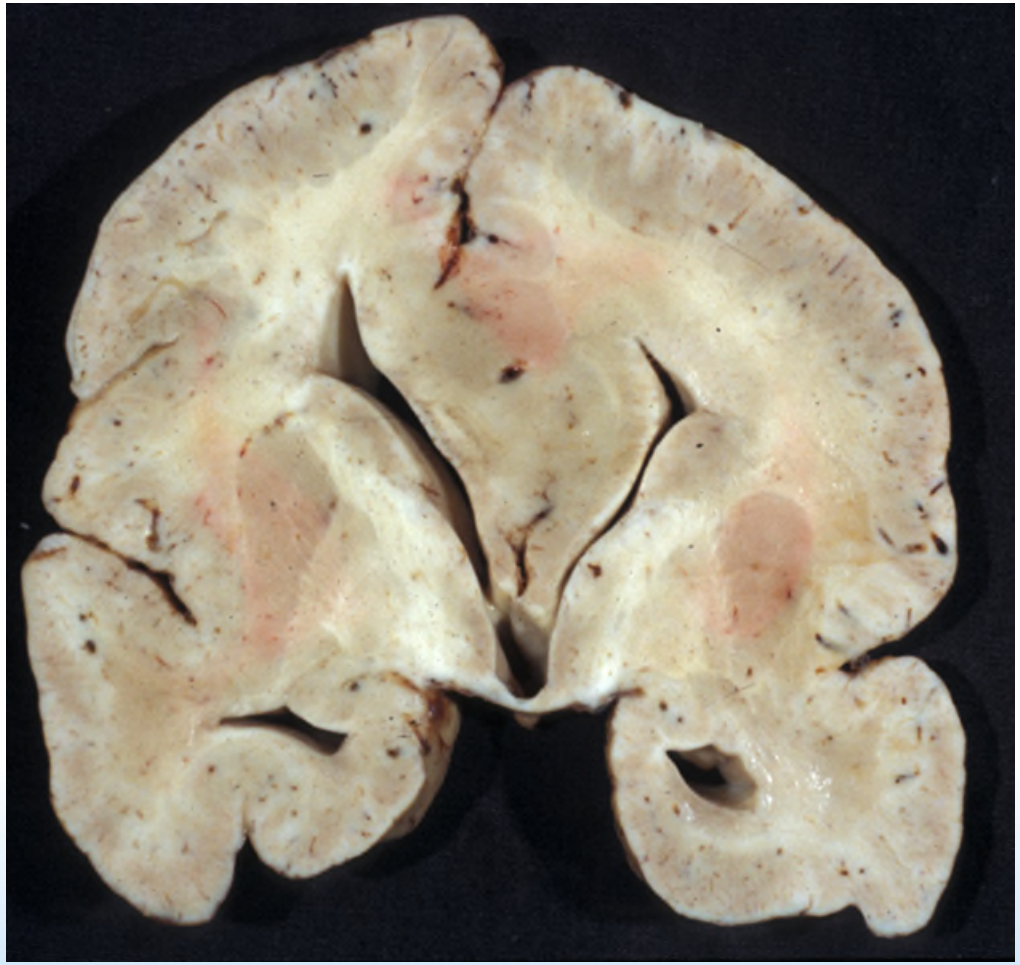
Images courtesy of Brian Harding, DPhil FRCPath

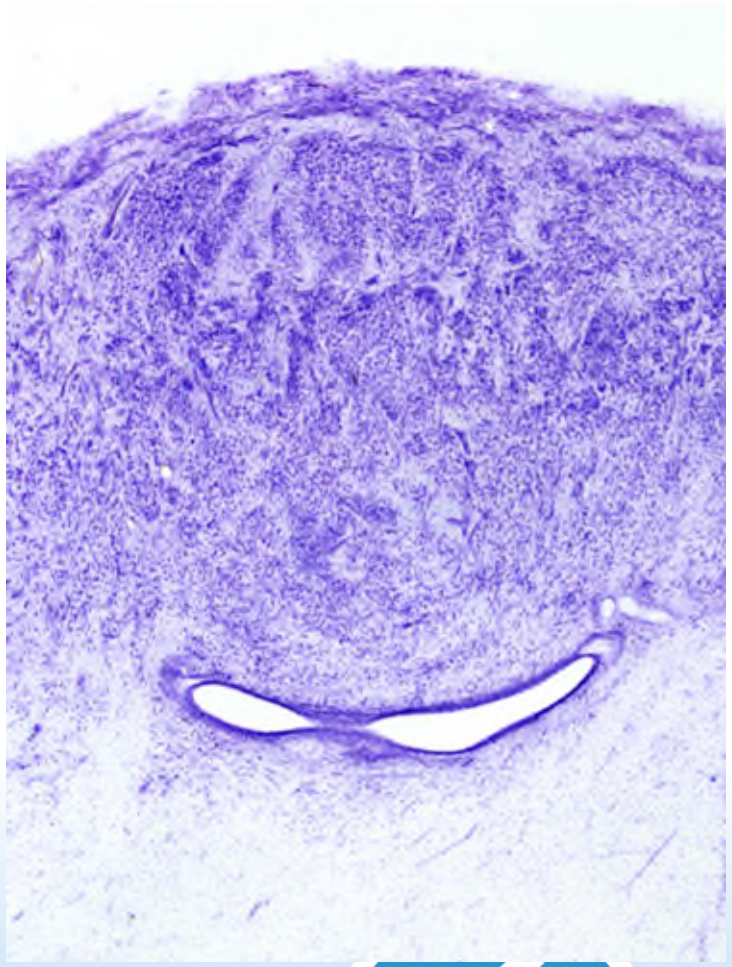
Lissencephaly Type II (Cobblestone)

- Autosomal recessive
- Cortex unlayered disorganized with cobblestone surface and thickened meninges
- Variable muscular and ocular involvement with CNS disorders

Lissencephaly Type II (Cobblestone)







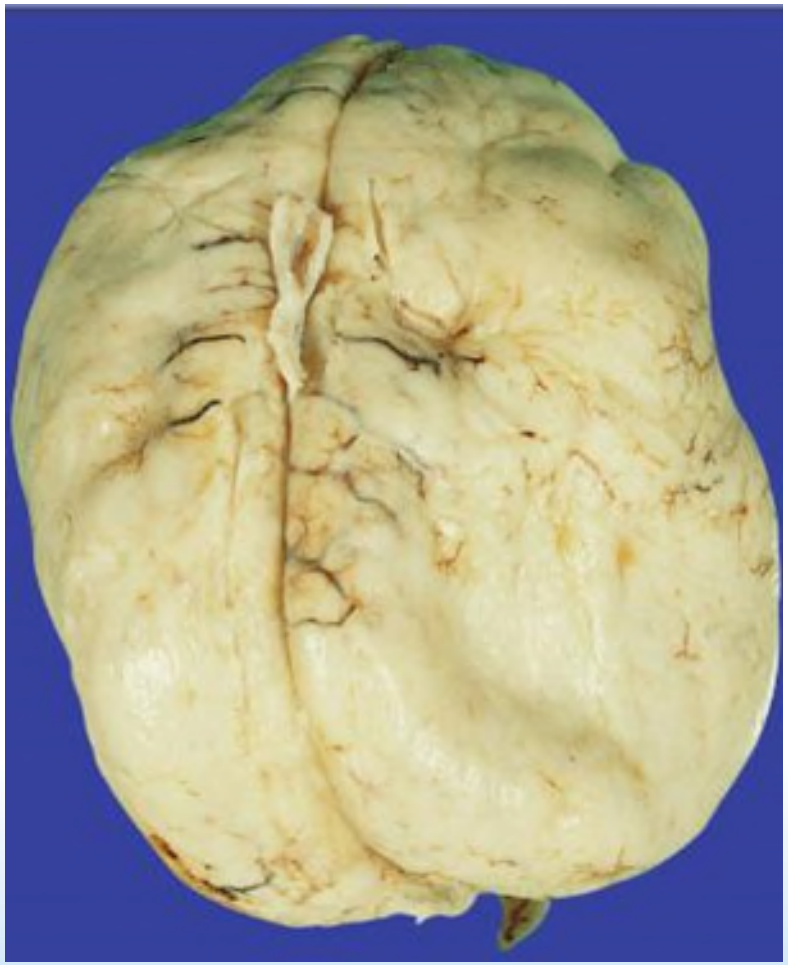
Disease	CNS	Gene	Function of product	Chromosome	Mouse model
Lissencephaly (type II): Fukuyama congenital muscular dystrophy	Cobblestone lissencephaly, polymicrogyria	*FCMD*	Fukutin: gene interrupted by retro-transposon insertion. A secreted protein, which may function as a glycosyl transferase in the Golgi	9q31	Targeted mutation of *FCMD* gene causes muscular dystrophy and cortical dysplasia
Lissencephaly (type II): muscle-eye-brain disease, type A, 5; type B, 5; type C, 5	Cobblestone lissencephaly, congenital myopia, glaucoma, retinal hypoplasia, mental retardation, hydrocephalus	*FKRP*	Protein targeted to the medial Golgi apparatus and necessary for posttranslational modification of dystroglycan	19q13.3	
Lissencephaly (type II): Walker-Warburg syndrome	Agyria, cobblestone lissencephaly, cerebellar dysplasia and vermal agenesis, hydrocephaly, occipital encephalocele	*POMT1* *POMT2*	O-mannosyl transferase 1: first enzyme in synthetic pathway of O-mannosyl glycans	9q31-q33 14q24.3	Large(myd) mutant and targeted mutation of α dystroglycan gene provide models of Walker-Warburg syndrome
Lissencephaly (type II): muscle-eye-brain disease	Cobblestone lissencephaly, congenital myopia, glaucoma, retinal hypoplasia, mental retardation, hydrocephalus	*POMGnT1*	O-mannose β-1,2-N-acetyl glucosaminyl transferase: second enzyme in synthetic pathway of O-mannosyl glycans	1p34-p33	Targeted mutation of POMGnT1 gene causes phenotype resembling muscle-eye-brain disease
Lissencephaly (type II): muscle-eye-brain disease	Cobblestone lissencephaly, congenital myopia, glaucoma, retinal hypoplasia, mental retardation, hydrocephalus	*LARGE*	Interacts directly with dystroglycan to allow glycosylation	22q12	

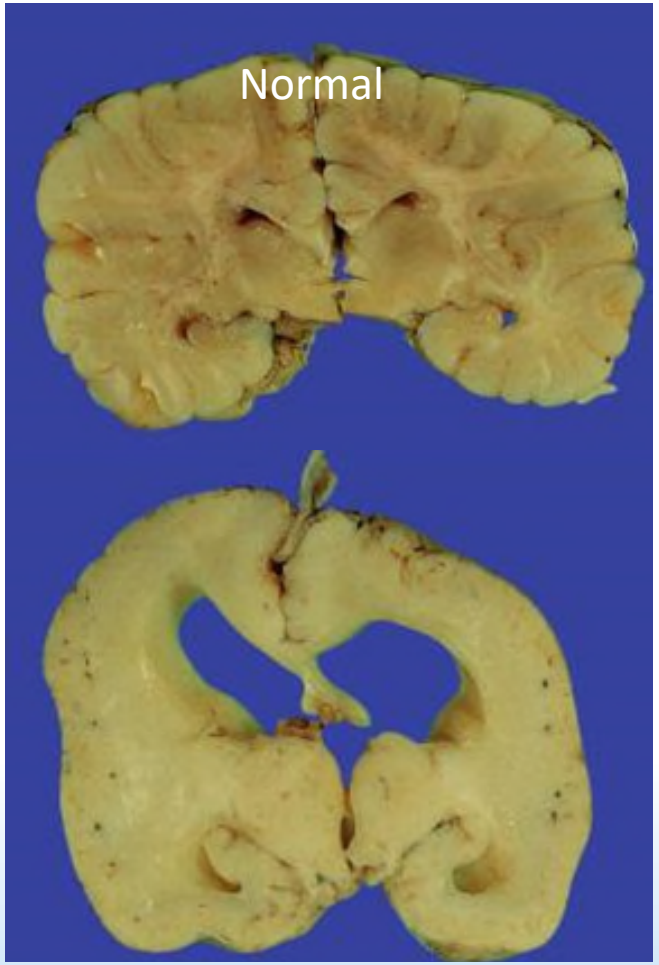
Lissencephaly Type II

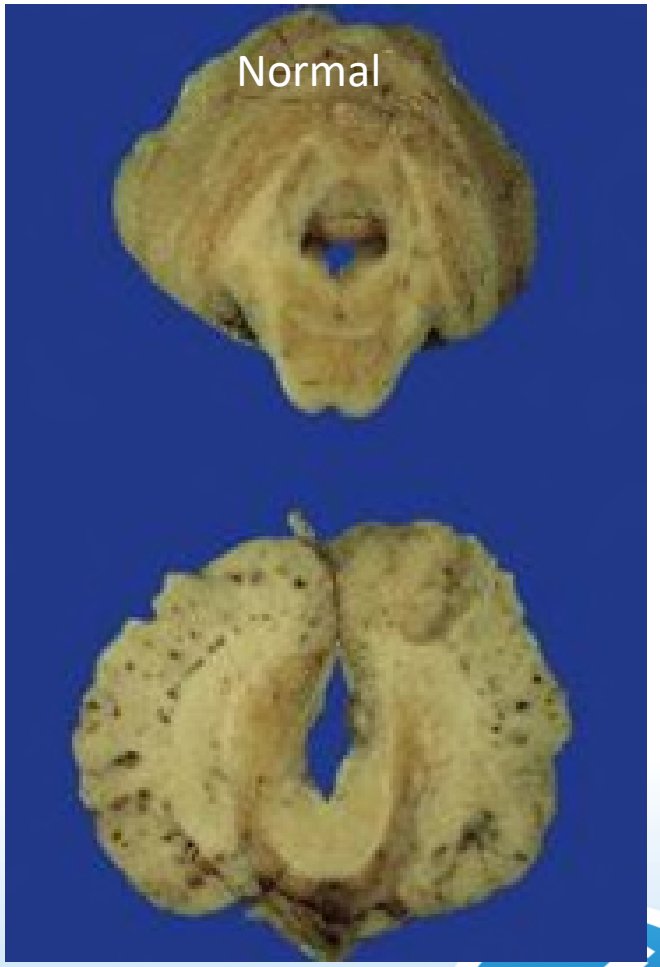
- Walker–Warburg syndrome
  - AKA HARD+E syndrome (hydrocephalus, agyria, retinal dysplasia, encephalocele) and cerebro-ocular dysplasia–muscular dystrophy syndrome
  - Cobblestone lissencephaly, cerebellar dysplasia and vermal agenesis, hydrocephaly, occipital encephalocele, congenital muscular dystrophy
  - Variety of ocular anomalies
  - Die in infancy
  - Associated with mutations in *POMT1* and *POMT2* genes

- Muscle-Eye-Brain disease
  - Generalized muscle weakness, contractures, seizures, eye anomalies, cobblestone lissencephaly
  - Associated with mutations in *POMGnT1*, *LARGE*, and *FKRP*

Lissencephaly Type II:Walker–Warburg syndrome







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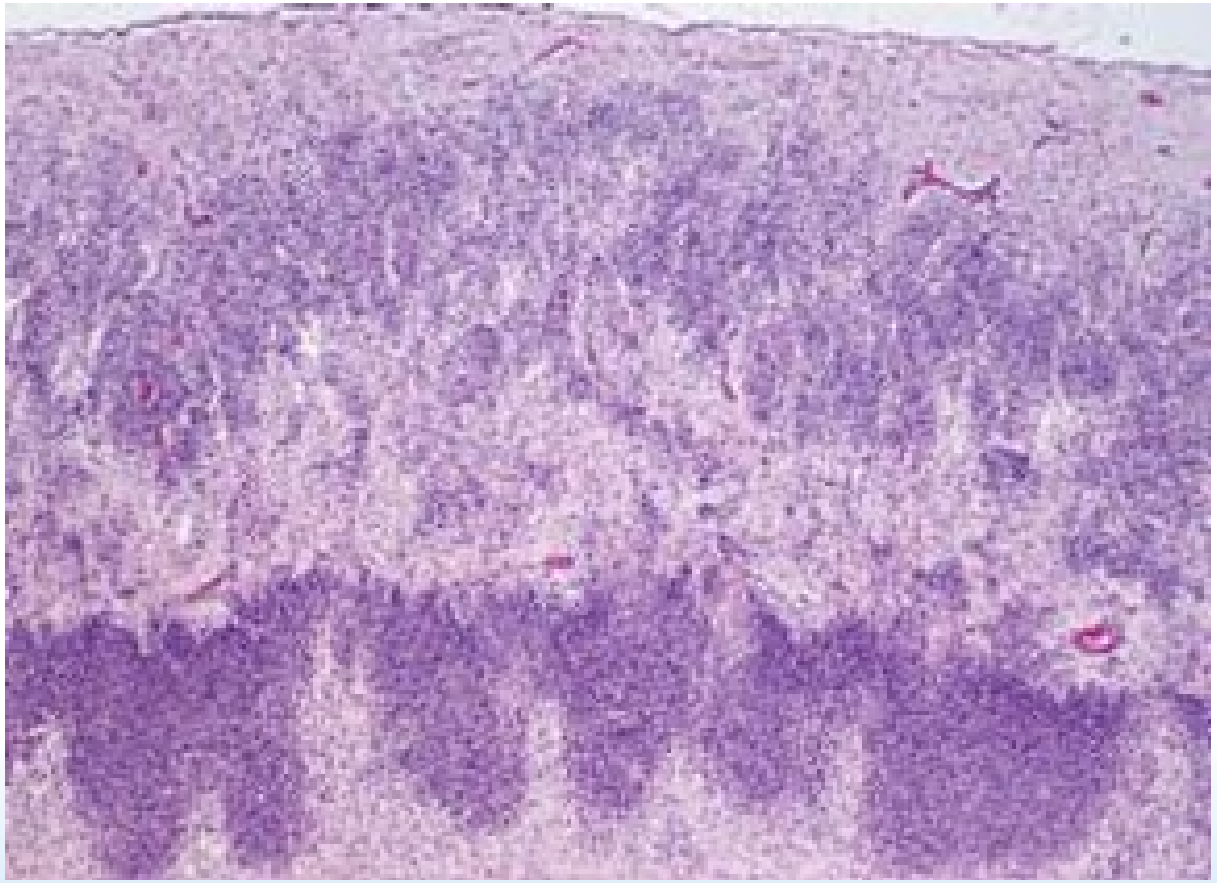
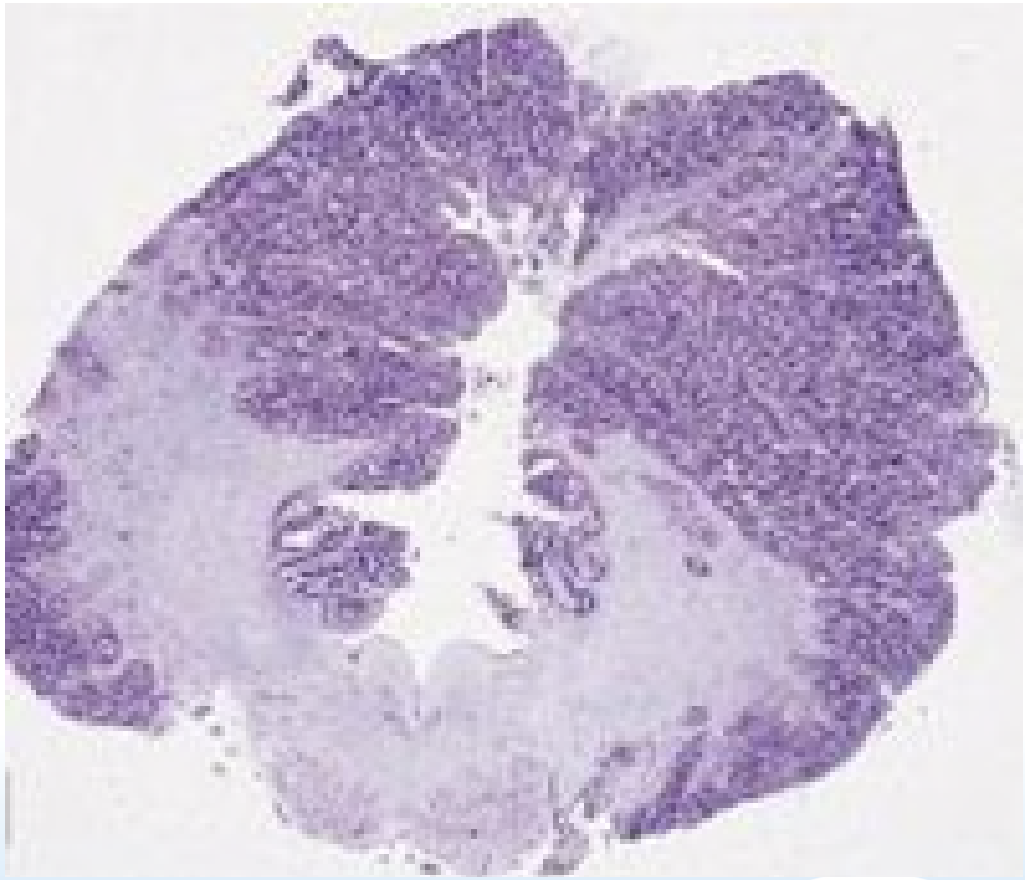
LISSENCEPHALY TYPE II: WALKER–WARBURG SYNDROME





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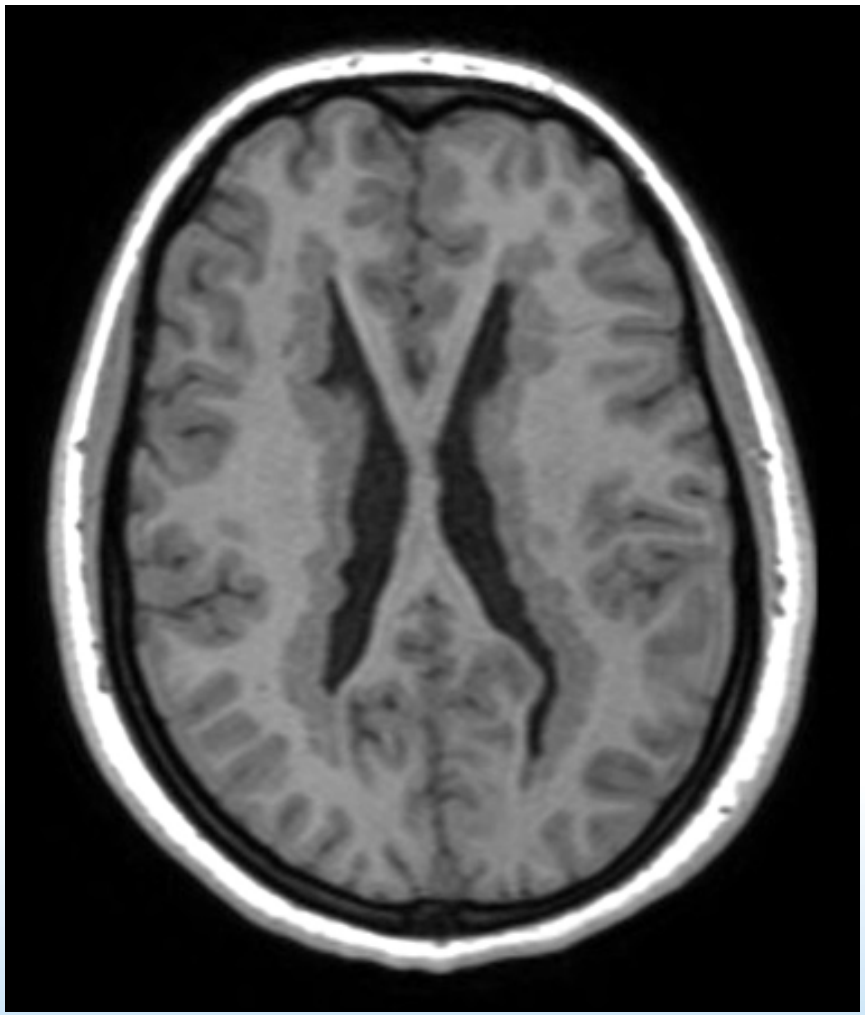
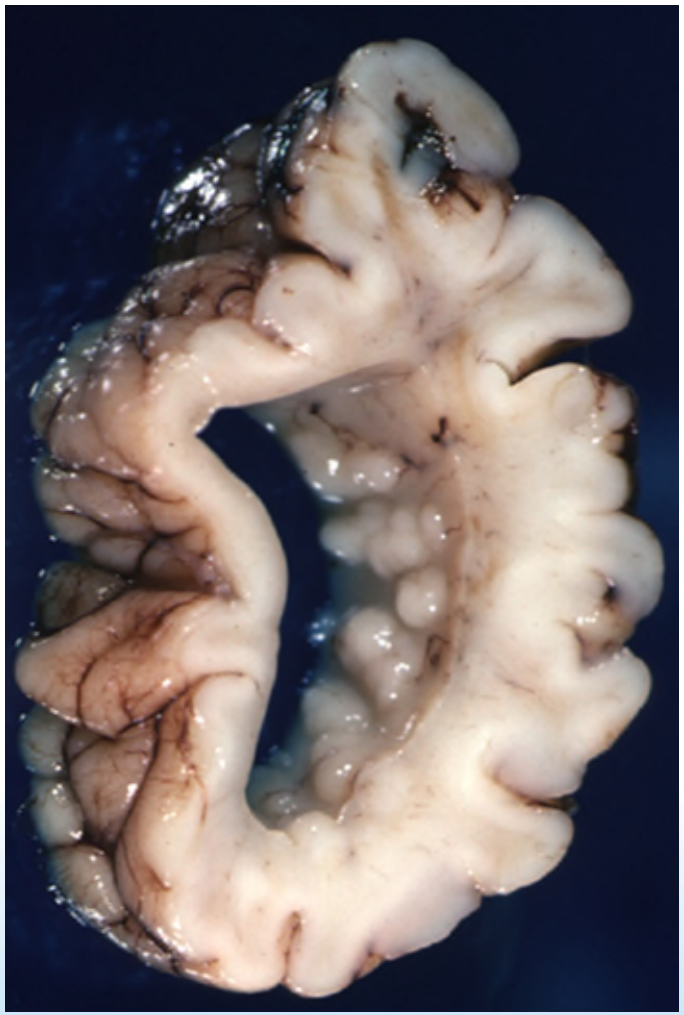
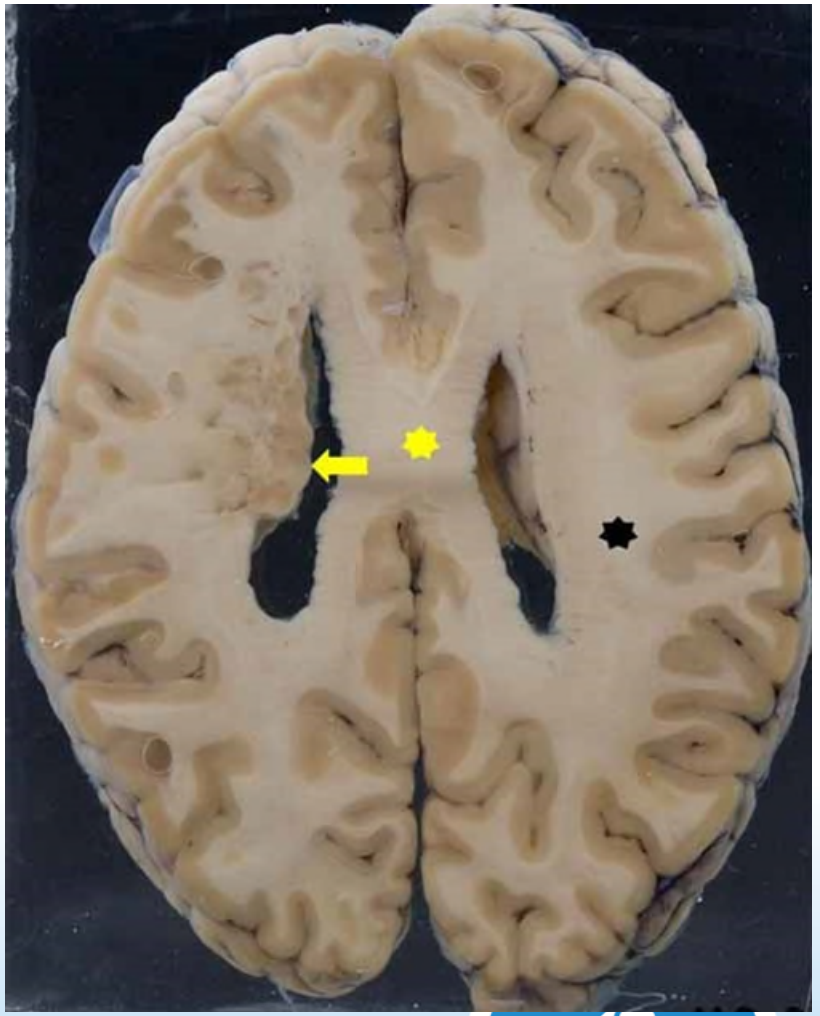
Gray Matter Heterotopia

- Clusters of neurons and glia that form a region of gray matter in an abnormal location
- May be single or multiple, line ventricles, in deep white matter, subcortical white matter, leptomeninges
- Overlying cortex can be normal or disrupted
- May have normal intelligence and normal neurologic exam

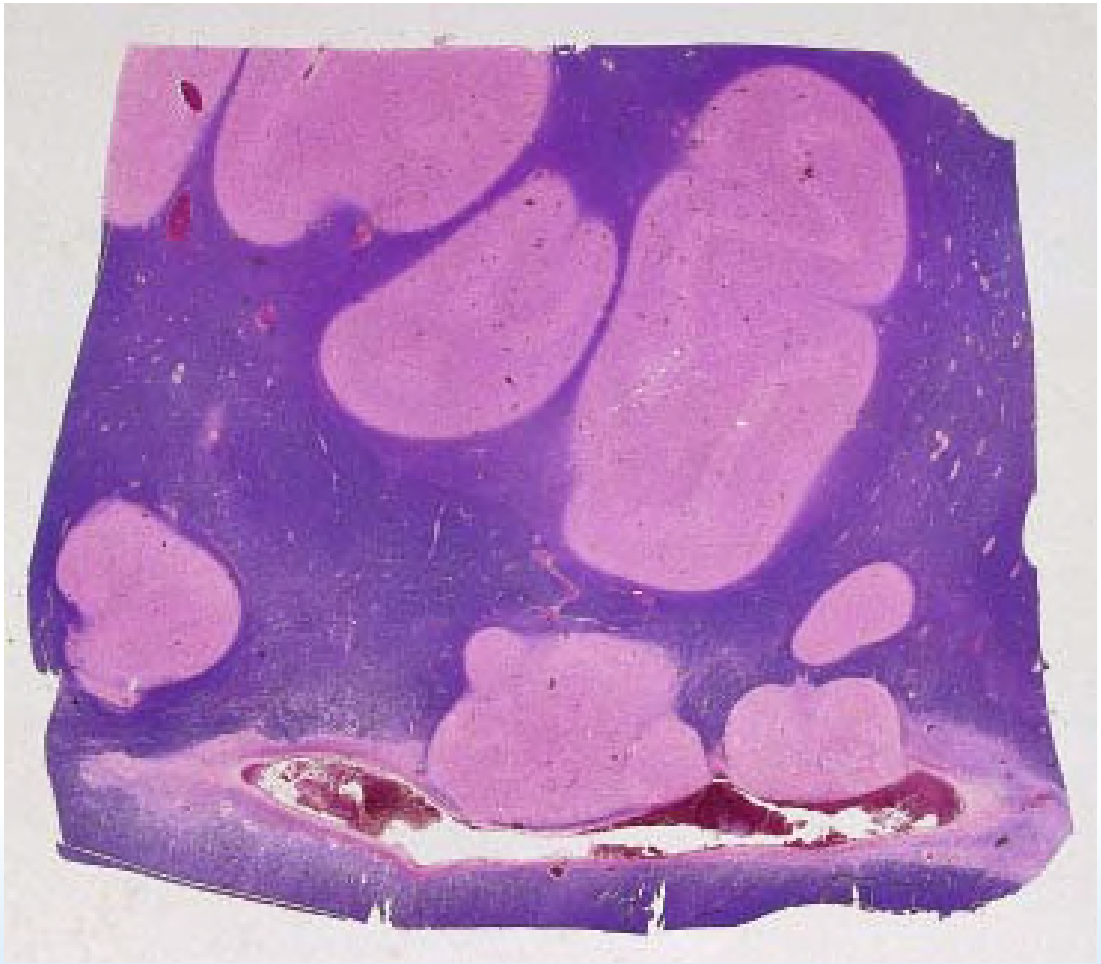
Nodular Heterotopia

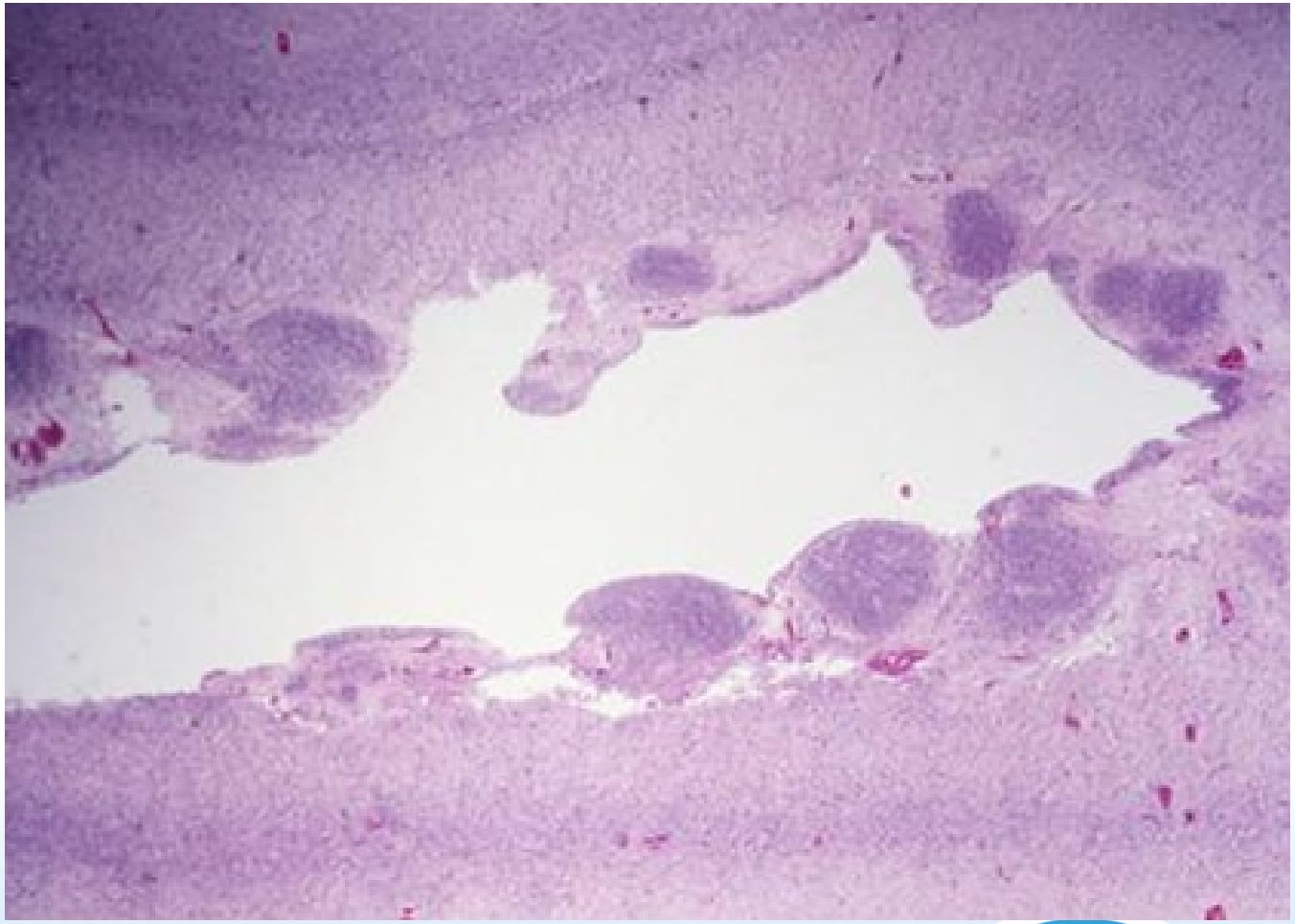






NODULAR HETEROTOPIA





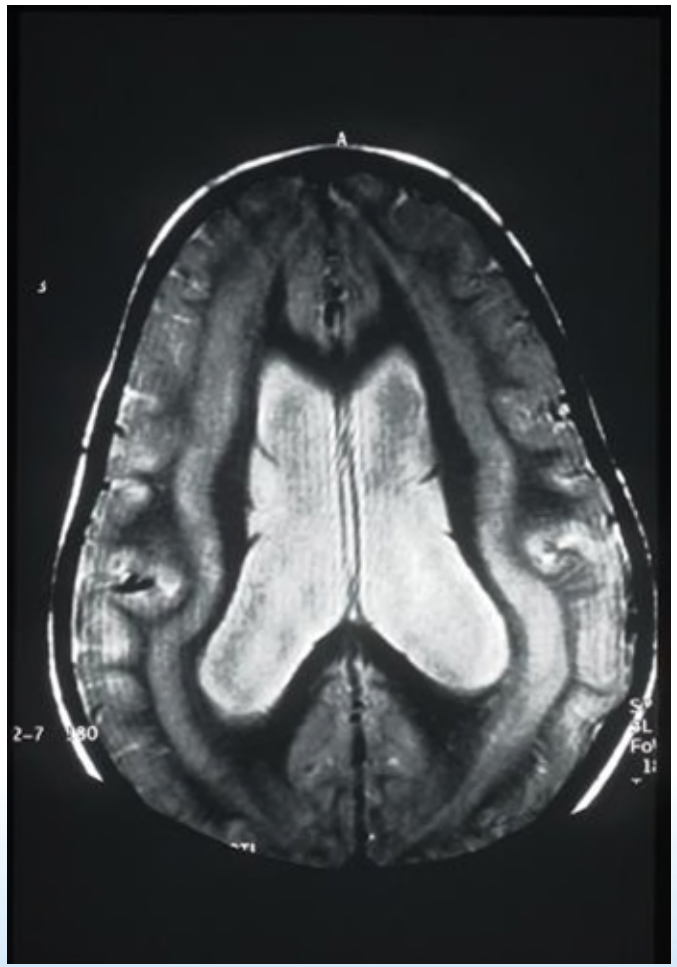
Nodular Heterotopias: Etiology

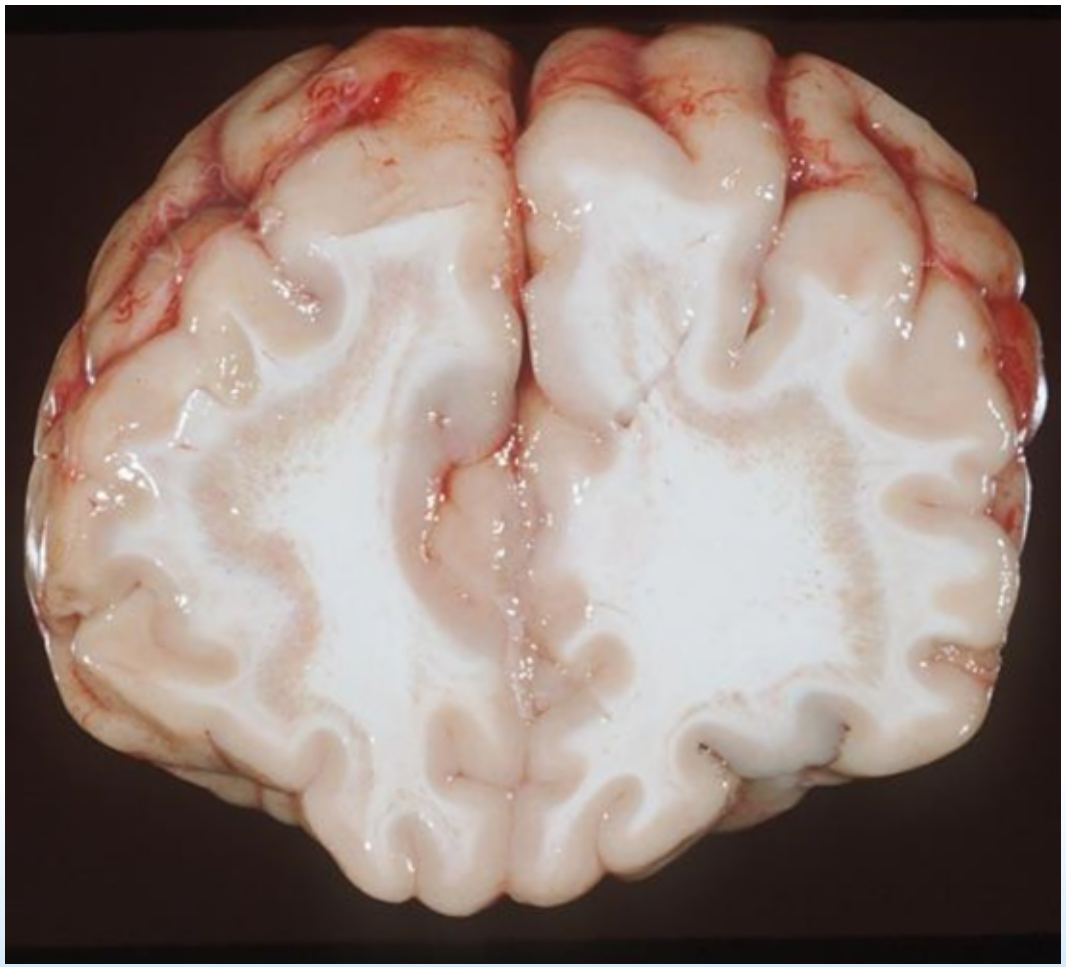
- Reported following fetal insults:
  - Sustained maternal hyperthermia
  - Methylmercury poisoning
  - Radiation
- Familial subependymal heterotopia usually found in females:
  - Consistent with X-linked dominant inheritance (lethal in males)
  - Strong correlation with epilepsy
  - Mutations in *Filamin 1 (FLNA)* on Xq28 → actin binding protein associated with cytoskeleton and is important for cell migration
- Periventricular nodular heterotopia with microcephaly
  - Mutation in *ARFGEF2*
  - Autosomal recessive

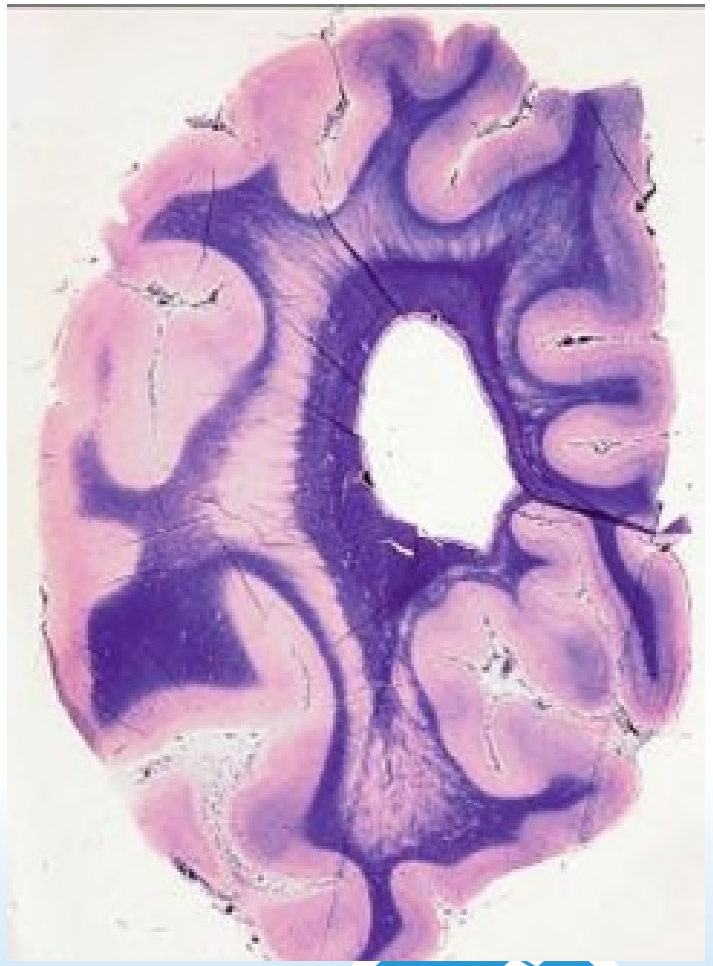
Band (Laminar) Heterotopia

- Bilateral bands of heterotopic gray matter in the white matter located between the lateral ventricular walls and the cortex
  - Overlying cortex may be normal or have simplified gyral pattern
  - Mild to moderate mental retardation
  - Seizures, often with later onset

Band Heterotopia







Images courtesy of Brian Harding, DPhil FRCPath

Band Heterotopia

- Rare, non-lethal
  - May cause epilepsy
- Predominantly in females
- *DCX* mutations detected in many patients

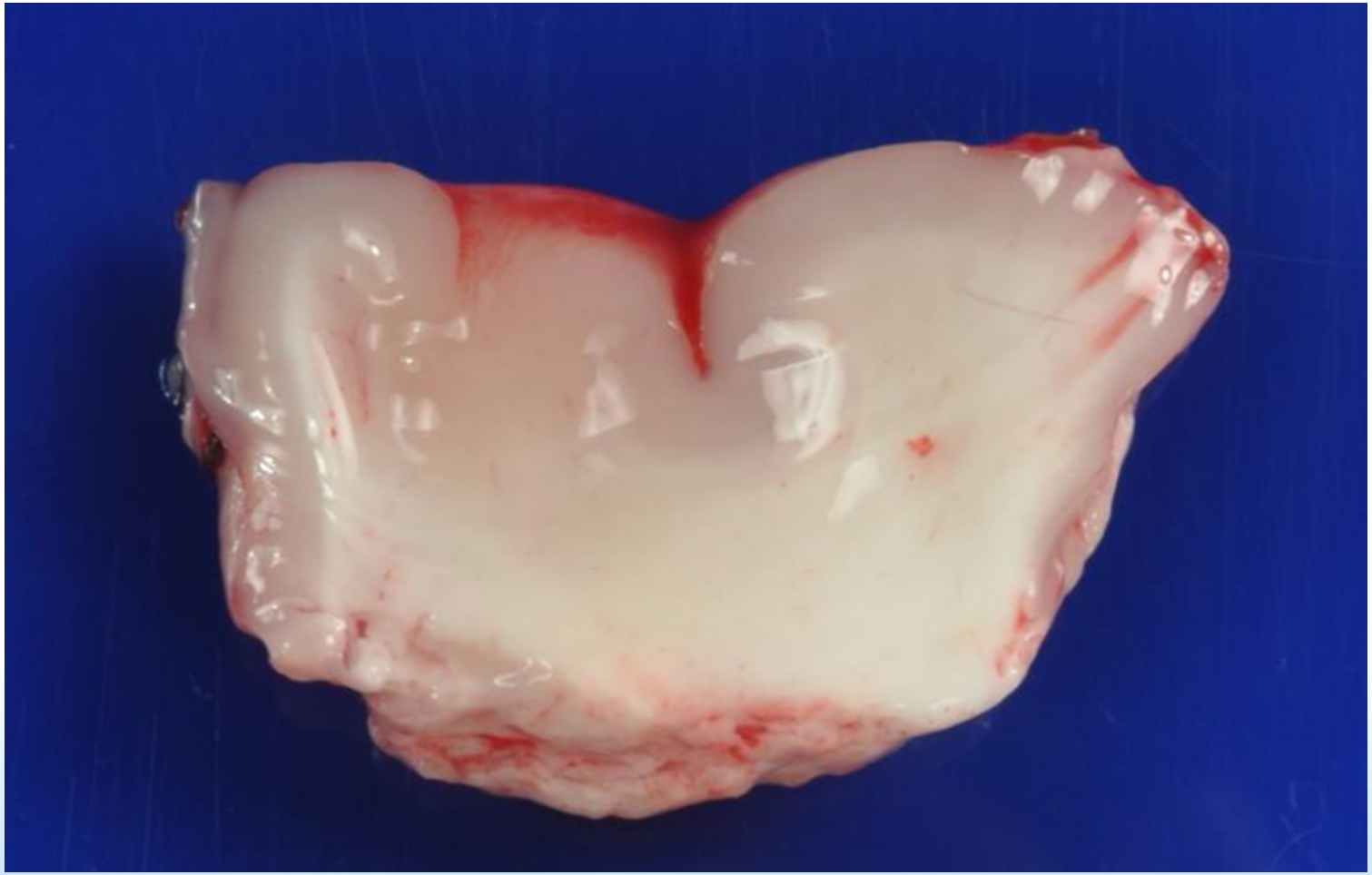
Cortical Dysplasia with Cytomegaly

- Focal cortical dysplasia
- Tuberous Sclerosis

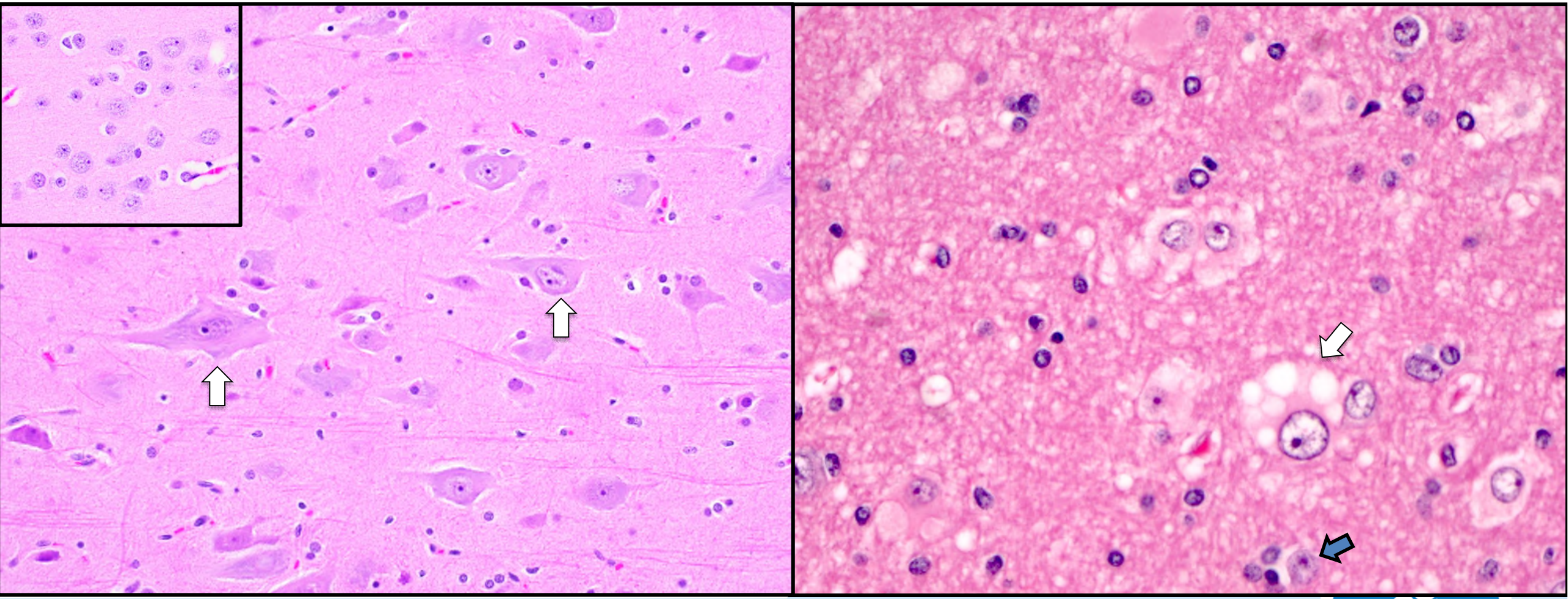
Focal Cortical Dysplasia

Three-tiered ILAE classification system of focal cortical dysplasia (FCD)	
Type I	**Isolated FCD**
Ia	Abnormal radial cortical lamination
Ib	Abnormal horizontal cortical lamination
Ic	Abnormal radial and horizontal cortical lamination
Type II	**Isolated FCD**
IIa	Dysmorphic neurons
IIb	Dysmorphic neurons and balloon cells
Type III	**Cortical lamination abnormalities associated with principal lesion**
IIIa	FCD in the temporal lobe + hippocampal sclerosis
IIIb	FCD adjacent to a glial or glioneuronal tumor
IIIc	FCD adjacent to a vascular malformation
IIId	FCD adjacent to an acquired lesion (ex. trauma, ischemic injury)

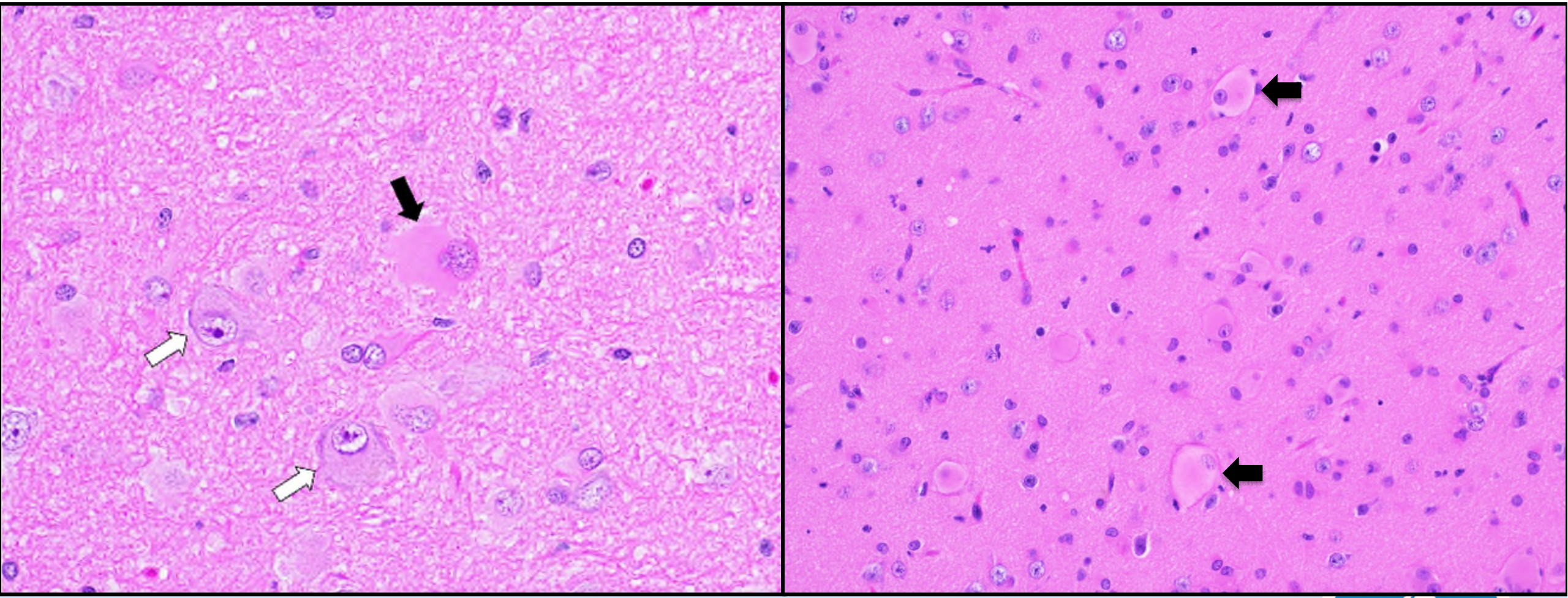
Focal Cortical Dysplasia



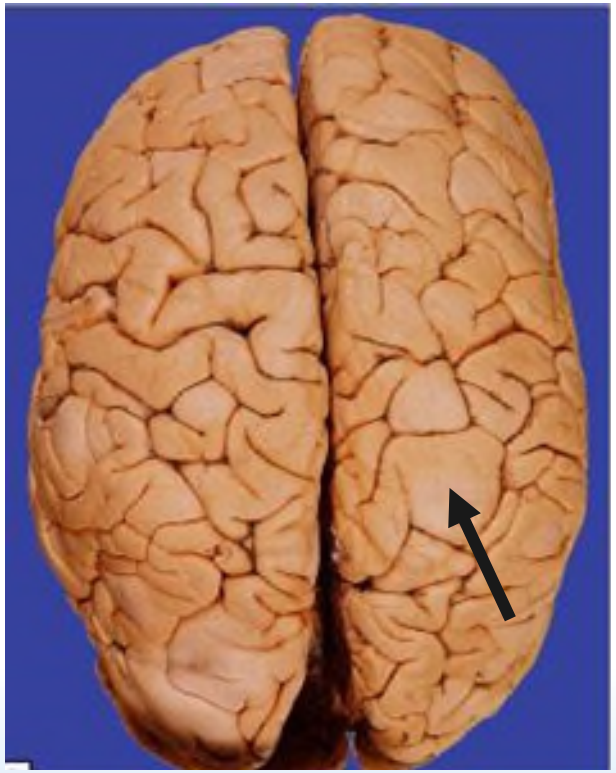
Focal Cortical Dysplasia, Type IIa

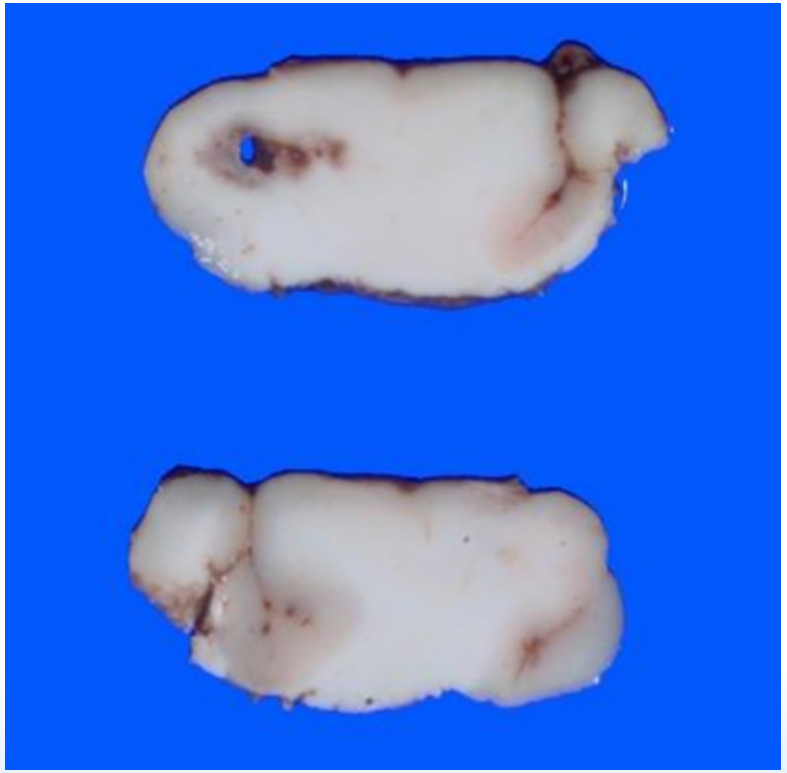


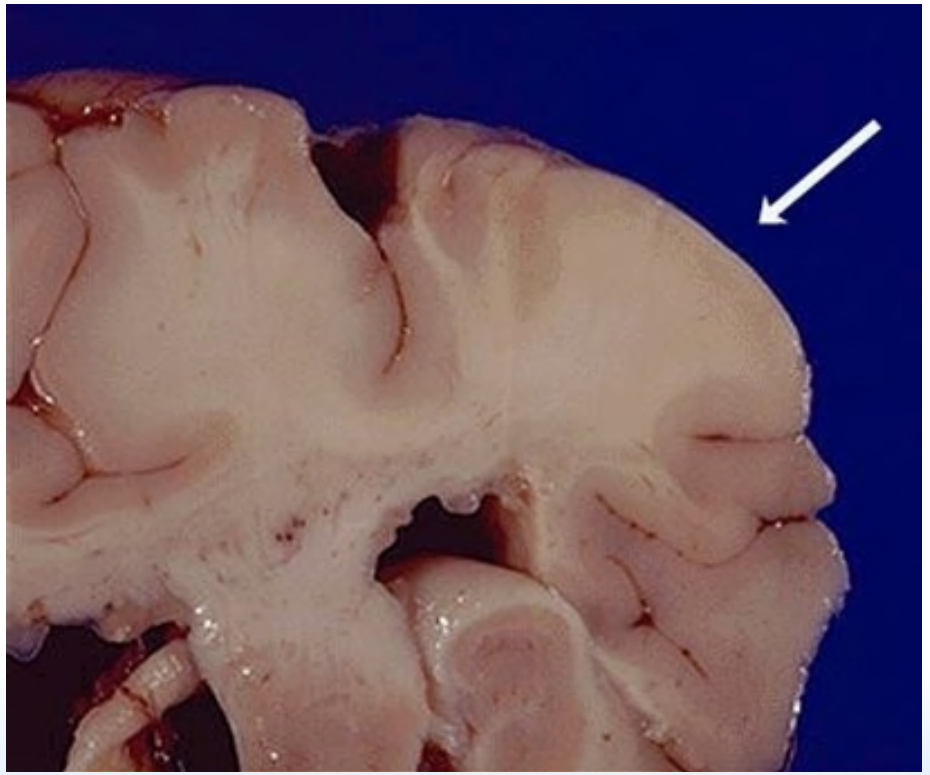
Focal Cortical Dysplasia, Type IIb



Tuberous Sclerosis







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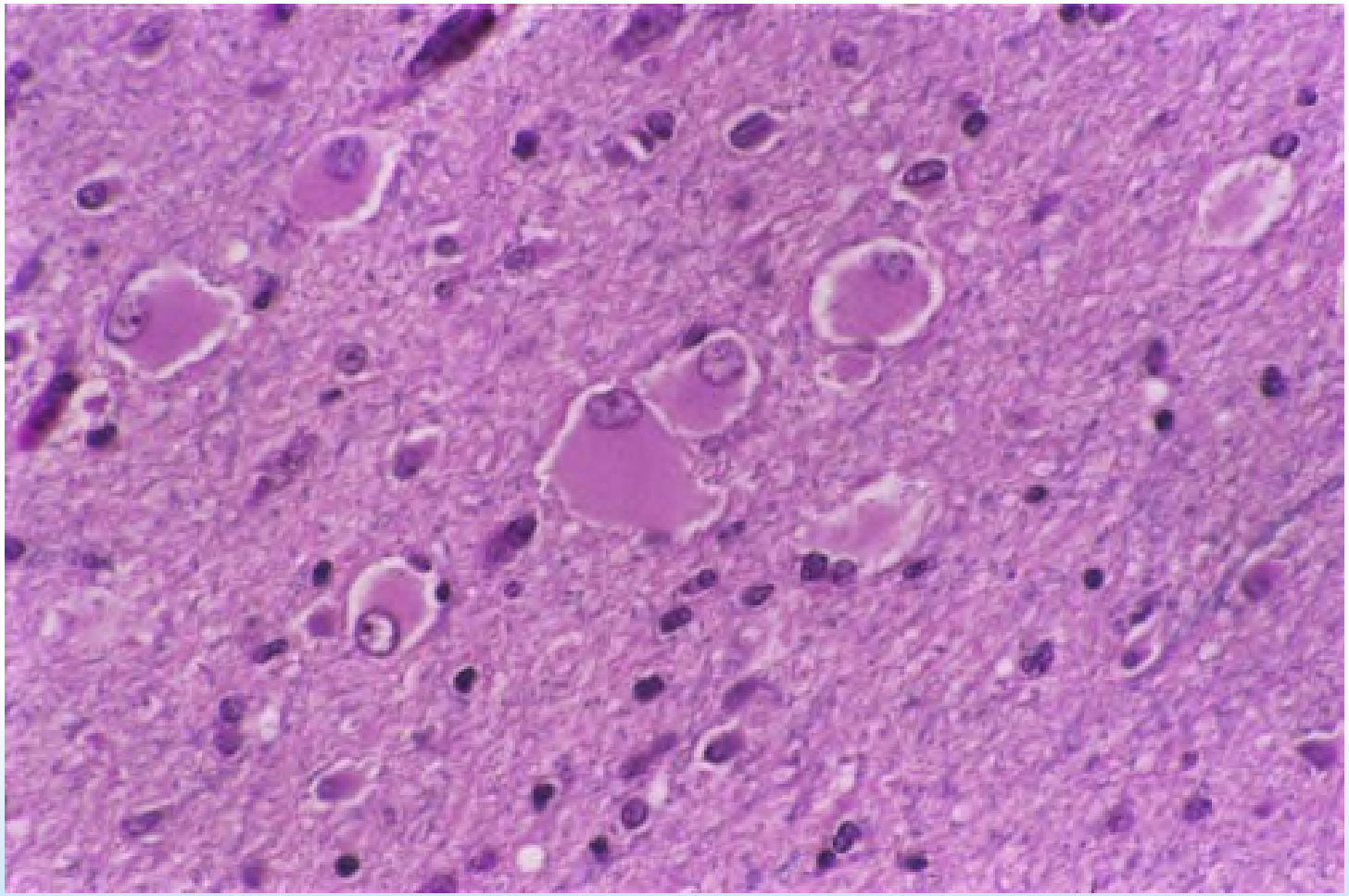
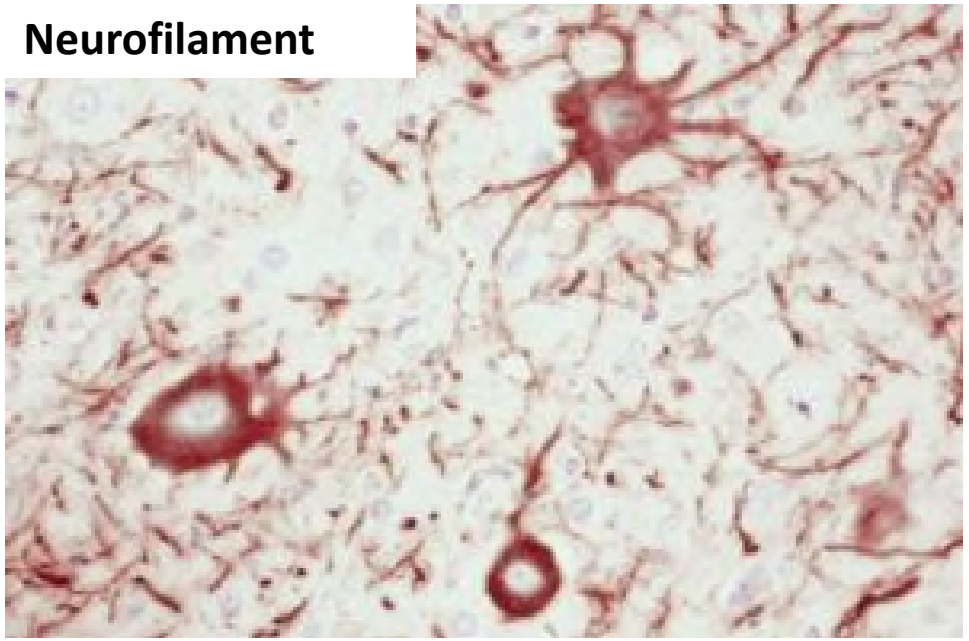
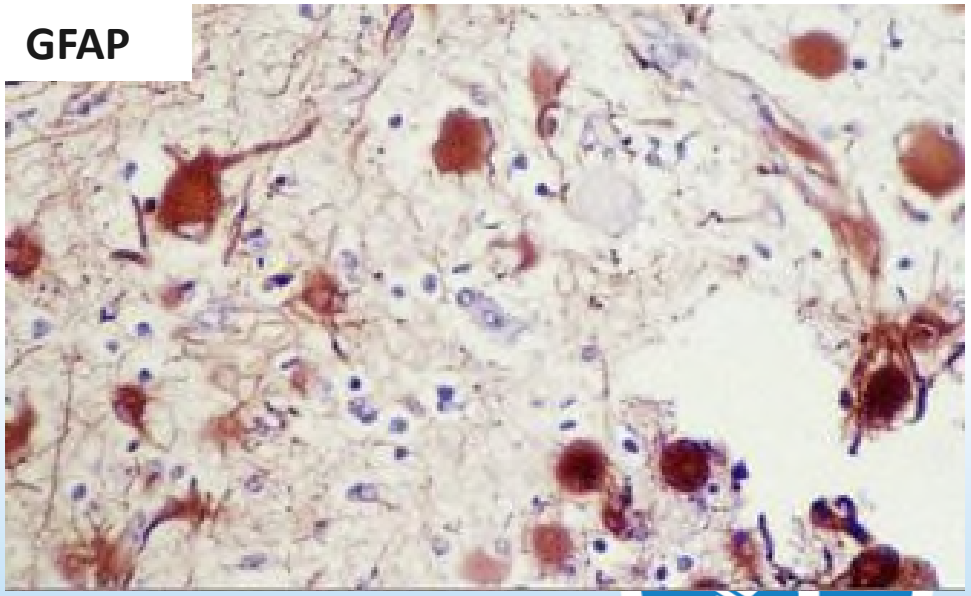
Tuberous Sclerosis



Neurofilament



GFAP

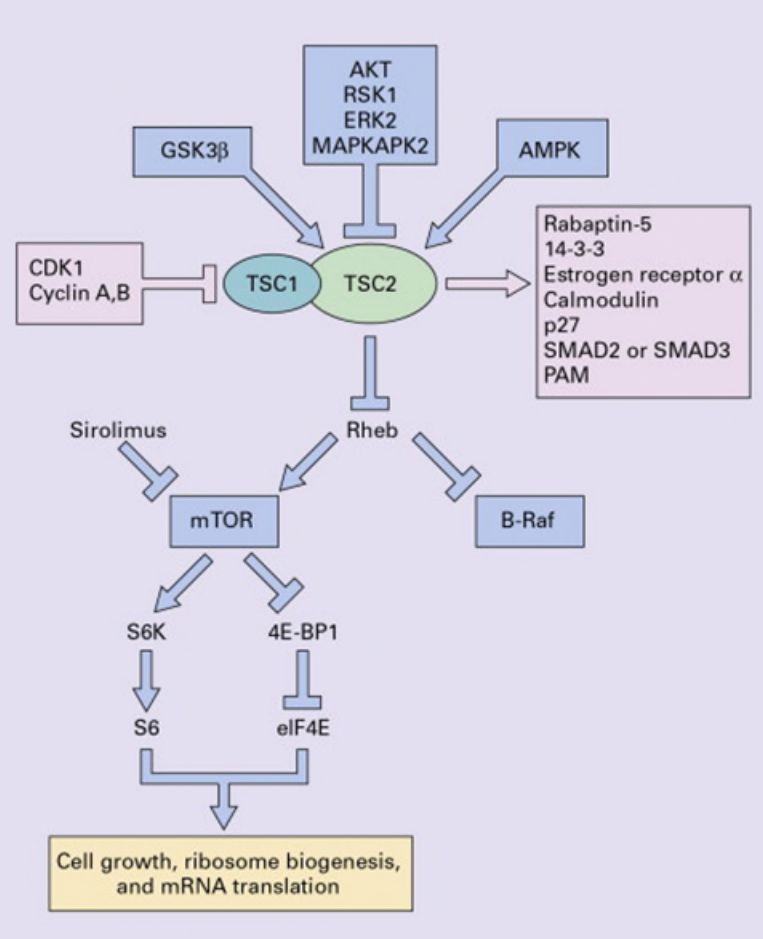


Images courtesy of Brian Harding, DPhil FRCPath; Figure 7.1-5, Pediatric Neuropathology: A Text-Atlas

Tuberous Sclerosis: etiology

- Locus heterogeneity with disease-determining genes:
  - *TSC1* on chromosome 9 (protein = hamartin)
  - *TSC2* on chromosome 16 *(*protein = tuberin)

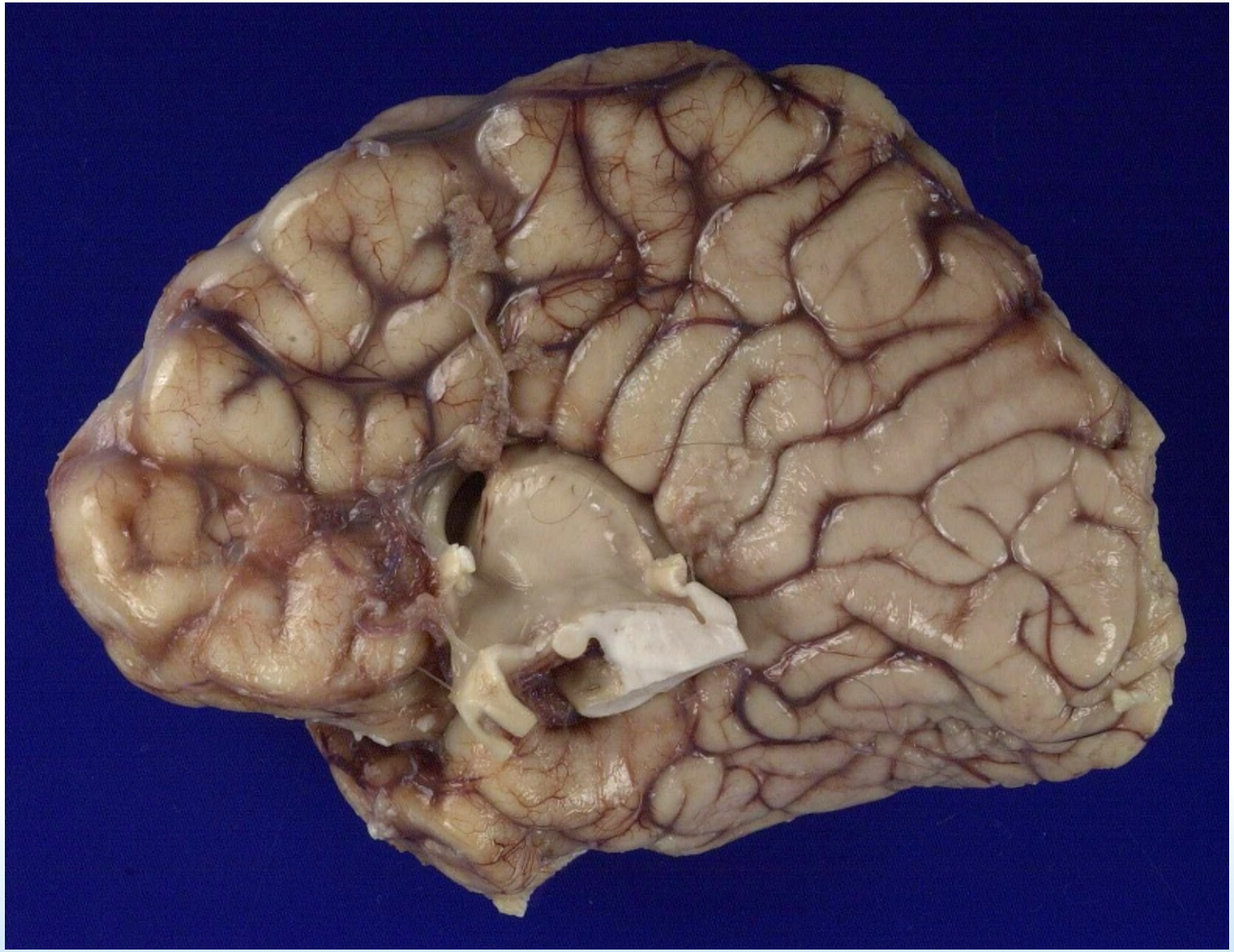
- *TSC1* and *2* gene products are strategically important in cell growth and turnover
  - Thought to be tumor suppressors
  - Mutations lead to hyperactivation of the mTOR signaling pathway

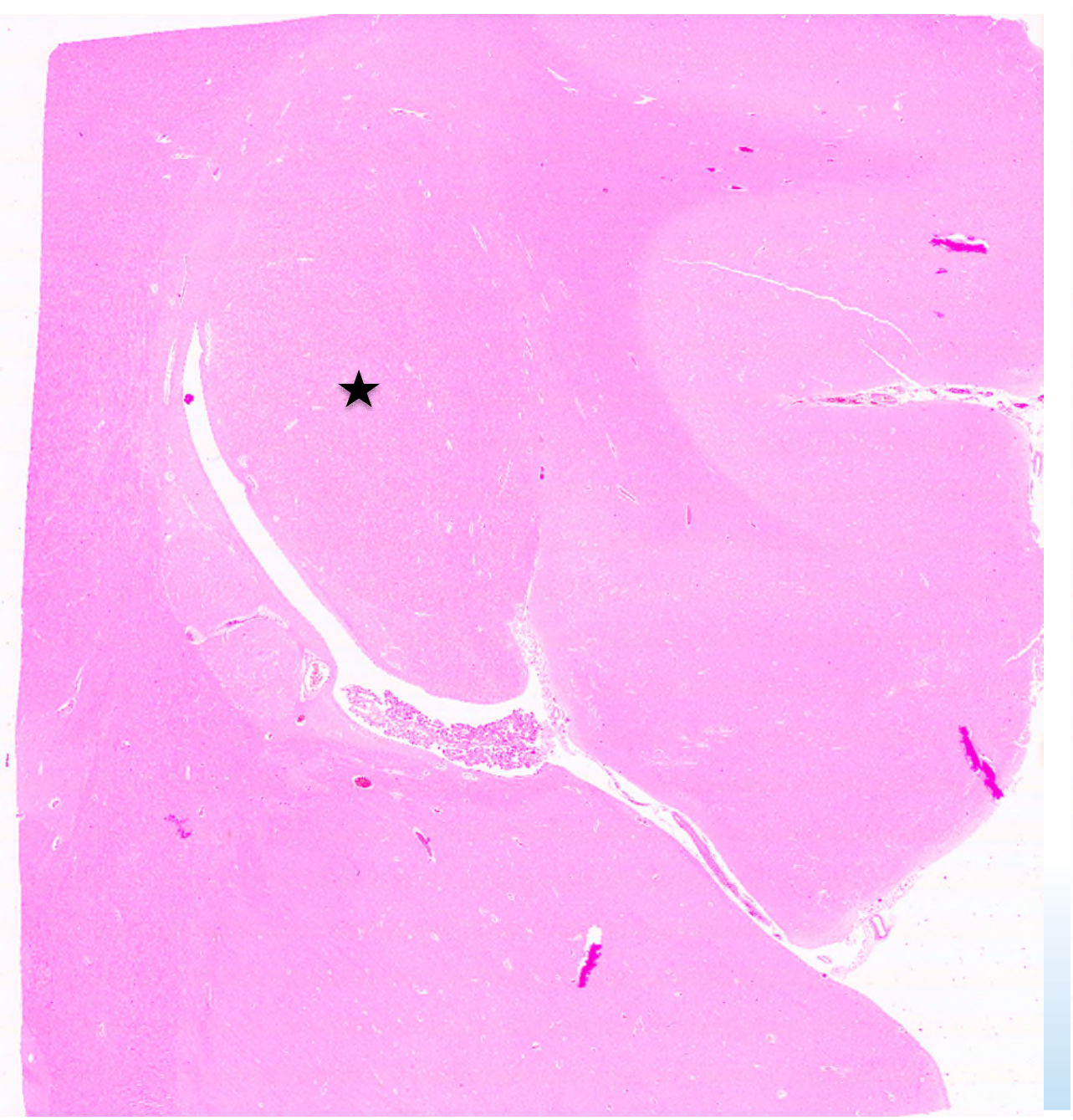


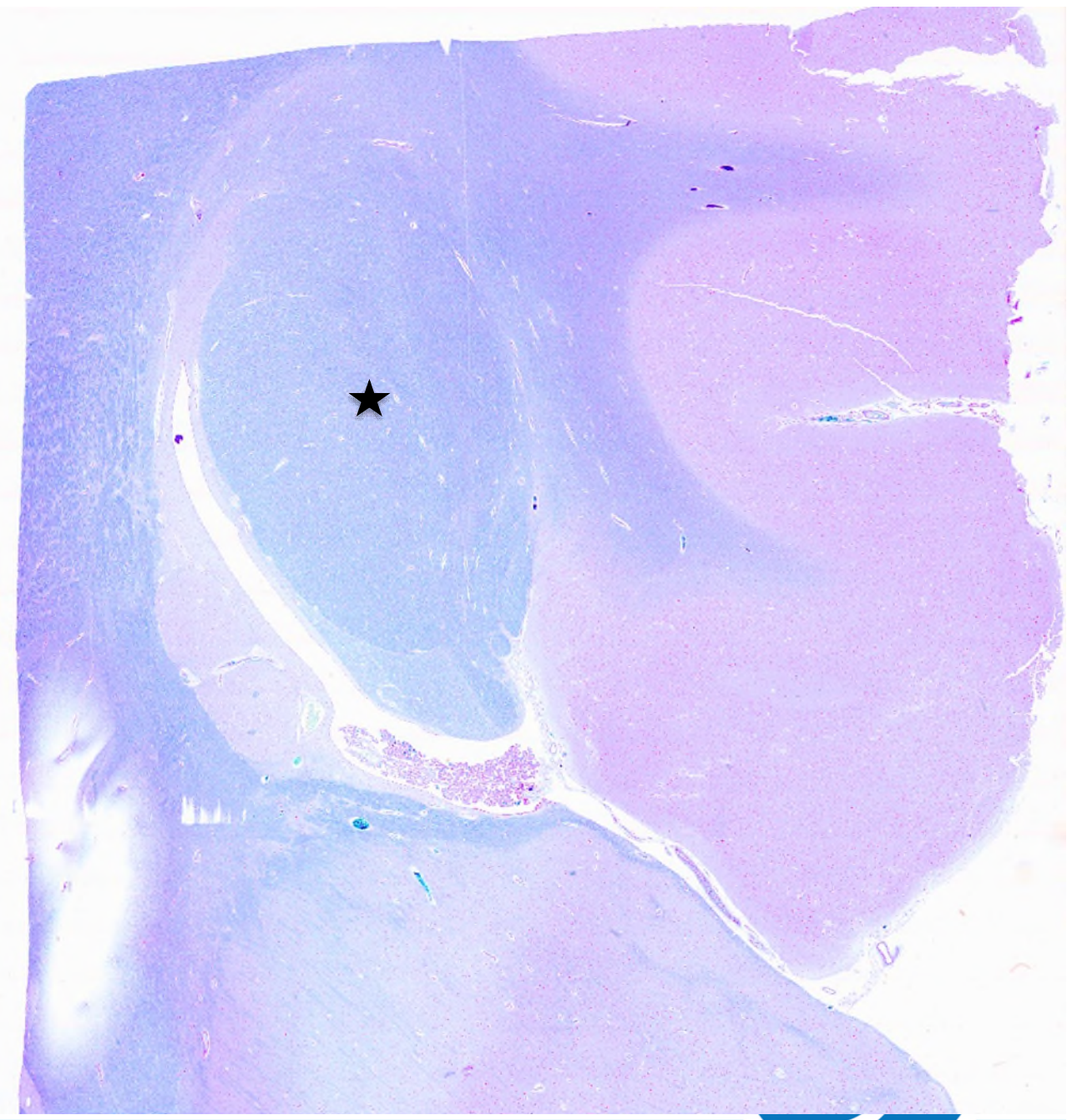
Crino PB, Nathanson KL, Henske EP. *N Engl J Med* 2006; 355(13):1345–1356.)

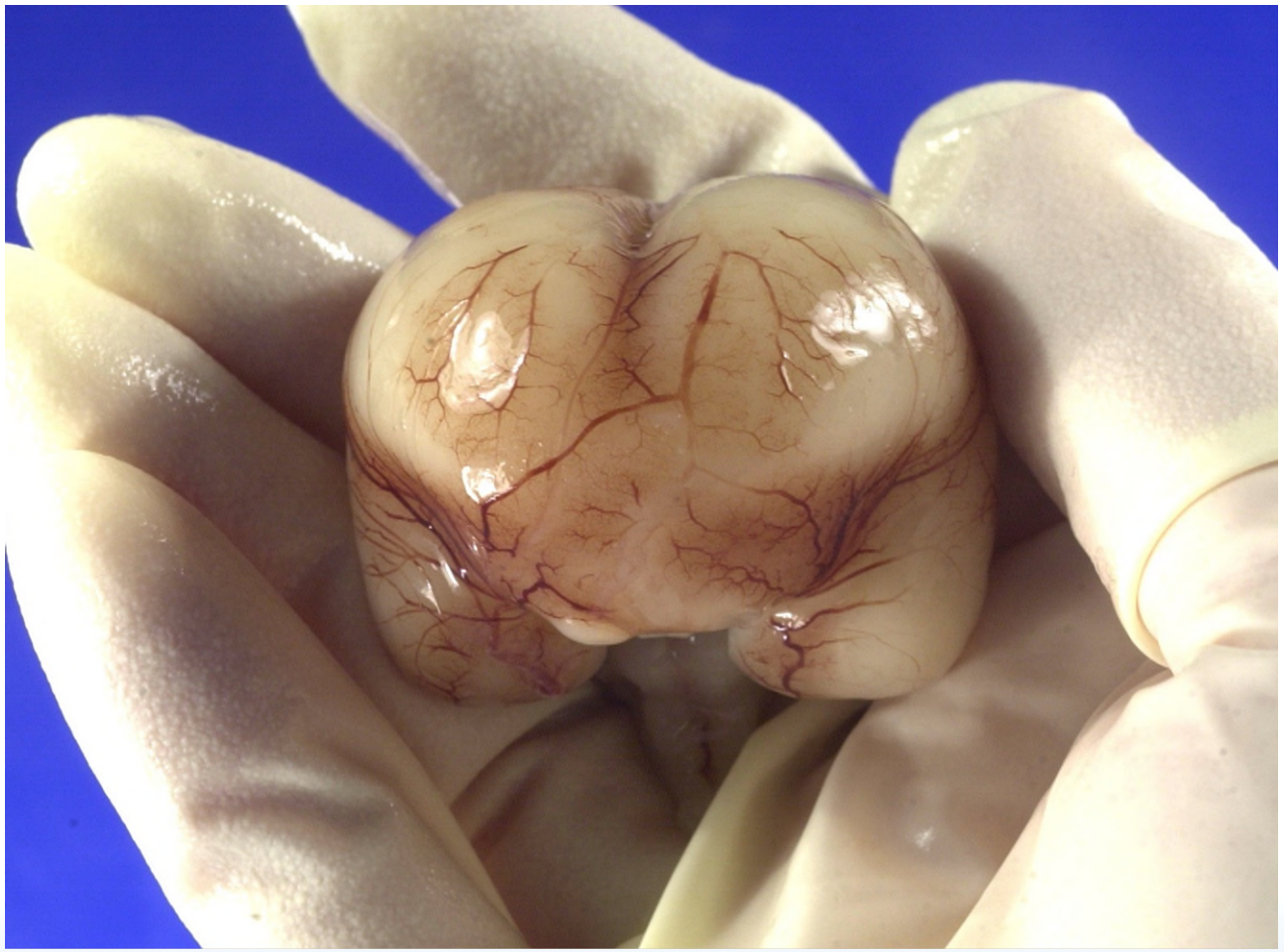
Virtual Slides

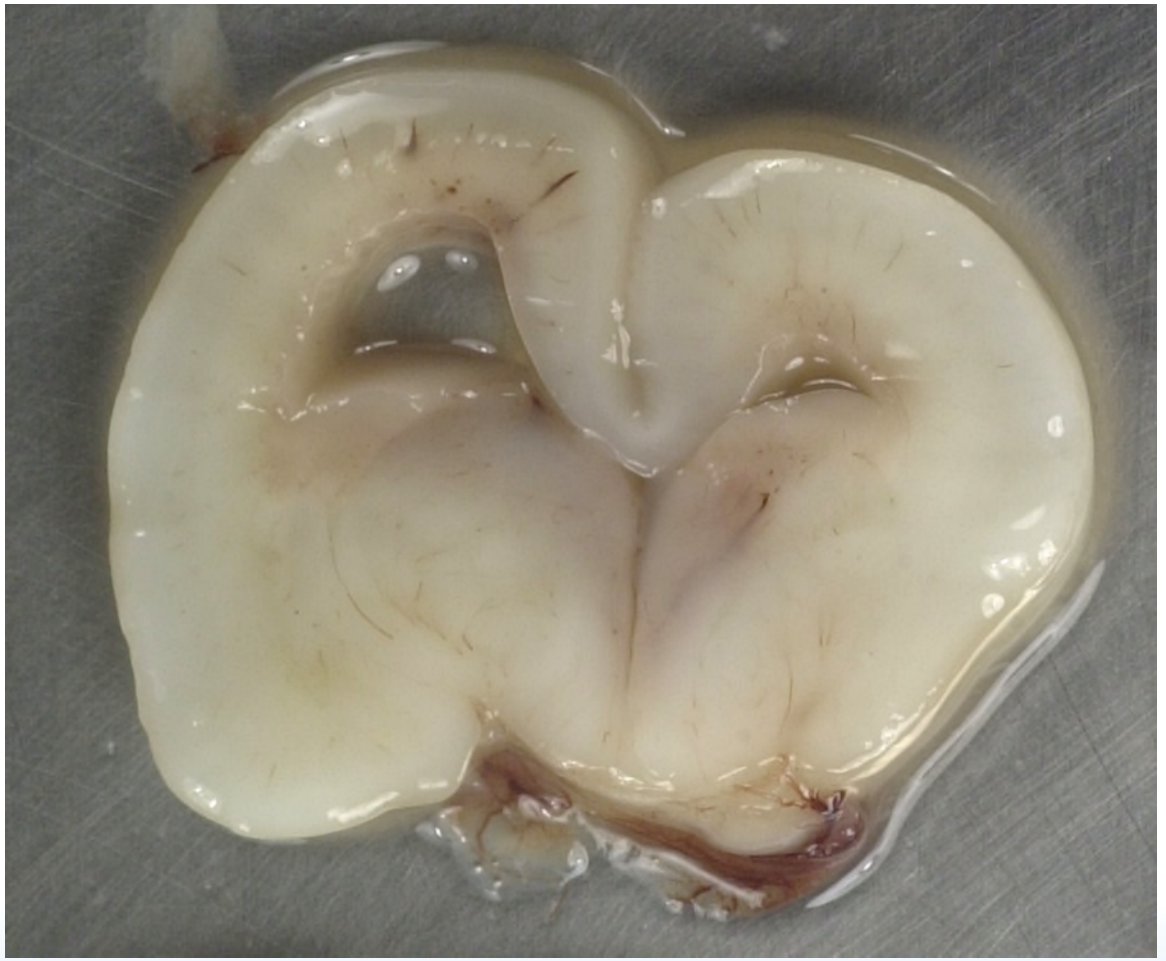
https://pathpresenter.net/#/public/display?token=bbc29011

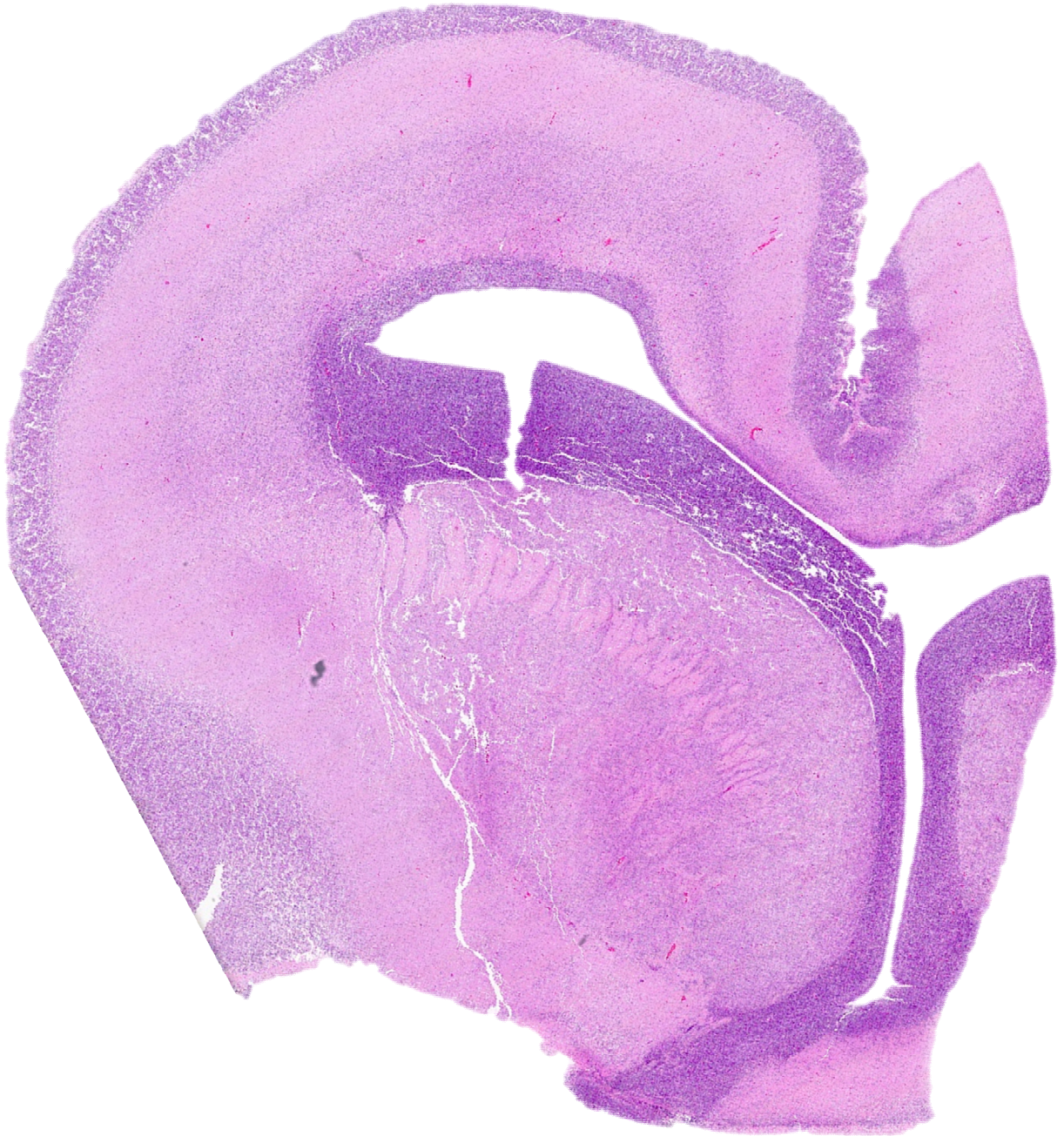


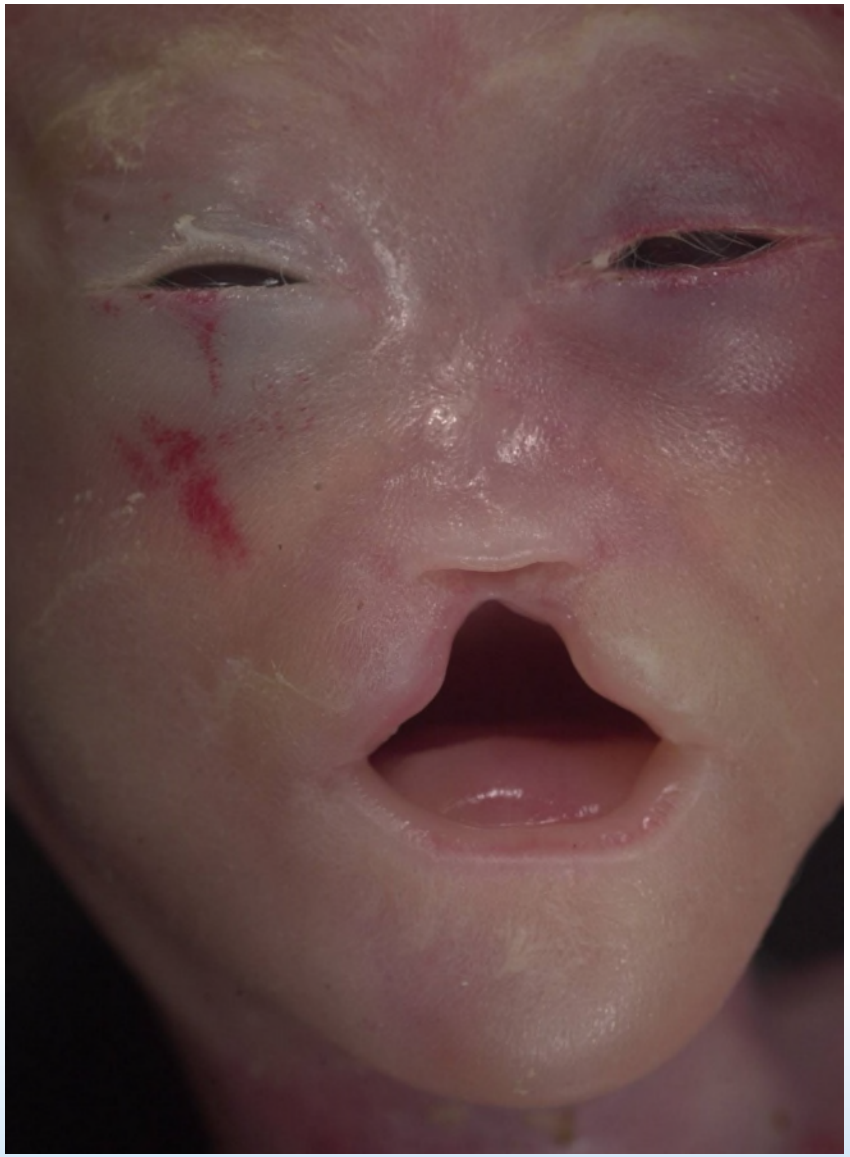


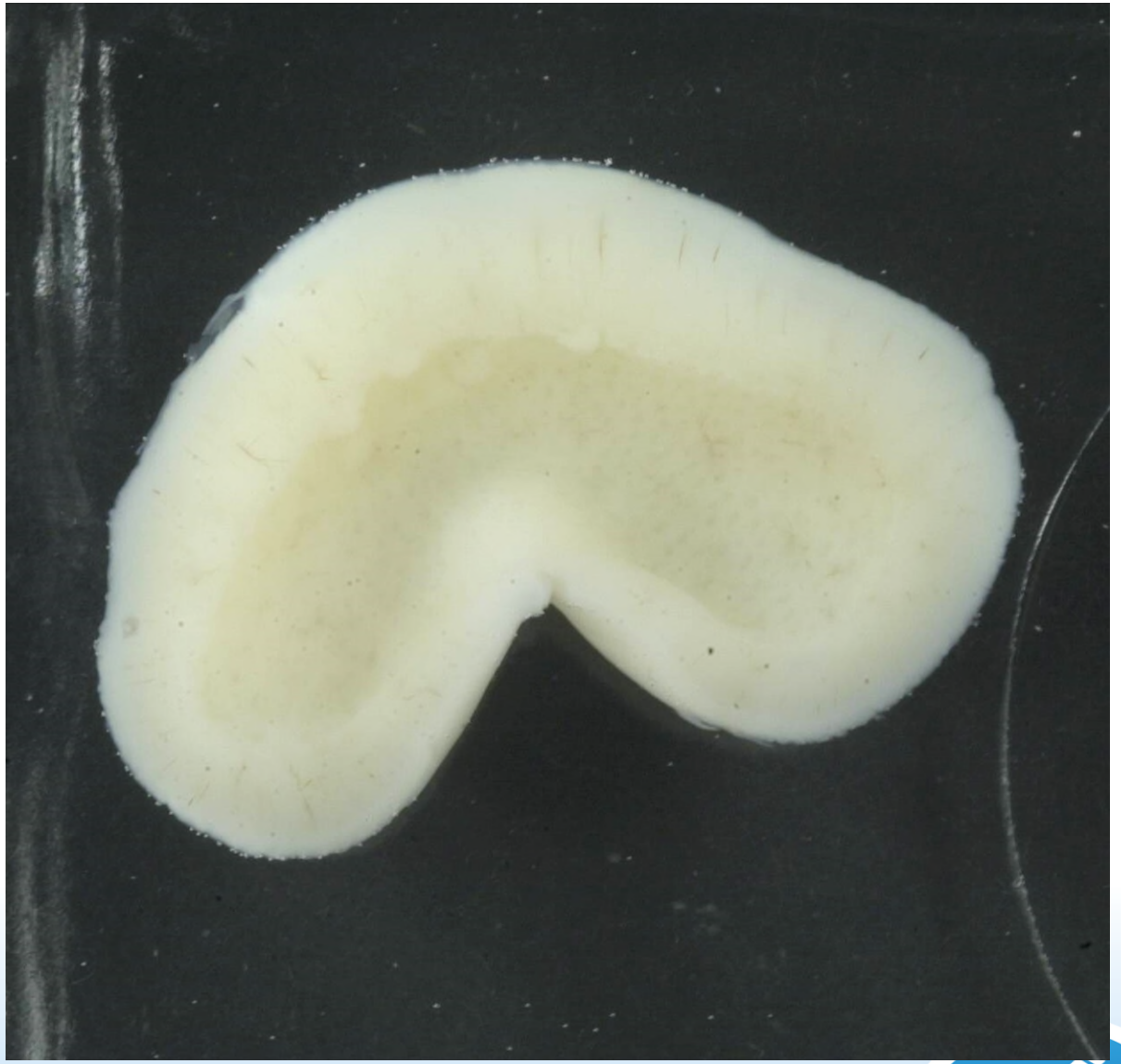


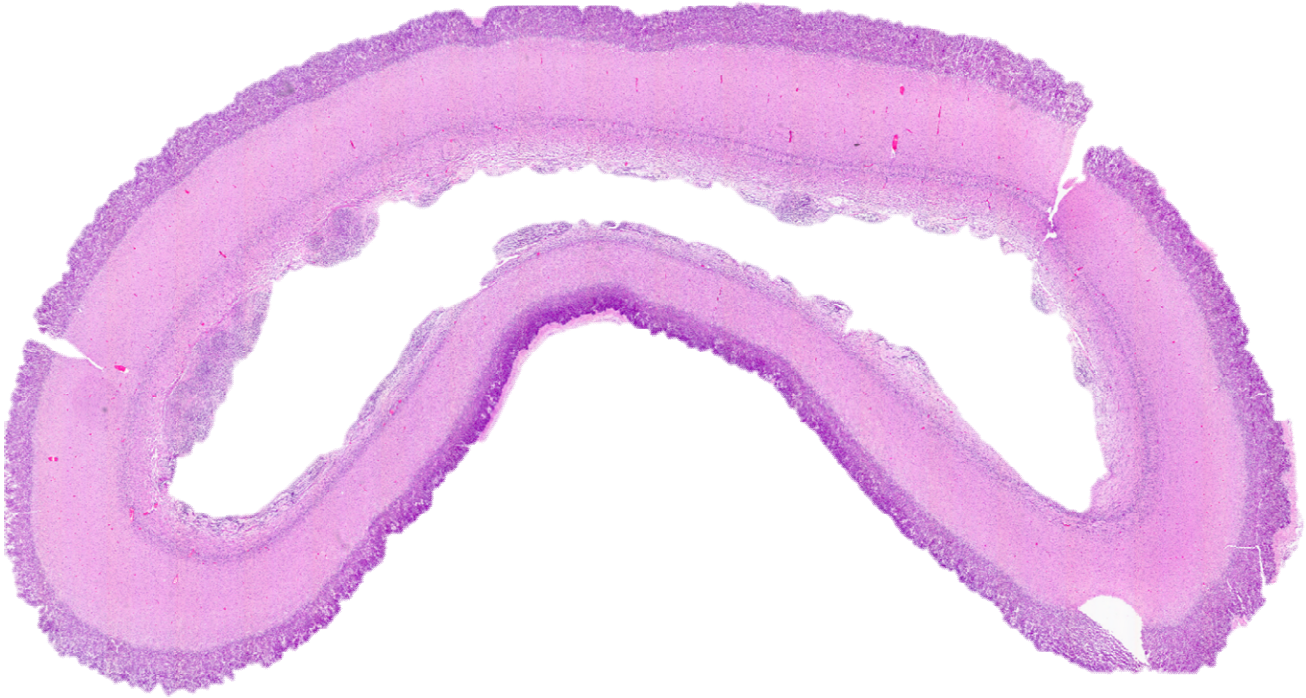


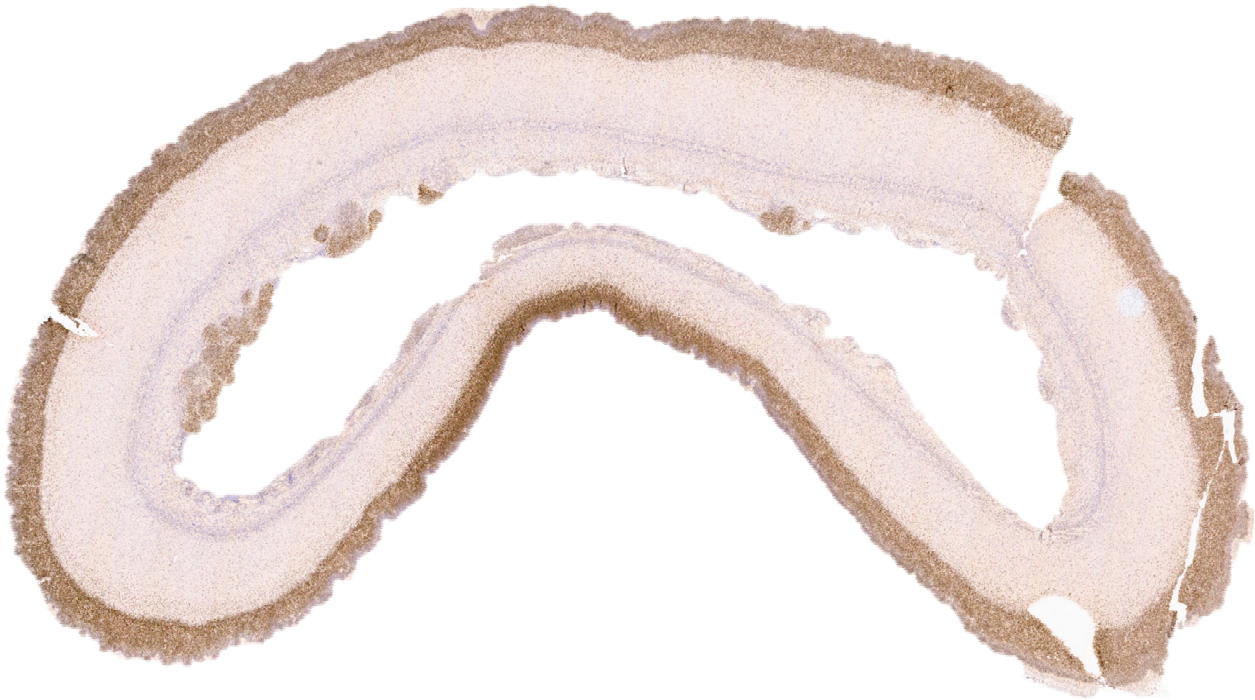












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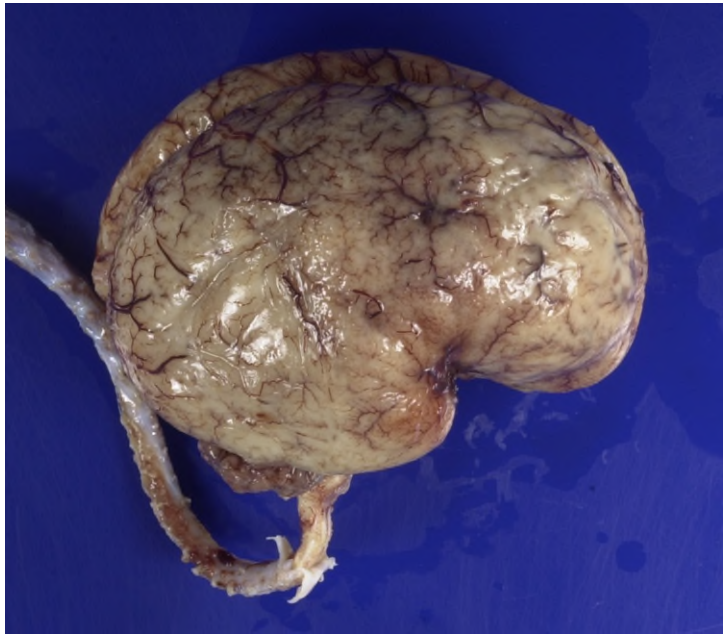

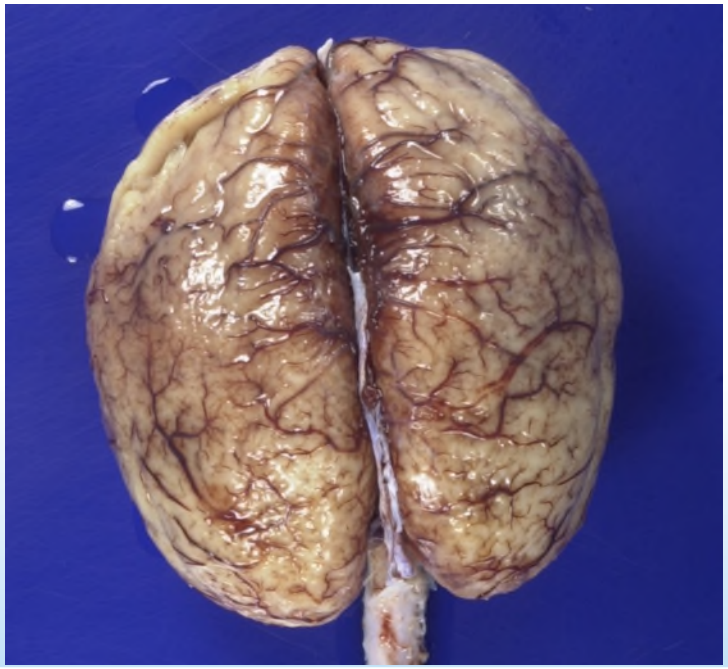

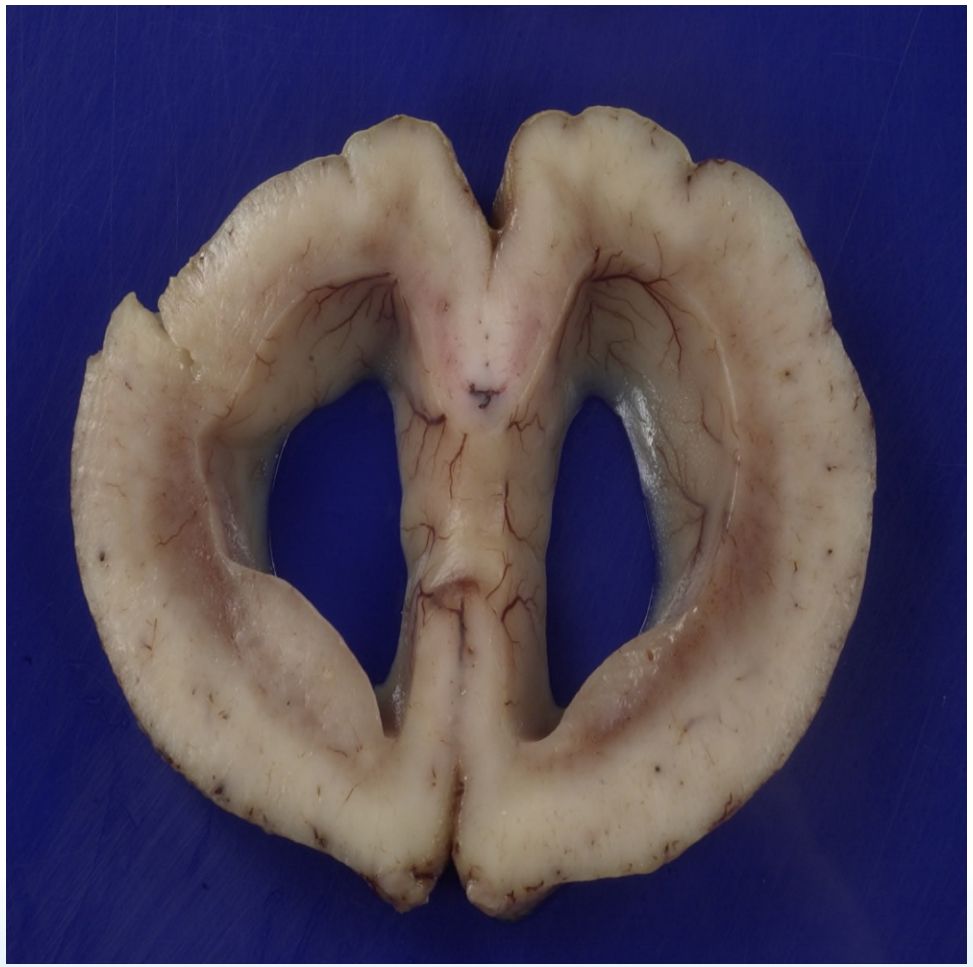

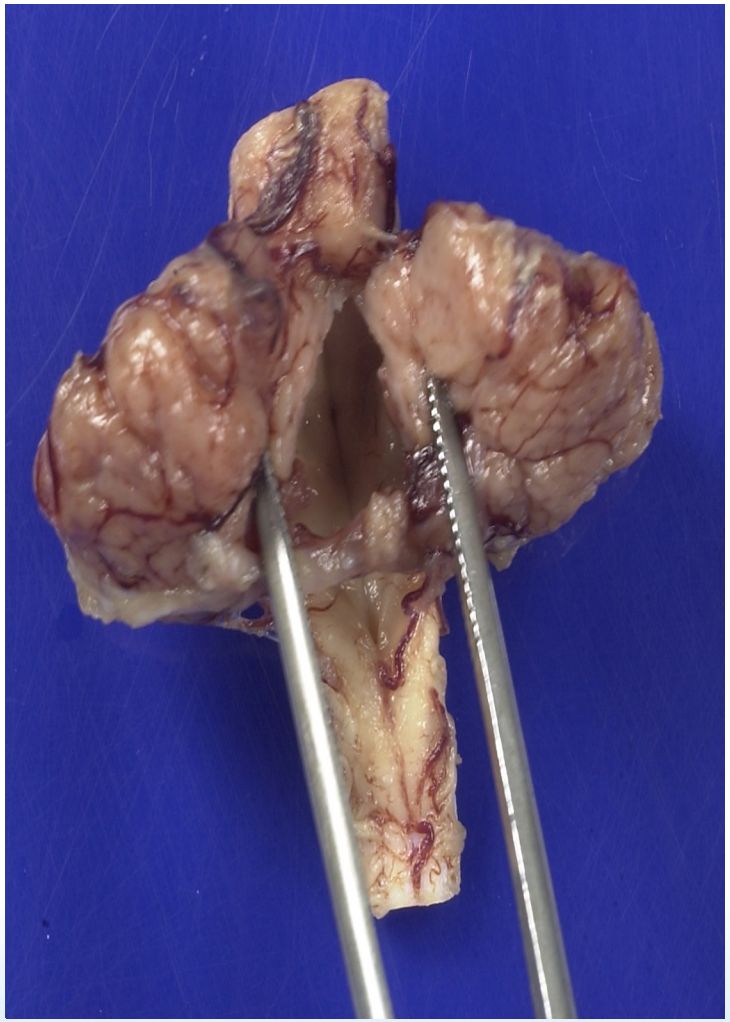

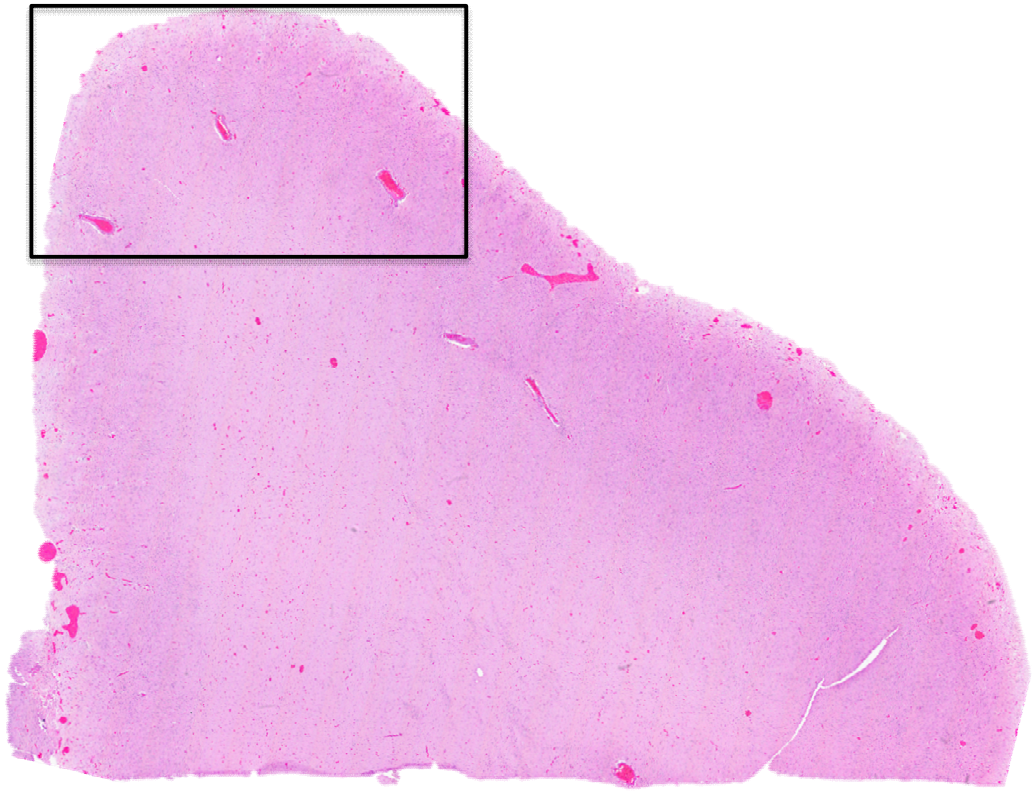

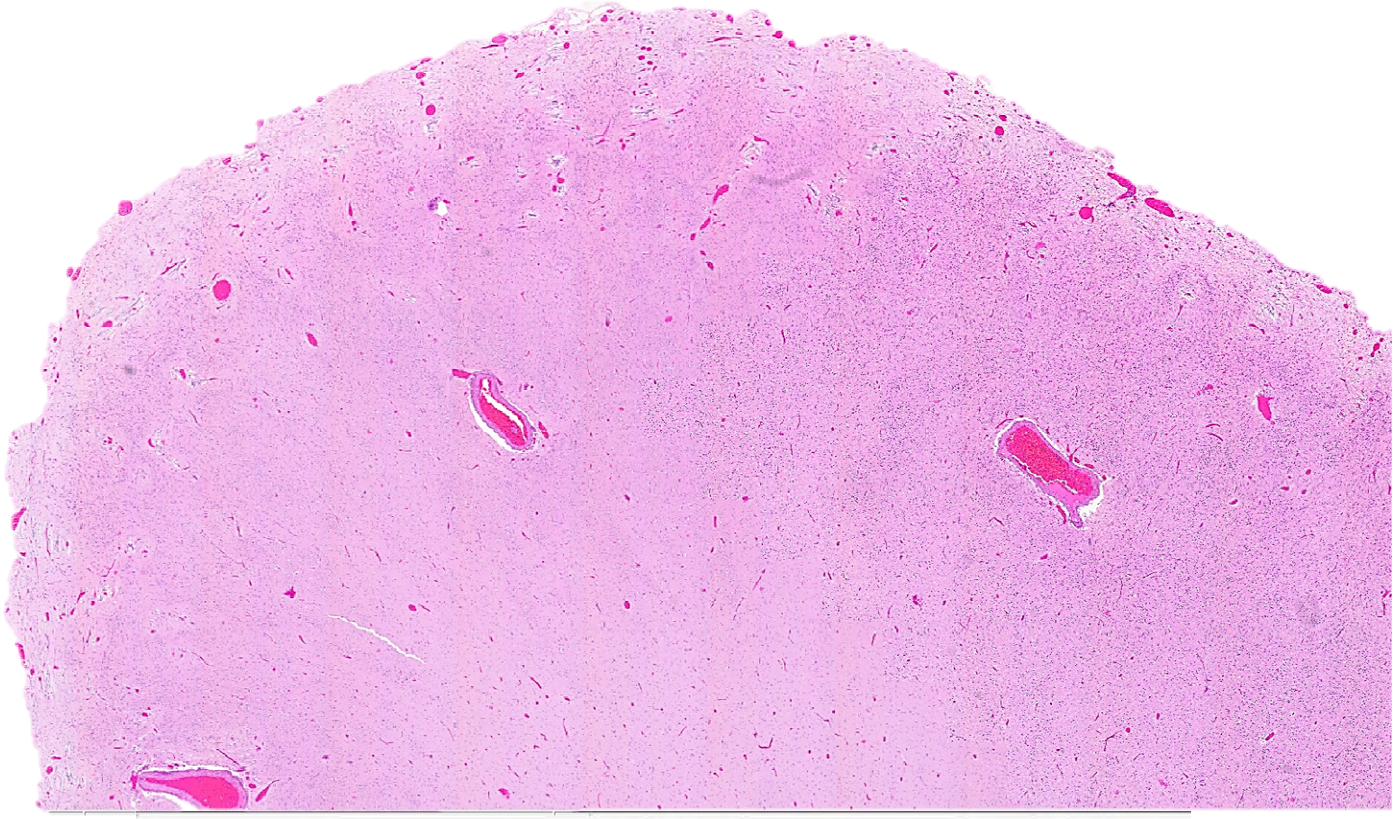


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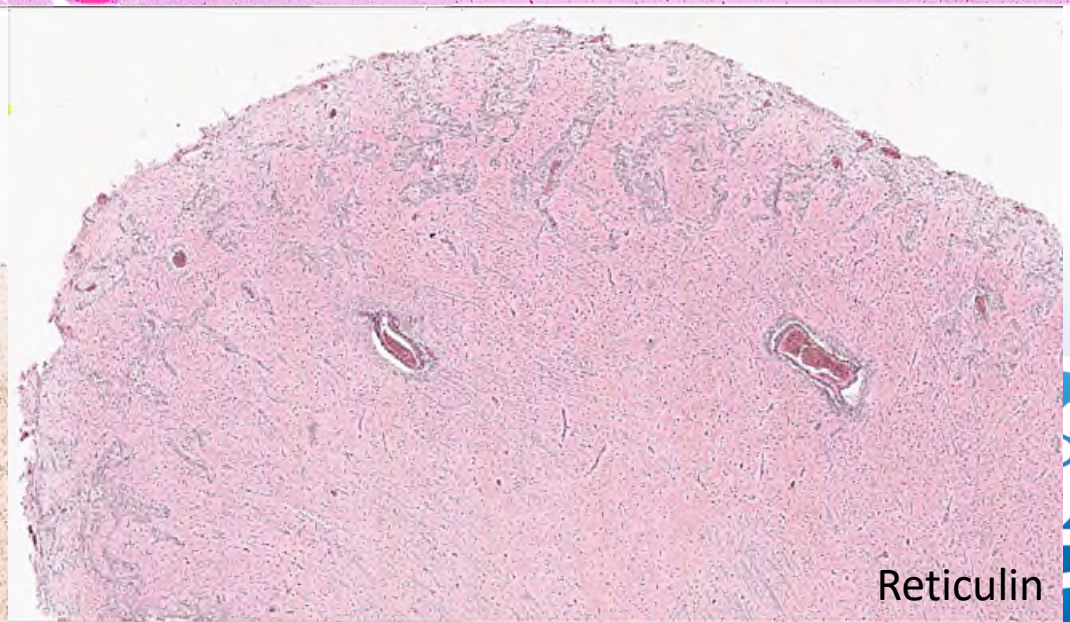
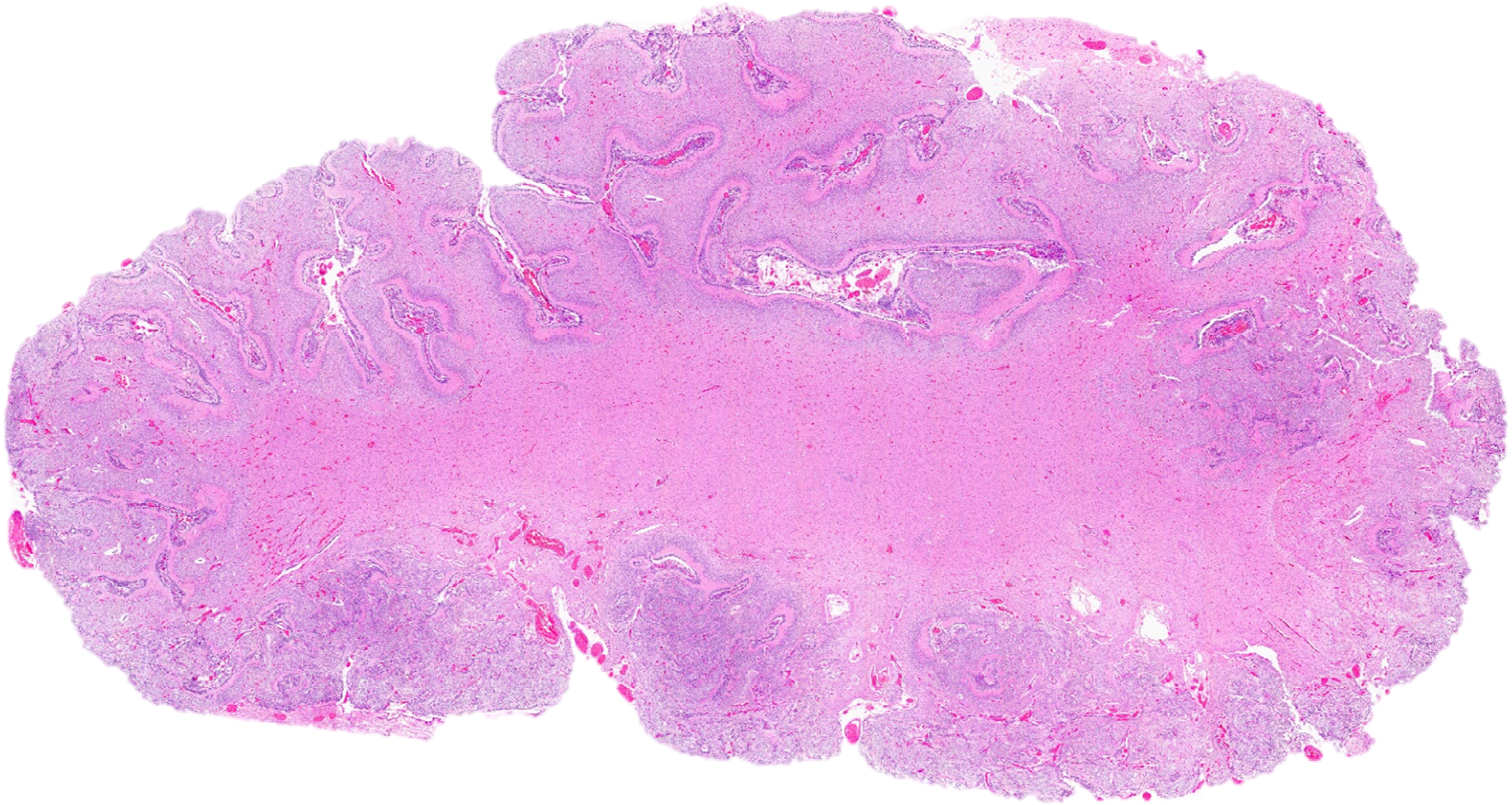
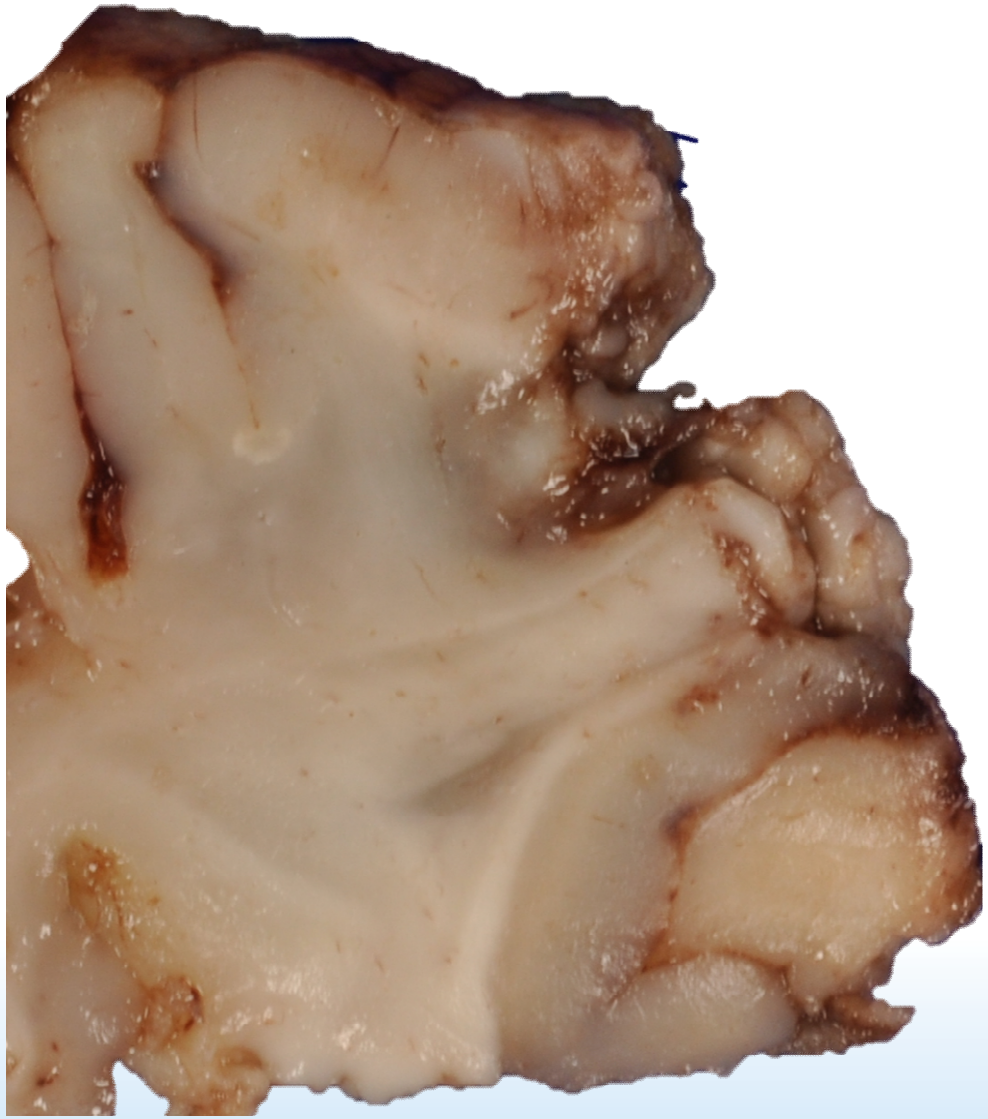
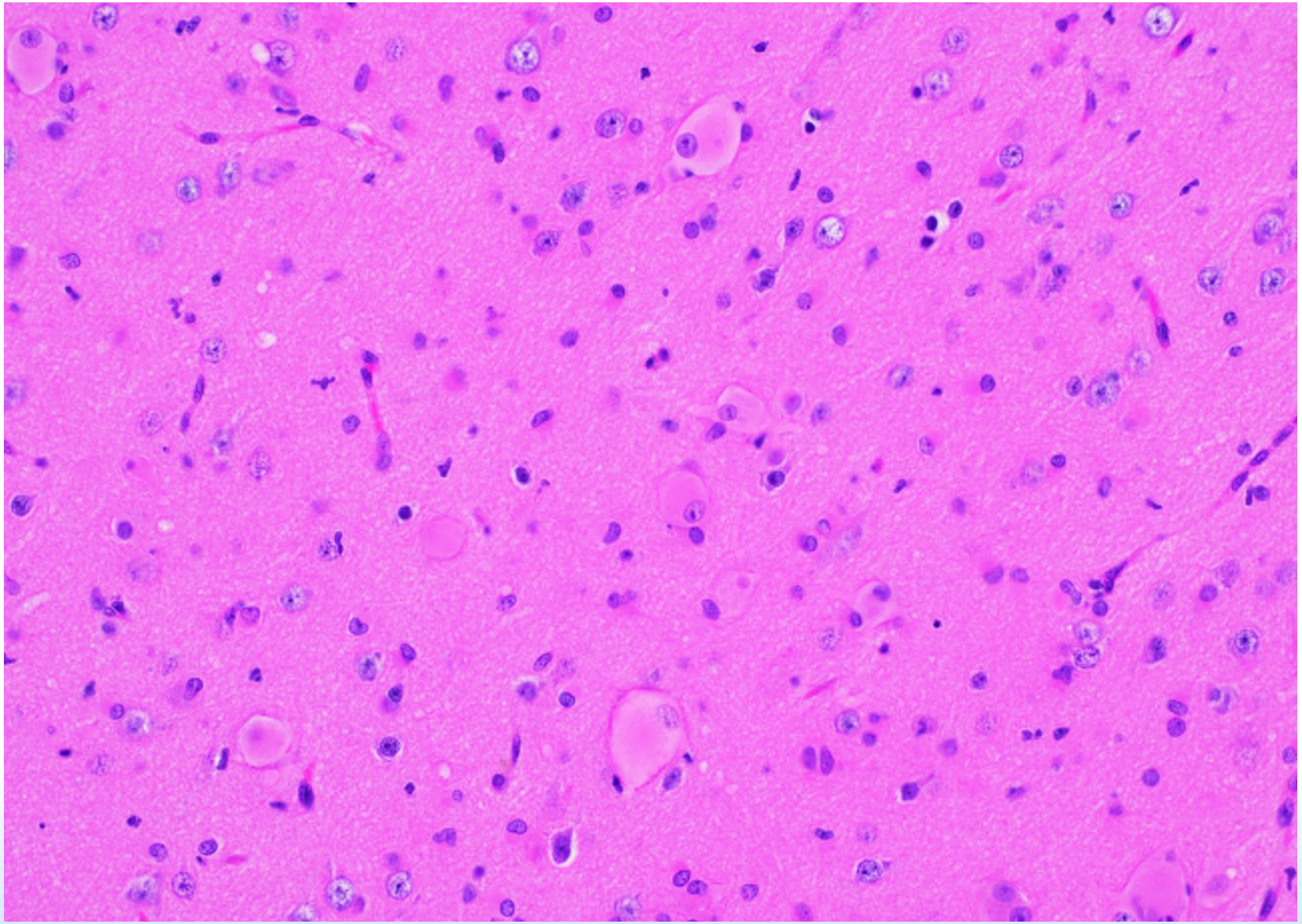

Reticulin







Summary

- Disorders of forebrain induction
  - Alobar holoprosencephaly
  - Semilobar holoprosencephaly
  - Lobar holoprosencephaly
  - Agenesis of the corpus callosum
- Malformations of cortical development
  - Lissencephaly
  - Heterotopias
  - Cortical dysplasia with cytomegaly
    - Focal cortical dysplasia
    - Tuberous Sclerosis

Questions?

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