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Seminars in PEDIATRIC NEUROLOGY

Congenital Brain Malformations: An Integrated Diagnostic Approach

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Congenital brain malformations are abnormalities present at birth that can result from developmental disruptions at various embryonic or fetal stages. The clinical presentation is nonspecific and can include developmental delay, hypotonia, and/or epilepsy. An informed combination of imaging and genetic testing enables early and accurate diagnosis and management planning. In this article, we provide a streamlined approach to radiologic phenotyping and genetic evaluation of brain malformations. We will review the clinical workflow for brain imaging and genetic testing with up-to-date ontologies and literature references. The organization of this article introduces a streamlined approach for imaging-based etiologic classification into malformative, destructive, and migrational abnormalities. Specific radiologic ontologies are then discussed in detail, with correlation of key neuroimaging features to embryology and molecular pathogenesis.
Semin Pediatr Neurol 42:100973

Introduction

Congenital brain malformations are abnormalities present at birth that can result from developmental disruptions at various embryonic or fetal stages. The clinical presentation is nonspecific and can include developmental delay, hypotonia, and/or epilepsy. An informed combination of imaging and genetic testing enables early and accurate diagnosis and management planning. In this article, we provide an integrated approach to radiologic phenotyping and genetic evaluation of brain malformations. We will review the clinical workflow for brain imaging and genetic testing with up-to-date ontologies and literature references. The organization of this article introduces an integrated approach for etiologic classification into malformative, destructive, and migrational abnormalities. Specific radiologic ontologies are then discussed in detail, with correlation of key neuroimaging features to embryology and molecular pathogenesis.

Abbreviations: MRI, magnetic resonance imaging; US, ultrasonography

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Declaration of interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Imaging Evaluation

During the fetal period, ultrasonography (US) of the pregnant mother is the first-line imaging modality. Level 1 (screening) obstetric US can be performed at various times during pregnancy (first, second, third trimester) to assess fetal viability, normal growth, placental location, amniotic fluid, and major defects. Level 2 (survey) US can be ordered in the second trimester for comprehensive evaluation of fetal anatomy including brain, visceral organs, umbilical cord, limbs, and genitalia; as well as growth (biometry measurements on gestational age). Level 3 US (advanced) is sometimes performed in the late second-third trimester for detailed evaluation of complex conditions. Key limitations of US include restricted acoustic window through the maternal abdomen, limited depth penetration, and artifactual shadowing from bowel gas or bone.[1,2]

Fetal positioning, maternal body habitus, oligohydramnios, overlying bone or gas, and small field of view can all restrict the US imaging window. When US is inconclusive and specific anomalies are suspected, fetal MRI is the next step in imaging workup. MRI can be performed from the early second through late third trimesters, when the fetal structures are sufficiently large and well developed to image. Inherent tradeoffs exist in fetal MRI timing, with the need for earlier diagnosis and/or intervention balanced against improved resolution, greater safety, and decreased motion in later gestation. Brain-specific indications for fetal MRI

https://doi.org/10.1016/j.spen.2022.100973
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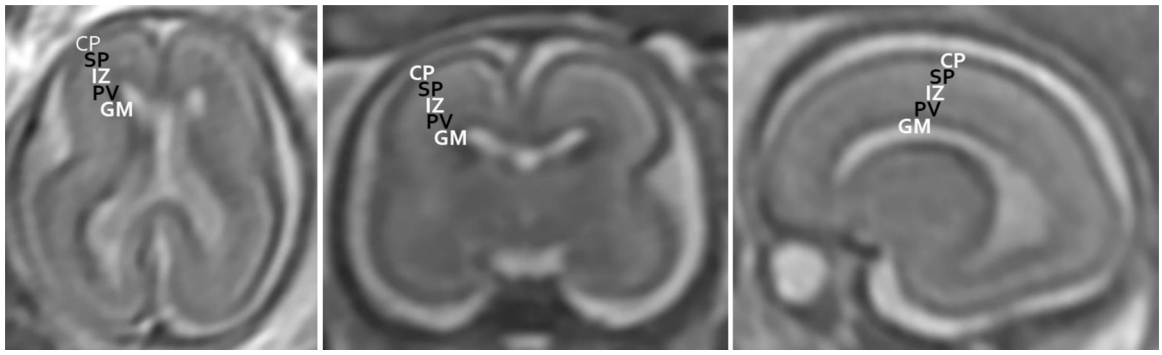


Figure 1 Normal 5-layer appearance of fetal brain at 23 weeks gestation. CP, cortical plate; GM, germinal matrix; IZ, intermediate zone; PV, periventricular crossroads; SP, subplate.

include suspected malformations, infarcts, hemorrhage, masses, and vascular anomalies.[3] Typically, 3-plane single-shot T2-weighted image are obtained to assess cerebral anatomy. Optional sequences include high-resolution steady-state, T1-weighted, diffusion-weighted, and gradient-recalled echo images. The normal fetal brain shows a normal multilayered appearance of alternating intensities, with 3 layers prior to 20 weeks, and 5 layers by 20-28 weeks gestation. Distinct cell populations include the germinal matrix, ganglionic eminences, periventricular crossroads, intermediate zone, subplate, and cortical plate. This yields multiple zones including ventricular (radial fibers), subventricular (tangential fibers), periventricular (crossing fibers), intermediate (glia), subplate (interstitial fibers), and cortical plate (gray matter) (**Figure 1**). Normal neurodevelopment also involves progressive myelination (axonal coating for rapid conduction) and sulcation (brain folding) that progresses from mid-second trimester through postnatal life.[4]

Radiologic classification of congenital brain malformations is complex and continually evolving. The spectrum of developmental times and etiologies can overlap for different lesion categories. Furthermore, accurate detection of abnormalities on fetal imaging depends on many factors including imaging technique, patient characteristics, and radiologist expertise. Therefore, multidisciplinary consensus evaluation is key to accurate patient/family counseling and optimizing the yield of genetic testing. In this article, we provide an etiology-based imaging classification consisting of malformative, destructive, and migrational abnormalities. Specific radiologic ontologies are discussed in detail, with correlation of key neuroimaging features to embryology and molecular pathogenesis (**Table**).[5-7]

Table Congenital Brain Malformation Phenotypes and Recommended Genetic Testing

Radiology Findings	Genetic Testing				
	Cytogenetics	Gene Panel	ES/GS	Do Not Test	Comment
Malformative lesions					
Callosal dysgenesis	Yes	No	Yes	No	
Septo-optic dysplasia	No	Yes	No	No	
Holoprosencephaly	Yes	No	Yes	No	
Chiari malformations	No	No	No	Yes	
Dandy-Walker spectrum	Yes	No	Yes	No	
Joubert syndrome-related disorders	Secondary	No	Yes	No	CNV in NPHP1 (nephrocystin 1)
Pontine tegmental cap dysplasia	No	No	No	Yes	
Rhombencephalosynapsis	Yes	No	No	No	ES/GS if combined with holoprosencephaly
Destructive lesions					
Acrania-exencephaly-anencephaly sequence	No	No	No	Yes	
Schizencephaly	No	No	Yes	No	
Porencephaly	No	No	Yes	No	
Hydranencephaly	No	No	Yes	No	
Maximal hydrocephalus					
Encephalomalacia	No	Yes	No	No	MoCD (molybdenum cofactor deficiency), sulfur metabolism
Migrational lesions					
Gray matter heterotopia	Yes	No	Yes	No	
Lissencephaly-pachygyria	Yes	No	Yes	No	CNV for Miller-Dieker syndrome
Cobblestone cortex	No	No	Yes	No	
Polymicrogyria	No	No	Maybe	No	Consider mosaicism when selecting tissue for testing
Megalencephaly	Yes	Yes	No	No	CNV for AKT3 (AKT Serine/Threonine Kinase 3), targeted testing for mosaicism
Focal cortical dysplasia	No	No	Yes	No	Consider paired analysis with affected tissue
Tubulinopathies	No	No	Yes	No	

CNV, copy number variant; ES, whole exome sequencing; GS, whole genome sequencing.

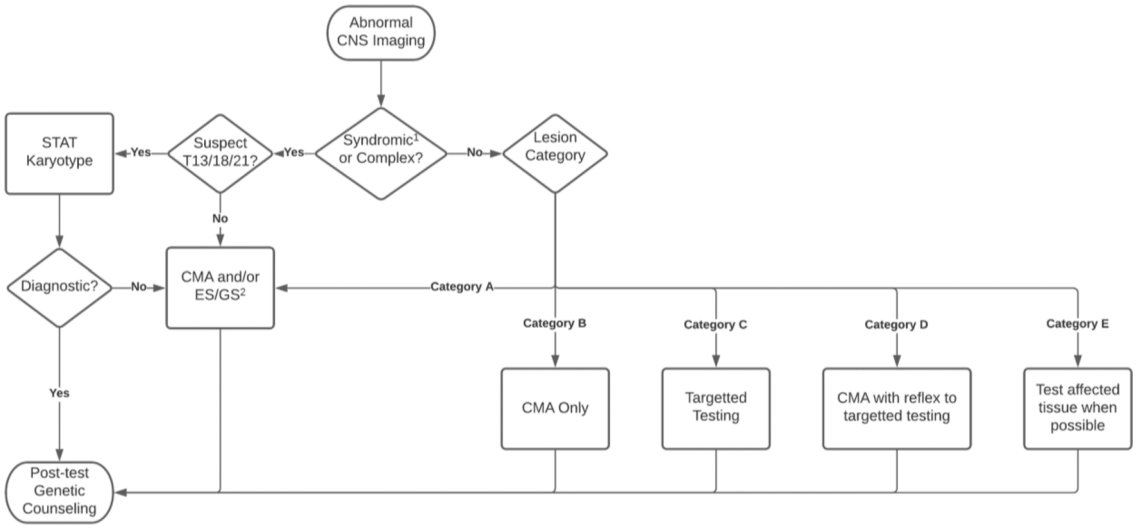


Figure 2 Categorical approach to genetic testing in patients with congenital brain malformations. Potential syndromic findings may require confirmation with laboratory testing and/or imaging. Complex cases are defined as having multiple CNS abnormalities. Patient acuity, hospital resources, and insurance considerations will guide whether testing is performed in parallel or sequentially. CMA, chromosomal microarray; CNS, central nerveous system; ES, whole exome sequencing; GS, whole genome sequencing; T, trisomy. Category A: callosal hypogenesis, holoprosencephaly, Dandy-Walker malformation, gray matter heterotopia, Miller-Dieker syndrome, lissencephaly-pachygyria, cobblestone cortex. Category B: rhombencephalosynapsis. Category C: septo-optic dysplasia, cystic encephalomalacia. Category D: megalencephaly. Category E: polymicrogyria, focal cortical dysplasia.

Genetic Testing

An extensive array of options are available for genetic testing in the antenatal and neonatal periods (**Table**). To maximize diagnostic efficiency and value, we advise a structured decision support workflow for genetic testing (**Fig. 2**). Patient acuity, hospital resources, and insurance considerations help guide the nature and timing of testing. Single-gene testing is performed when there is high suspicion for a certain syndrome or a known familial genetic mutation, rarely the case for structural brain abnormalities. Narrow testing, that is gene panels for brain malformations, are offered by different providers with varying coverage and accuracy. Cytogenetic testing assesses chromosomal numerical (aneuploidy) and structural abnormalities (duplication, deletion, translocation, inversion, insertion). Karyotyping is the leading method to stain and visualize chromosomes during metaphase using Giemsa banding, with a resolution of 5-10 megabases.[8] Chromosomal microarray analysis (CMA) is a newer method in which oligonucleotide probes are used to label genomic DNA through hybridization. CMA can be performed on raw samples without culturing and is sensitive for smaller deletions and duplications, such as copy-number variants (CNV) in the kilobase range, and single nucleotide polymorphisms (SNP) of specific base-pair locations.[9] If the above tests are unrevealing, the next step is broad next-generation sequencing of the whole exome (ES) or whole genome (GS).[10]

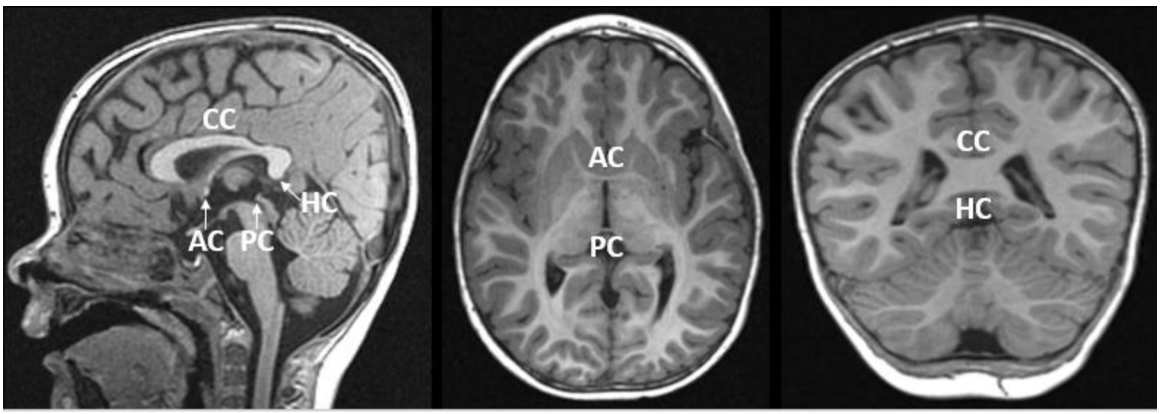


Figure 3 Cerebral commissures. AC, anterior commissure; CC, corpus callosum; HC, hippocampal commissure; PC, posterior commissure.

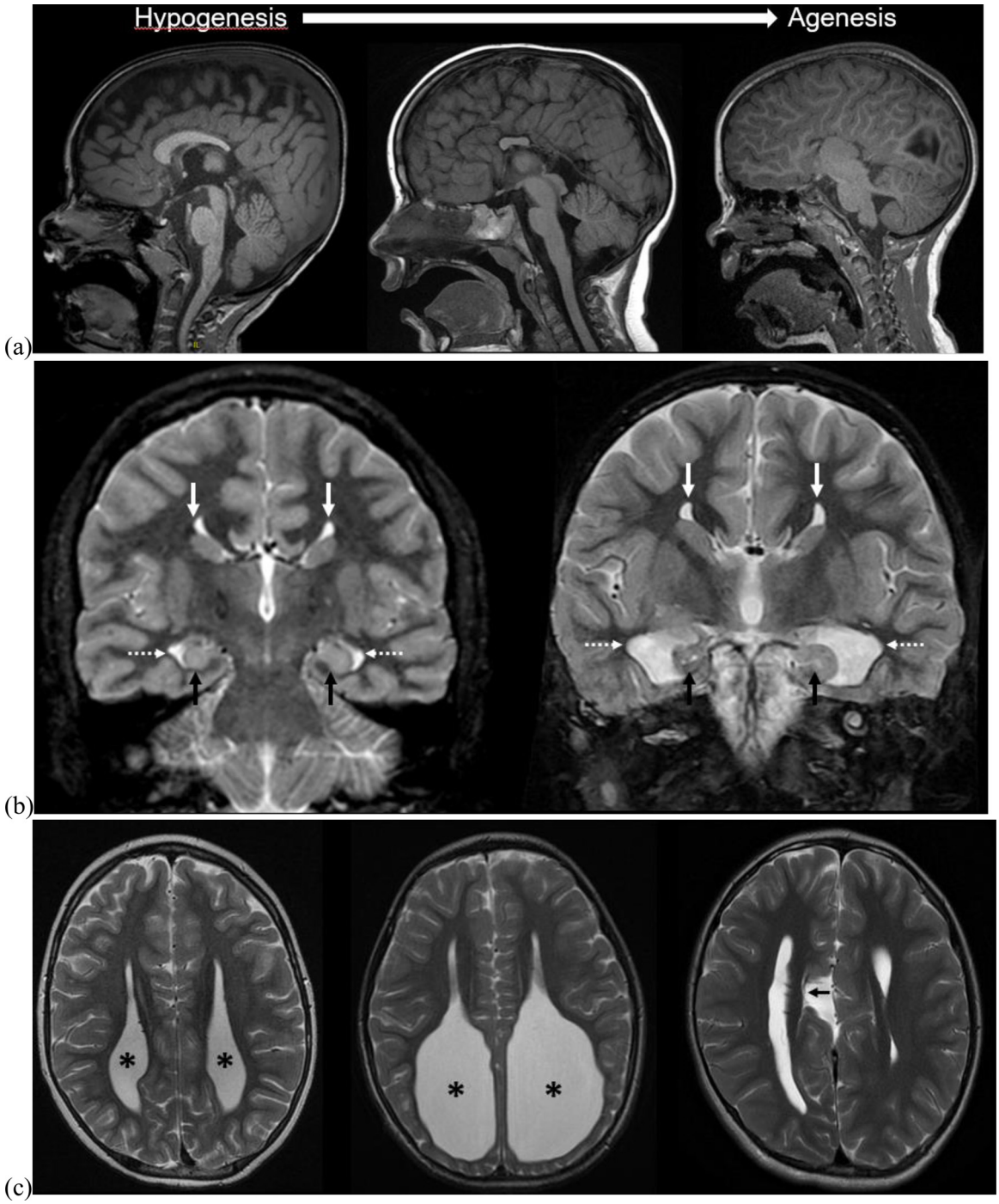
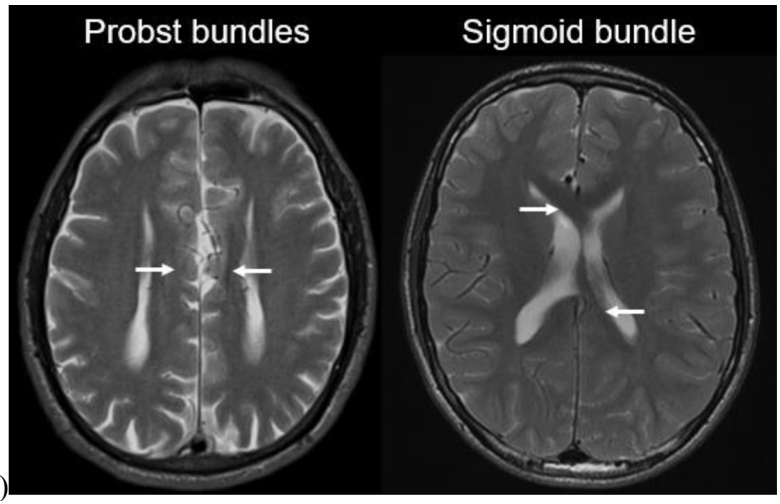


Figure 4 Callosal hypogenesis. (A) Callosal anomalies range from hypogenesis (partial absence), with foreshortening and/or posterior tapering; to agenesis (complete absence) with "sunburst" gyri radiating directly from the roof of third ventricle. (B) Callosal dysgenesis affects global brain folding with everted cingulate gyri and absence of cingulate sulci. The frontal horns demonstrate a "steer"/"ram" morphology (white arrows). Temporal lobes and hippocampi are malrotated (black arrows) with "keyhole" temporal horns (dashed white arrows). (C) Colpocephaly describes the ventricular configuration in callosal hypogenesis. Lateral ventricles are parallel with a "teardrop" morphology, created by bulging atria and occipital horns (asterisks) in the absence of delimiting optic radiations. Interhemispheric cysts (arrow) can form near midline with variable configuration, ventricular communication, and associated migrational anomalies. (D) Anomalous connectivity in callosal agenesis includes Probst bundles (left panel, arrows), with homotopic connections from anterior to posterior in a single cerebral hemisphere. In callosal hypogenesis, sigmoid bundles (right panel, arrows) represent heterotopic connection between the frontal lobe of one hemisphere and the occipital lobe of the contralateral hemisphere.

In the prenatal setting, it is important to distinguish syndromic from nonsyndromic etiologies. Multisystem abnormalities on imaging, involving central nervous system (CNS) and/or non-CNS structures, can suggest a specific diagnosis. When cytogenetic testing is nondiagnostic and prenatal molecular diagnosis is desired, the neurologist may be



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consulted (in conjunction with a genetic counselor or medical geneticist) to choose between a gene panel or exome sequencing. Two key considerations in making this recommendation are the proportion of similar cases diagnosed by panel versus exome, and the consequences of delayed diagnosis for the suspected genetic disorder. Generally, panels are preferred if known to be of high diagnostic yield, and in settings where delayed diagnosis is unlikely to change medical decision making or ultimate pregnancy outcome. In situations where panels offer lower diagnostic yield (eg, unusual combination of multisystem features), and/or delayed diagnosis could adversely impact management or outcome (eg, anticipated fetal intervention, birth complications, critical postnatal illness, planning goals of care), prenatal exome sequencing is justified as a first-line sequencing modality. However, insurance coverage for prenatal exome sequencing remains limited, therefore this choice may not be available to many patients.[11]

In the neonatal setting, key factors include the severity of patient illness and potential for adverse outcomes resulting from delayed diagnosis (sequential testing compared to early use of rapid or ultrarapid genome sequencing). When obtained in the appropriate clinical setting, genome sequencing shows high diagnostic yield and clinical utility with minimal impact on psychosocial outcomes.[12,13] At our institution, we recommend that the neurologist consider worst-case scenarios when contemplating sequential testing, and not order more than one panel before reflexing to exome sequencing.

Finally, while imaging plays a central role in phenotyping patients with congenital brain malformations, the radiologist is seldom directly involved in ordering genetic testing. Luckily, the neurologist is uniquely positioned to bridge the communication gap between radiology and primary providers, particularly when ES or GS is being considered. Provider guidelines for prior authorization vary widely, such that awareness and understanding of terminology for congenital brain malformations is critical. The accepted genetic ontology for phenotyping in rare diseases is Human Phenotype Ontology (HPO),[5] which incompletely overlap with radiologic taxonomy.[5] When a clear taxonomic match is not apparent, close collaboration between the neurologist and neuroradiologist will help determine the most appropriate ontologic terms to provide to the genetic testing laboratory. To simplify understanding, we utilize an etiology-based classification of radiology phenotypes into malformative, destructive, and migrational abnormalities. Within this framework, we discuss specific taxonomy of congenital brain malformations including leading etiologic theories, key imaging findings, and up-to-date genetic understanding.

Malformative Lesions

In malformative lesions, the brain fails to form normally due to a primary error of development. Malformations vary in appearance and severity, based on the etiology and stage of development; and can affect various locations including forebrain, midbrain, and hindbrain.

Callosal Dysgenesis

Cerebral commissures are white matter tracts that cross midline and connect the cerebral hemispheres. The corpus callosum (CC) is the largest midline commissure in placental mammals. It progressively myelinates and achieves a mature configuration by 8-9 months of age, with a slightly bulbous appearance of the splenium (forceps major) posteriorly and genu (forceps minor) anteriorly. Other cerebral commissures include the anterior commissure, which connects the temporal lobes and crosses anterior to the forniceal pillars; posterior commissure, which connects the pretectal nuclei and crosses dorsal to the cerebral aqueduct; and hippocampal commissure, which connects the hippocampi and crosses inferior to the splenium (**Fig. 3**).

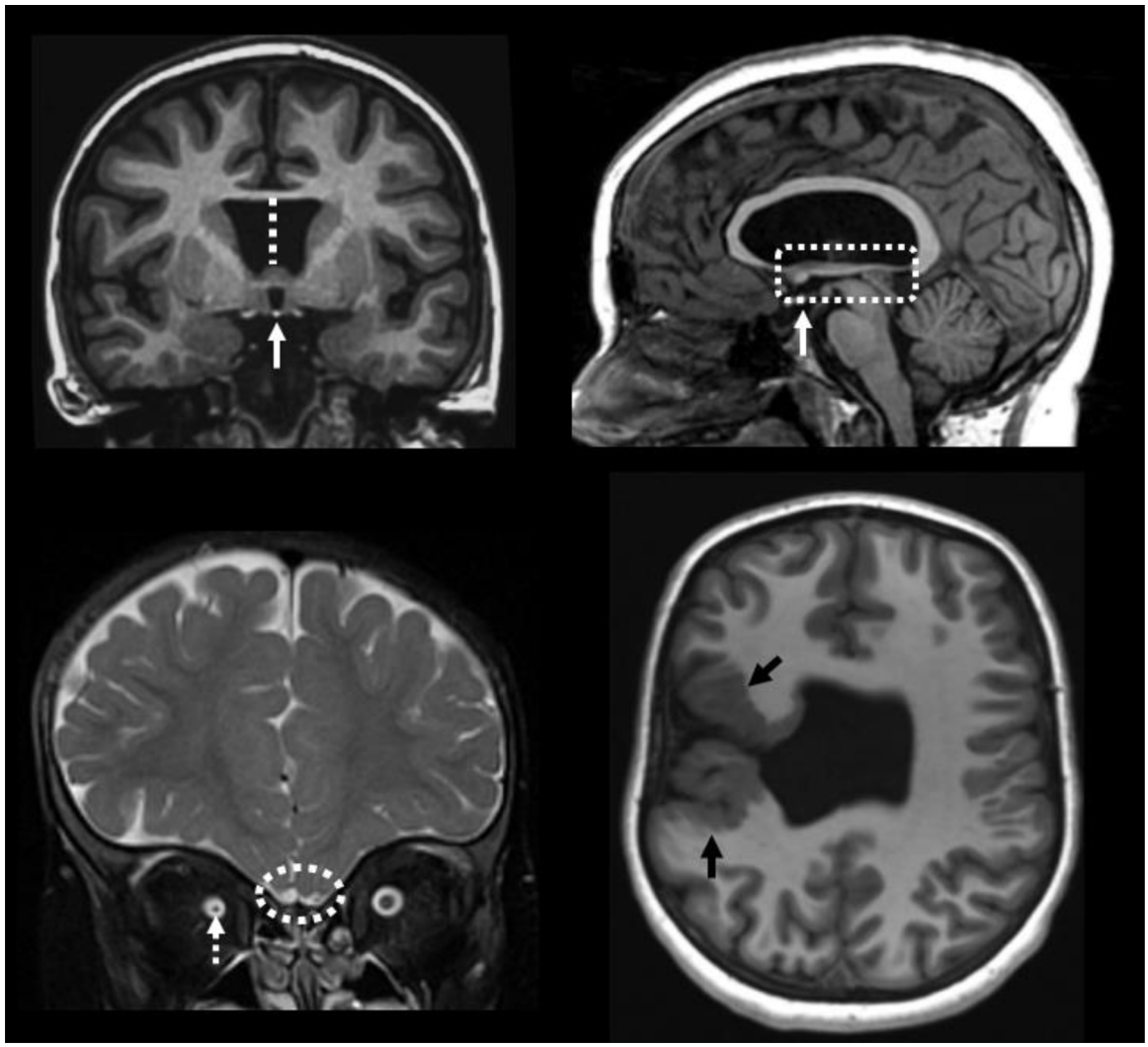


Figure 5 Septo-optic dysplasia. Callosal hypogenesis with absent septum pellucidum (dotted line) yielding "boxcar" frontal horns and low-lying fornices (dotted rectangle), ectopic posterior pituitary bright spot (white arrows), optic nerve hypoplasia (dotted arrow), olfactory hypoplasia (dotted oval), and schizencephaly (black arrows).

Callosal dysgenesis can range from hypogenesis (partial absence, HCC or pACC) to agenesis (complete absence, ACC). During development, the callosum grows both anteriorly and posteriorly from the embryonic glial sling, with greater volume anteriorly due to the large frontal lobes in humans. Therefore, callosal hypogenesis can manifest with a foreshortened and/or posteriorly tapered appearance. Callosal agenesis manifests with "sunburst" gyri radiating directly from the roof of third ventricle. Anterior, posterior, and hippocampal commissures are usually also small or absent (**Fig. 4A**).[14,15]

Callosal abnormalities affect global developmental brain folding, producing a constellation of associated findings. The cingulate sulci fail to invert over the callosum, such that the cingulate gyri remain everted. Parasagittal bands of white matter (Probst bundles) course along their respective hemispheres, rather than crossing midline. This produces thin curved "steer"/"ram" frontal horns (white arrows). The temporal lobes and hippocampi also fail to rotate and invert, producing globular hippocampi and "keyhole" temporal horns (**Fig. 4B**).[16]

The ventricular configuration in callosal dysgenesis is known as colpocephaly. Lateral ventricles demonstrate a parallel orientation and "teardrop" morphology with bulging of the atria and occipital horns (asterisks). This is due to absent crossing of the optic radiations, which normally limit lateral expansion of the ventricles. In contrast, the frontal horns are medially confined by the Probst bundles and laterally confined by the lentiform nuclei. Associated paramedian lipomas[17,18] or interhemispheric cysts can be present. Interhemispheric cysts vary in location, communication with the ventricular system, and associated malformations.[19-21] They are frequently asymmetric, with the more involved hemisphere demonstrating more severe structural malformations (AVID = asymmetric ventriculomegaly, interhemispheric cyst, and dysgenesis of the corpus callosum) (**Fig. 4C**).[22,23]

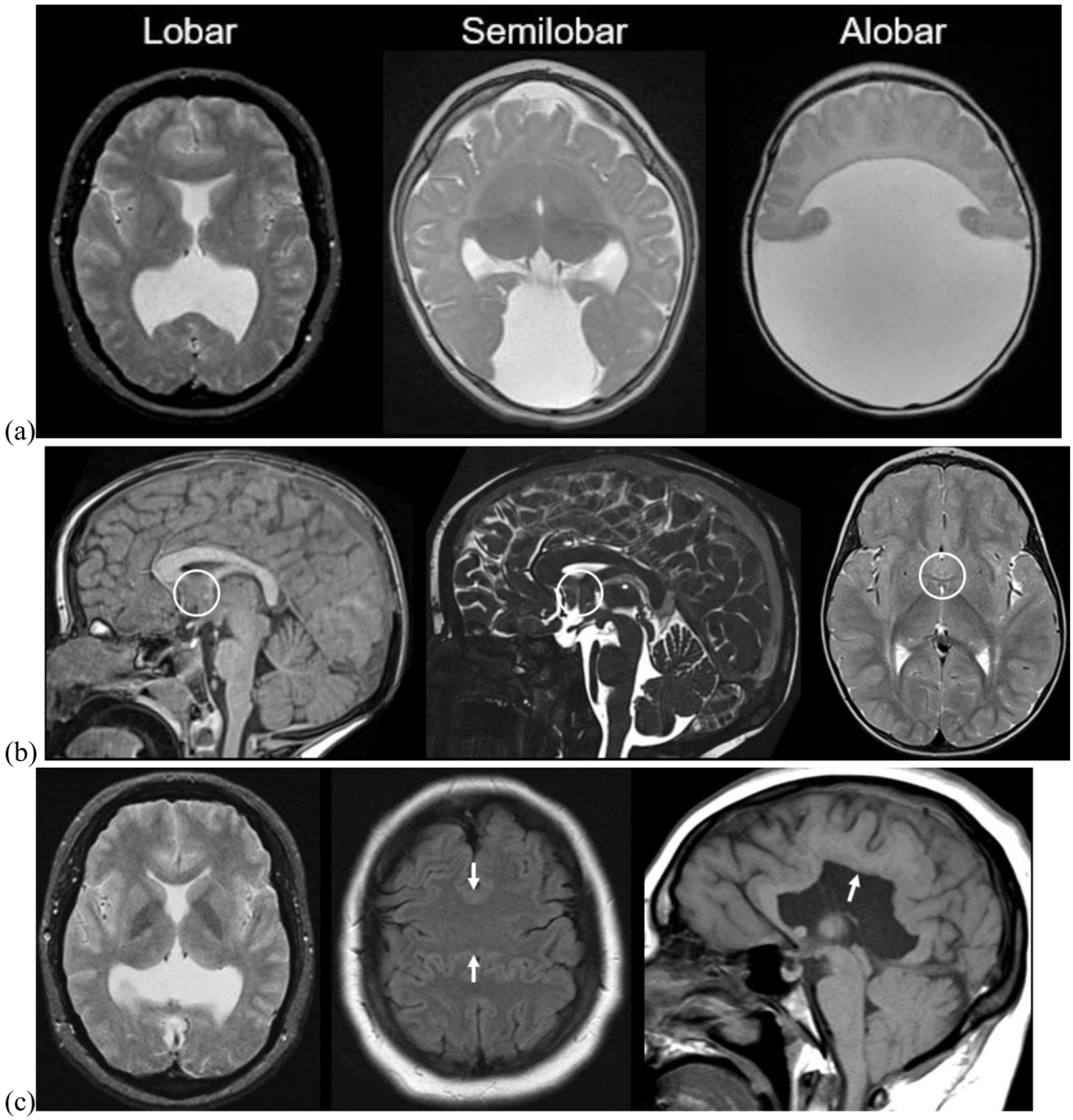


Figure 6 Holoprosencephaly. (A) Varying degrees of forebrain can be present. Lobar HPE refers to mild fusion of the basal frontal lobes and anterior corpus callosum, with small frontal horns. Semilobar HPE involves partial fusion and malrotation of the frontal lobes and deep gray nuclei, with a small third ventricle and dorsal cyst. Alobar HPE consists of a rudimentary "pancake" brain with conglomerate fusion and gaping monoventricle. (B) Sublobar HPE involves the basal forebrain in the septal and preoptic regions (circles). (C) Syntelencephaly or middle interhemispheric variant of HPE involves fusion of the dorsal forebrain (arrows, posterior frontal and parietal lobes), with greater separation of deep gray nuclei than in conventional HPE (ventral forebrain).

Aberrant connectivity patterns are common in callosal dysgenesis. With callosal agenesis, Probst bundles reflect homotopic connectivity from anterior to posterior within a single cerebral hemisphere. In callosal hypogenesis, sigmoid bundles may be observed connecting the frontal lobe of one hemisphere to the contralateral occipital lobe. These represent heterotopic connectivity from anterior to posterior between different cerebral hemispheres. Widespread disruptions of connectivity have been detected even in the fetal stage (**Fig. 4D**).[24-28]

Anomalies of the corpus callosum are among the most common incidental imaging findings in the general population, and are overrepresented in children with neurodevelopmental disabilities. As such, much of the pediatric literature regarding genetic epidemiology[29] is less relevant when compared to more unbiased prenatal studies.[30,31] Copy number variants (CNV) account for 9.4% of ACC.[32] In two recent small case series, 5/19[33] and 7/10[34] fetuses undergoing ES for ACC/HCC had a molecular diagnosis. Multiple genetic causes of ACC have been

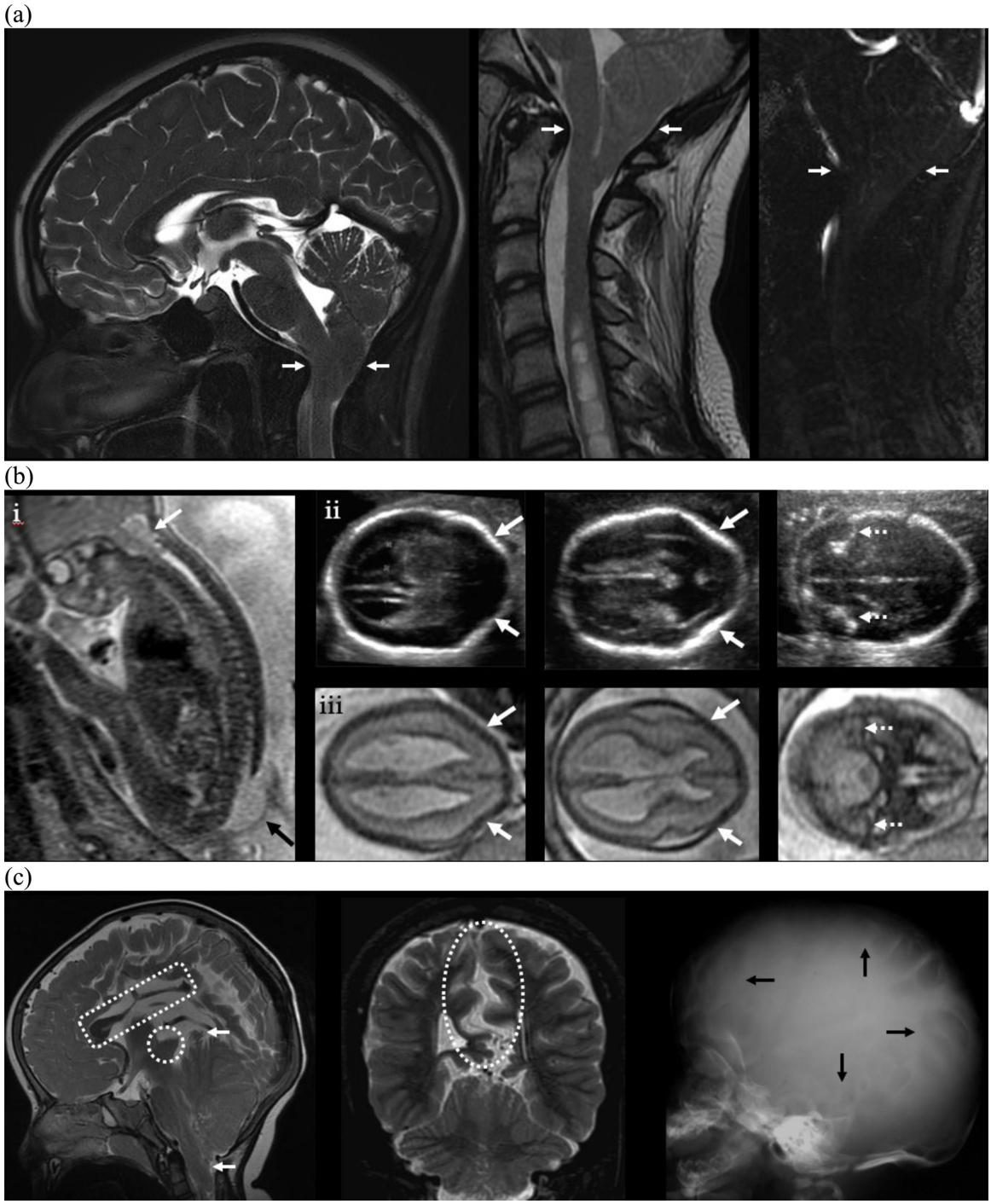
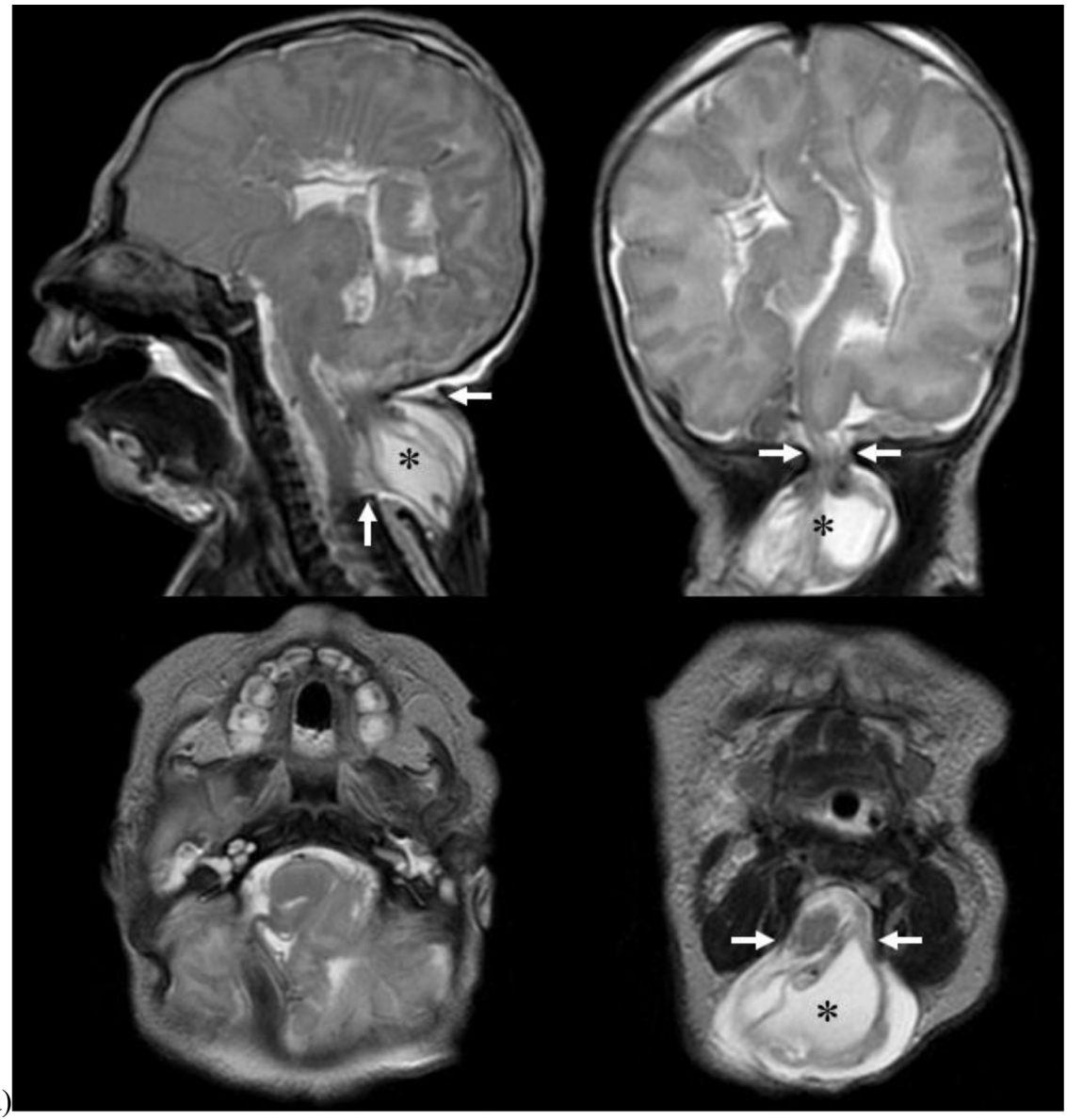


Figure 7 Chiari malformations. (A) Chiari 1 malformation due to platybasia with posterior fossa crowding (arrows). The cerebellar tonsils are pointed and inferiorly herniated, with cervical cord syrinx and decreased CSF flow through the craniocervical junction. (B) Fetal imaging of Chiari 2 malformation with lumbosacral spine myelomeningocele (i, black arrow) and resulting cerebellar tonsillar descent (i, white arrow). Brain US (ii) and MRI (iii) show ventriculomegaly, "lemon" sign with bifrontal concavity (solid arrows), and "banana" sign with herniated cerebellar tonsils surrounding the brainstem (dotted arrows). (C) Postnatal Chiari 2 with posterior fossa hypoplasia resulting in towering cerebellum and herniated cerebellar tonsils (white arrows), tectal beaking (dotted circle), callosal hypogenesis (dotted rectangle), paramedian stenogyria (dotted oval), and Luckenschädel skull (black arrows). (D) Chiari 3 with cervico-occipital encephalocele (arrows) resulting in cerebellar and occipital lobe herniation with encephalomalacia (asterisks).

linked to abnormalities of axonal guidance, cilia development, cell adhesion, proliferation, differentiation, and migration.[35] Complete and partial ACC are listed in the HPO (HP:0001274) and described at least once in ~350 rare disorders linked to ~250 genes or chromosomal loci, almost all syndromic.[5]



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Septo-Optic Dysplasia

Septo-optic dysplasia (SOD) encompasses a wide spectrum of forebrain malformations. At least two of the classic de Morsier triad should be present for diagnosis: (1) callosal hypogenesis with absent septum pellucidum, (2) optic nerve hypoplasia, and (3) hypothalamic-pituitary dysfunction.[36] Importantly, nonvisualization of the septum pellucidum without associated midline findings is not an indication for genetic workup. The septum can be poorly seen due to imaging technique, as well as acquired thinning or perforation associated with ventriculomegaly.[37] Cavum septum pellucidum refers to fluid filling the potential space between the septal leaves, and represents normal anatomic variation particularly in fetuses and neonates.[38,39] When the septum is truly absent, there is a lack of indentation between the frontal horns, creating a "boxcar" appearance. In addition, the absence of membranous connection between the callosum and fornices leads to sagging of the latter. Optic nerve hypoplasia is an ophthalmologic diagnosis, but may be visible on MRI if severe. Hypothalamic-pituitary dysfunction is based on hormonal testing, and can be present even if the pituitary gland appears normal on MRI. Potential imaging abnormalities include posterior pituitary ectopia, stalk interruption, or panhypopituitarism may be identified at imaging. The olfactory region is another forebrain derivative that can be affected, producing Kallmann syndrome with hyposmia or anosmia.[40] Overall, the spectrum of SOD manifestations is broad and includes incomplete SOD, complete SOD, and

"SOD plus" with additional cerebral, cerebellar, and/or orbital malformations.[41,42] Most cases are sporadic, and a genetic etiology is seldom identified. Only a small number of genetic loci have been implicated (HESX1, SOX2/3, OTX2), collectively accounting for <1-5% of cases (Fig. 5).[43,44]

Holoprosencephaly

Holoprosencephaly (HPE) refers to a spectrum of ventral induction abnormalities with varying degrees of forebrain fusion/dysplasia along the ventral floor plate, essentially representing a more severe version of SOD.[45-48] Fusion can involve the frontal lobes, deep gray nuclei, ventricles, and cerebral arteries (azygos anterior cerebral artery). The anterior corpus callosum may be deficient, which effectively distinguishes HPE from pACC. Craniofacial structures can also be involved, with manifestations including hypotelorism and single median maxillary central incisor. Anatomically and clinically, the most severe form is alobar HPE with a rudimentary "pancake" brain located in the anterior cranial cavity and large dorsal monoventricle. Semilobar HPE involves partial fusion and malrotation of the frontal lobes and deep gray nuclei. The third ventricle is characteristically small and a midline dorsal cyst may be present. Lobar HPE refers to mild fusion of the basal frontal lobes and anterior corpus callosum. The frontal horns may be hypoplastic and sylvian fissures anteromedially displaced.[49,50] More recently described variants include sublobar or septopreoptic HPE, with minimal fusion of the basal forebrain[51]; and syntelencephaly or middle interhemispheric variant (MIH) involving the dorsal roof plate, typically posterior frontal and anterior parietal lobes.[52,53]

Likely because of the fundamental biological processes involved, chromosomal aberrations (most commonly trisomy 13, but various additional chromosomes and mechanisms) account for 25%-50% of HPE cases; therefore HPE is one of the few remaining justifications for karyotyping in the neonatal period. CNVs detectable by microarray account for another 10% of cases. 18%-25% of cases have identifiable single nucleotide variants (SNV) or indels in single genes, though most are syndromic and exceedingly rare. The most common causes of nonsyndromic HPE include SHH, GLI2, SIX3, TGIF (ventral floor plate) and ZIC2 (dorsal roof plate), which collectively cause 17% of HPE (Fig. 6).[54-57]

Chiari Malformations

Chiari malformations are congenital posterior fossa abnormalities with a diverse imaging classification. The unifying imaging feature is a small posterior fossa with dysplastic tonsils herniated below the skull base. Such a configuration can obstruct cerebrospinal fluid (CSF) flow through the craniocervical junction, producing a spinal cord syrinx. In Chiari 1, the posterior fossa abnormality is isolated.[58] In higher Chiari malformations, there are additional brain abnormalities due to a congenital neural tube defect, that is lumbosacral myelomeningocele in Chiari 2 and cervico-occipital encephalocele in Chiari 3. The presence of a CSF leak *in utero* causes developmental CSF hypotension with global brain manifestations, which can include aberrant sulcation, stenogyria (multiple small folds), polymicrogyria, heterotopia, callosal hypogenesis, enlarged massa intermedia, tectal beaking with fused superior and inferior colliculi, small tentorial incisura with upward and downward cerebellar herniation, and dorsal cervicomedullary kink. The Management of Myelomeningocele Study (MOMS) demonstrated that fetal myelomeningocele closure reduces hydrocephalus and hindbrain herniation, and improving short and long-term outcomes compared to postnatal surgery.[59-61]

True diagnosis of Chiari requires clinical confirmation with a high-pressure, position-dependent occipital headache. For patients with worsening symptoms, surgical posterior fossa decompression with optional tonsillectomy can relieve pressure on the brainstem and restore CSF flow through the craniocervical junction. Of note, other disorders can mimic Chiari malformations on imaging but require different management. For example, CSF hypotension, posterior fossa tumors, and craniofacial syndromes can also present with tonsillar crowding and herniation. Additional proposed Chiari subtypes are somewhat controversial, but include Chiari 0 (cord syrinx without posterior fossa abnormality), Chiari 0.5 (isolated brainstem sag), Chiari 1.5 (tonsillar and brainstem descent), Chiari 4 (hypoplastic cerebellum), Chiari 5 (absent cerebellum with occipital horn herniation) (Fig. 7).[62]

Given the vast heterogeneity of Chiari malformations, underlying etiology and genetics are poorly understood.[63,64] Various chromosomal aberrations have been described in Chiari 1 patients.[65] Secondary (complex) Chiari 1 is associated with several genetic syndromes including the FGFR, ERF, RAS/MAPK, and PTEN-PI3K/AKT pathways.[66]

Dandy-Walker Spectrum

Dandy-Walker malformation refers to a wide spectrum of infratentorial malformations characterized by cerebellar underdevelopment with incomplete downward rotation. Regional leptomeningeal development is also impaired, resulting in cystic dilation of the subarachnoid space. True Dandy-Walker malformation (DWM) involves cerebellar hypoplasia and incomplete rotation. An inferiorly gaping fourth ventricle communicates openly with the cisterna magna, producing a "keyhole" appearance. The torcular herophili can be elevated above the level of the lambdoid sutures (torcular-lambdoid inversion). Occipital cephalocele and other CNS malformations can be present. Dandy-Walker variant (DWV) is a milder form of DWM, with less severe cerebellar hypoplasia and malrotation. Mega cisterna magna (MCM) refers to dilation of the posterior fossa subarachnoid space, sometimes with scalloping of the occipital inner table due to leptomeningeal underdevelopment. Isolated MCM, in which the cerebellum is fully developed, does not require clinical or genetic workup (Fig. 8).[67-70] MCM should be distinguished from arachnoid cyst, which is delimited from surrounding walls and exerts asymmetric mass effect on the cerebellum. Another differential diagnosis is the Blake pouch

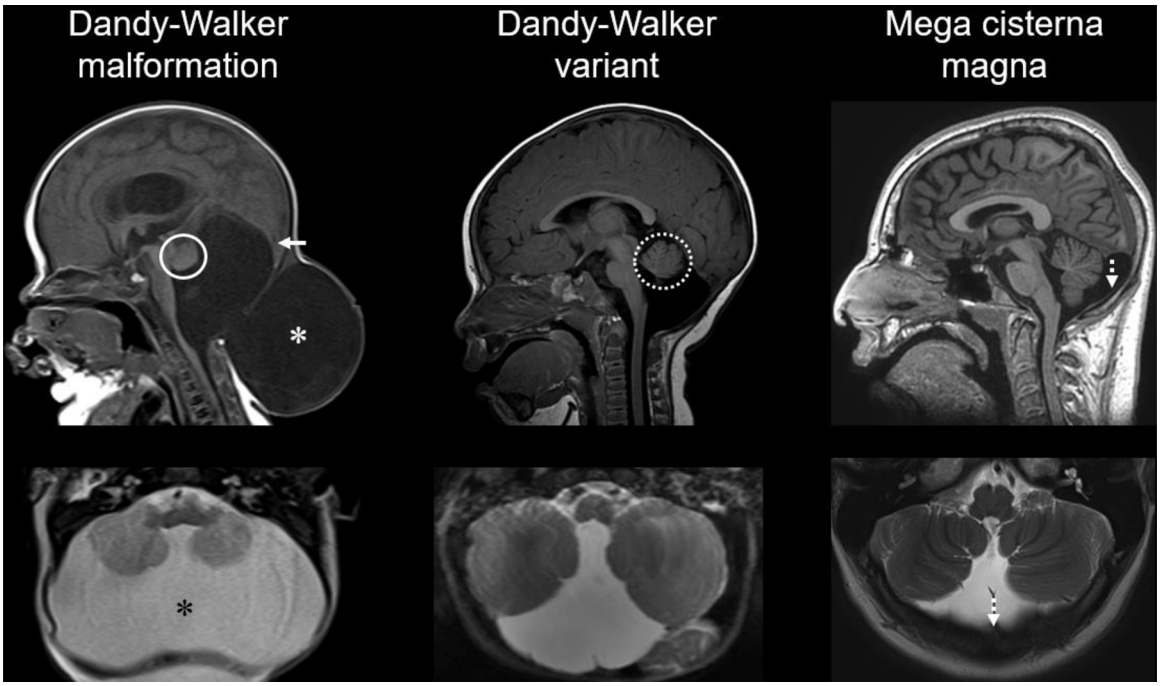

Figure 8 Dandy-Walker spectrum. True Dandy-Walker malformation shows hypoplastic cerebellum (circle) with counterclockwise rotation, torcular elevation "torcular-lambdoid inversion" (solid arrow), and occipital cephalocele (asterisk). Dandy-Walker variant is a milder manifestation with less severe cerebellar hypoplasia and malrotation (dotted circle). Mega cisterna magna refers to dilation of the posterior fossa subarachnoid space, sometimes with scalloping of the occipital inner table (dotted arrows).

cyst, which results from embryonic nonperforation of the tela choroidea at the foramen of Magendie, with progressive cystic dilation and uplifting of a normally formed cerebellum.[71,72]

Although the pathogenesis of DWM is not fully understood, several cases are linked to genetic loci, including numerous chromosomal aberrations (most commonly trisomy 18) and copy number variations.[73] Deletions or loss of function variants in three transcription factors (FOXC1, ZIC1 and ZIC4) are best described, but account for only 5% of cases.[74] DWM is associated with over 70 monogenic loci overall in the HPO.[5] Syndromic malformations and congenital infections can also manifest with DWM, frequently in combination with other CNS malformations. A comprehensive effort to exhaustively search for genetic causes of DWM demonstrated a diagnostic yield of exome sequencing of 16%.[75]

Joubert Syndrome-Related Disorders

Joubert syndrome-related disorders (JSRD) are a complex group of posterior fossa dysplasias with a characteristic "molar tooth" appearance of the midbrain at imaging.[75-77] On diffusion tensor imaging, there is absent decussation of the superior cerebellar peduncles, resulting in a deep interpeduncular fossa ("crown" of molar tooth). The superior cerebellar peduncles fail to decussate (analogous to Probst bundles), and appear thickened, parallel, and horizontal ("roots" of molar tooth). Hindbrain malformations can include cerebellar dysplasia with hypoplastic vermis and internally malrotated hemispheres (**Fig. 9**).[78,79] Cerebellar clefts, heterotopias, and rhombencephalosynapsis have also been reported. Patients can have additional ocular, renal, liver, craniofacial, and digital abnormalities.[80]

JSRD have been widely linked to abnormalities of cilia development and function. While a large number of genetic loci have been described, the most commonly reported ciliopathy mutations are AHI1, CPLANE1, CC2D2A, CEP290, KIAA0586, MKS1 and TMEM67, which have been reported in >5% of affected cases for at least one reasonably sized cohort. Nearly all described JSRD loci are autosomal recessive, except for oro-facial-digital syndrome (OFD1) which is X-linked, The sensitivity of sequencing is very high, except in nephronophthisis (NPHP1) where 25% of cases have a CNV. Therefore, a reasonable approach is to perform comprehensive sequencing of known JSRD loci, plus CNV analysis of NPHP1 and a few other loci reported to yield a diagnosis in the majority of patients (60 to over 95%, depending on the series). Also, panel testing is highly likely to be successful, and is a reasonable alternative to ES/GS per patient/family preference or when resources are constrained.[80-84]

Pontine Tegmental Cap Dysplasia

Pontine tegmental cap dysplasia is an unusual malformation in which transverse pontine fibers course ectopically along the dorsal brainstem, yielding a characteristically small basis pontis and dorsal pontine "cap" (**Fig. 10**).[85,86] Associated findings include cranial nerve, brainstem, internal auditory

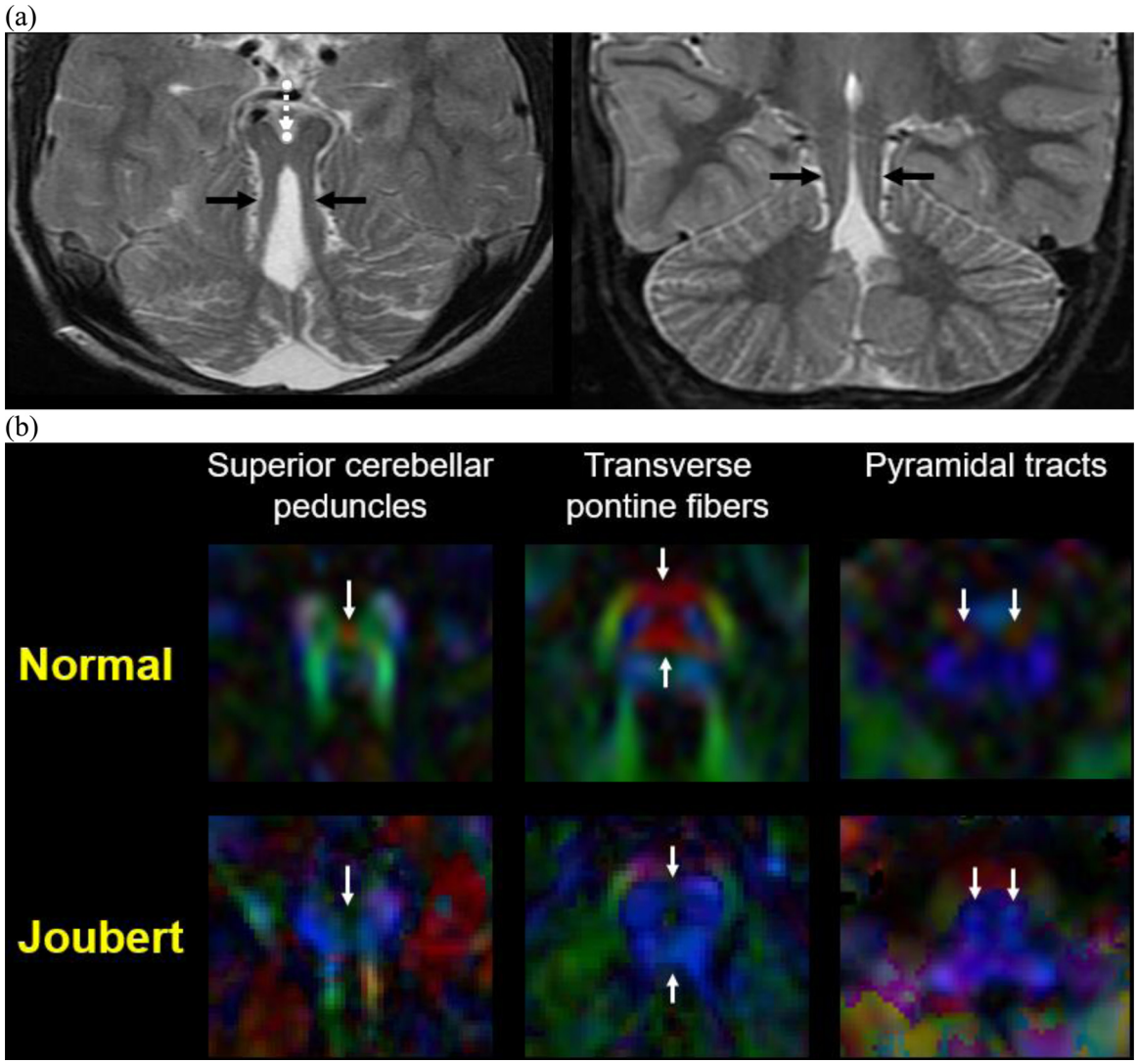

Figure 9 Joubert syndrome-related disorders. (A) Joubert syndrome-related disorders are characterized by a "molar tooth" appearance of the midbrain, which results from absent decussation of the superior cerebellar peduncles with a deep interpeduncular fossa (dotted white arrow) and thickened parallel superior cerebellar peduncles (black arrows). The cerebellum is variably dysplastic with small vermis and malrotated hemispheres. (B) Diffusion tensor imaging fractional anisotropy maps demonstrate the "central red dots" (top row, arrows) corresponding to normal midline decussations in the brainstem at the level of midbrain, pons, and medulla. These decussations are absent in Joubert syndrome (bottom row, arrows). (Color version of figure is available online.)

canal and ocular anomalies.[87] Diffusion tensor imaging can reveal additional connectivity changes, such as ectopic peripontine arcuate fibers.[88-90] This disorder is theorized to reflect abnormal axonal pathfinding and/or neuronal migration, though a clear locus has not been identified. A few cases have been reported with genetic overlap in cerebellar and oculoauriculovertebral spectrum disorders.[91-95]

Rhombencephalosynapsis

Rhombencephalosynapsis (RES) refers to partial or complete absence of the cerebellar vermis and cerebellar hemispheres, including lobules, nuclei, and afferent/efferent connections. The folia and white matter tracts course horizontally across midline, and the deep gray nuclei are medialized or fused (Fig. 11). Patients may have additional brain malformations, craniofacial abnormalities, and visceral defects (cardiac, renal, musculoskeletal).[96-100]

RES has broad genetic heterogeneity and has been described with various chromosomal abnormalities. Given the rarity of familial occurrences, linkage studies have yet to be undertaken to identify causal genes. RES has been reported in association with Gómez-López-Hernández (cerebello-trigeminal-dermal dysplasia) syndrome, GM1 gangliosidosis, VACTERL association, and autosomal dominant polycystic kidney disease.[101-107] MN1 C-terminal truncation syndrome is a newly described condition with partial RES, perisylvian polymicrogyria, and craniofacial abnormalities.[108,109] In the HPO, N-terminus CAG repeat single gene mutations associated with RES are seen exclusively in conjunction with HPE.[5,110]

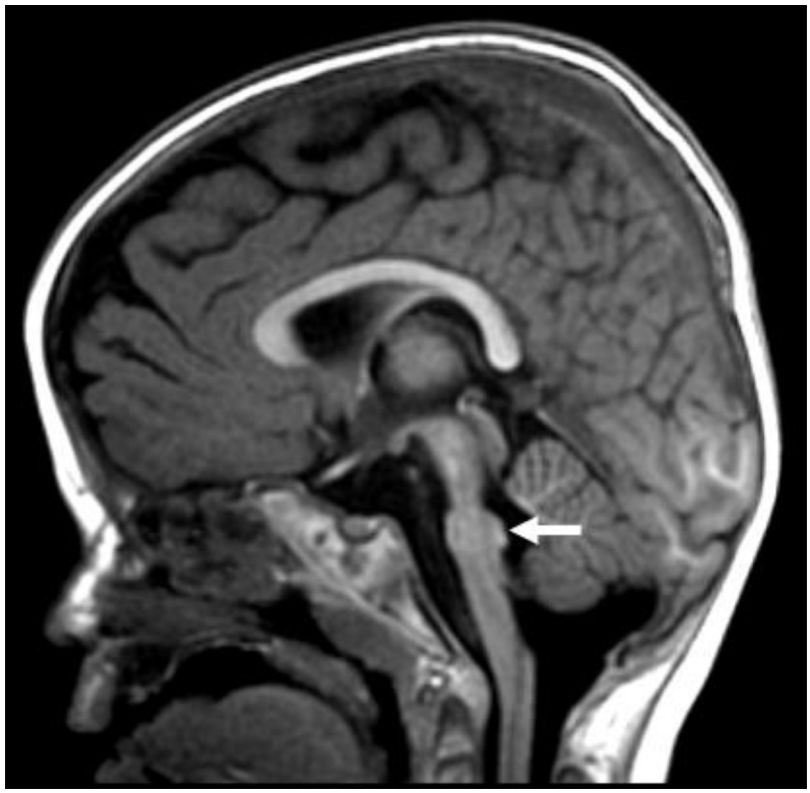

Figure 10 Pontine tegmental cap dysplasia. Sagittal image shows small basis pontis with ectopic dorsal pontine bump (arrow).

Destructive Lesions

Destructive (encephaloclastic) lesions occur when the normally developing brain is damaged by an acquired insult, such as infection, ischemia, or trauma. The resulting malformations have characteristic appearances based on the developmental stage at the time of insult. Prenatal history and laboratory testing may point to an inciting congenital infection or other disruptive event. Most cases are nongenetic, though workup may be indicated for atypical or severe presentations.

Acrania-Exencephaly-Anencephaly Sequence

The acrania-exencephaly-anencephaly sequence is the earliest and most severe destructive brain insult that occurs during gestation. Acrania refers to partial (merocrania) or total (holocrania) absence of the cranial vault. This exposes the brain parenchyma to repeated mechanical trauma, as well as chemical injury by amniotic fluid. Most cases are sporadic with increased risk of maternal folate deficiency, as with other neural tube defects. There is association with additional ectodermal defects including amniotic band syndrome,

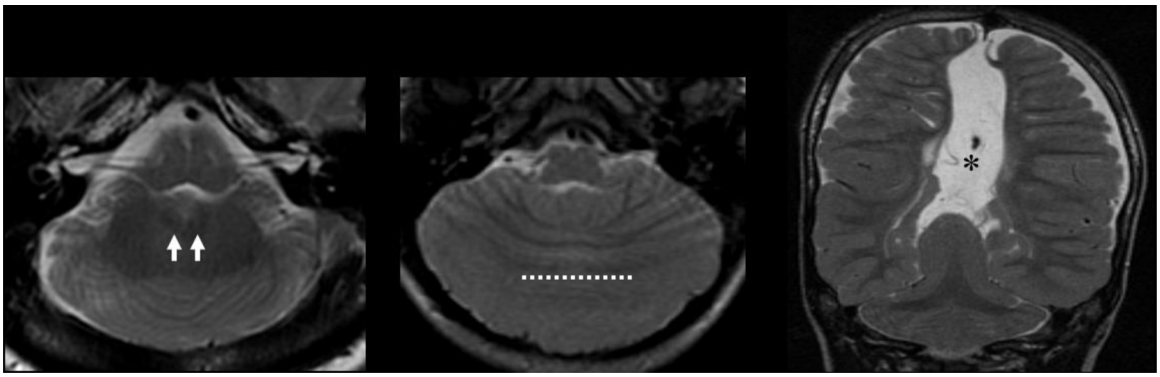

Figure 11 Rhombencephalosynapsis. Fused cerebellar hemispheres with absent vermis, medialized dentate nuclei (arrows), and horizontal folia (dotted lines). Supratentorial abnormalities are frequently associated (asterisk).

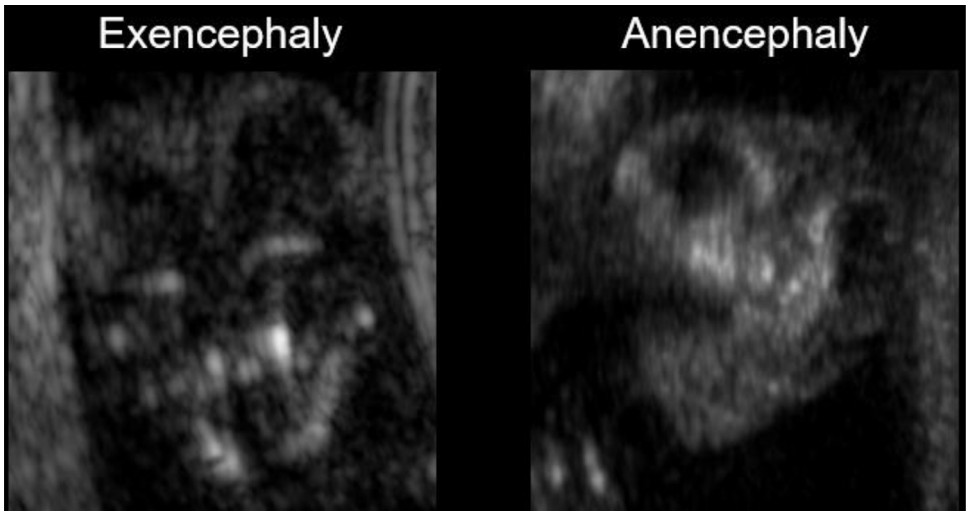

Figure 12 Acrania-exencephaly-anencephaly sequence. Absence of the cranial vault in utero (acrania) results in chemical and mechanical damage to the developing brain. As the cerebral hemispheres degenerate, they form a "Mickey Mouse" appearance (exencephaly). In the end stage, there is a "frog face" appearance with minimal angiomatous stroma and no intact supratentorial brain parenchyma.

limb–body wall complex, and pentalogy of Cantrell. Exencephaly represents the intermediate stage with partial degeneration of cerebral hemispheres, whileanencephaly represents the end stage of degeneration into angiomatous stroma with residual facial structures (Fig. 12).[111-116]

Schizencephaly & Porencephaly

Schizencephaly is caused by an early gestational insult (<20-24 weeks) that occurs prior to migration of cortical progenitor cells. The resulting defects can be closed-lip, narrow open-lip, or wide open-lip, with larger defects demonstrating greater neurological deficits. As development progresses, cortical cells migrate to the periphery of the intact brain, including the edges of the destroyed cavity, which become lined by disorganized gray matter (polymicrogyria). Optimal imaging evaluation of schizencephaly requires high-resolution multiplanar technique, since low-resolution studies may suffer from volume averaging. A unique imaging feature is the ventricular "dimple", which marks the pial-ependymal seam of CSF connecting the ventricular system to the subarachnoid space (Fig. 13).[6,117-120]

Porencephaly is caused by a mid-gestational (~second trimester) insult, at which point cortical neurons have already fully migrated to the surface of the brain. As a result, the encephaloclastic cavity becomes lined by white matter with relatively smooth margins. Due to the immaturity of supporting astroglial cells, porencephalic cysts show near-complete internal liquefaction and minimal surrounding scarring. Cysts adjacent to the ventricle can fully resorb, creating an ex vacuo appearance (Fig. 14).[6,120,121]

Genetic evaluation of encephaloclastic disease has been historically focused on severe cerebrovascular disease, for example mutations of collagen type IV (COL4A1, COL4A2) causing fetal hemorrhage and/or ischemia, which were originally thought to account for up to 50% of cases.[122-126] Subsequent investigations have demonstrated a larger range of causal genes and wider uncertainty of the fraction of disease presently explainable by genetic testing. The Neuro-MIG Group, a pan-European multidisciplinary network on brain

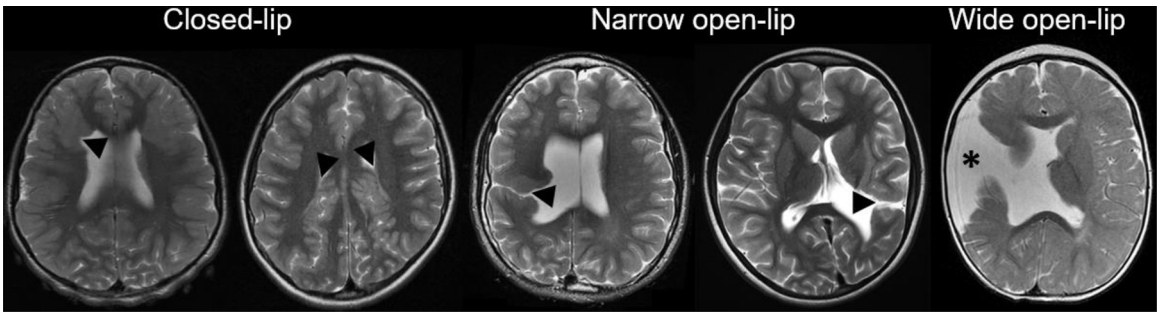

Figure 13 Schizencephaly. Early gestational insults produce grey matter-lined polymicrogyric clefts that can be closed- or open-lip, depending on the severity of brain destruction. Associated ventricular "dimple" reflects the encephaloclastic nature of the insult, with formation of a contiguous pial-ependymal seam (arrowheads).

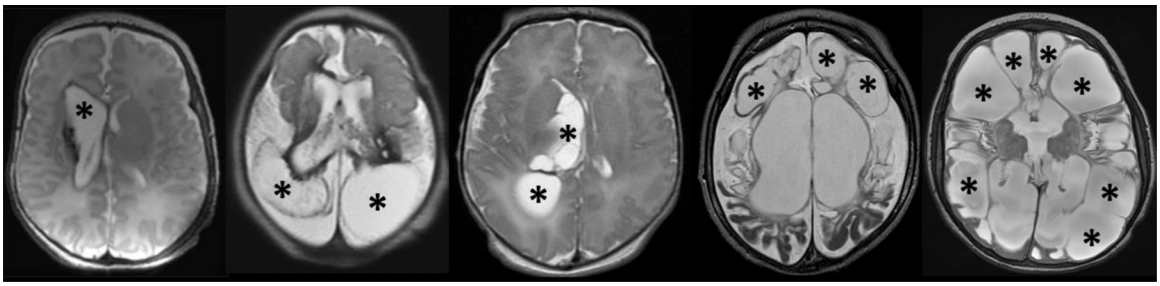

Figure 14 Porencephaly. White matter-lined encephaloclastic cavities (asterisks) abutting the lateral ventricles with minimal astrogliosis, reflecting midgestational ischemic insults.

malformations, has summarized 27 known encephaloclastic genes, and recommends evaluation of all loci whenever a genetic cause of schizencephaly or porencephaly is sought. In practice, it may be difficult to ensure that a commercial panel meets the Neuro-MIG standard. Therefore, it may be easier to obtain ES or GS and direct the lab's attention to relevant mutations (Neuro-MIG also endorses 'exome slice' with reflex to ES).[6]

Hydranencephaly

Hydranencephaly is a severe form of porencephaly affecting nearly the entire cerebral mantle ("transmantle"), with minimal sparing of the posterior cerebrum, basal ganglia, and infratentorial structures due to autoregulation.[127-130] Again, because of astroglial immaturity at this stage, the majority of supratentorial brain is resorbed and replaced by CSF cavities. Most cases are felt to be sporadic and related to severe prenatal insults (ischemic, infectious, metabolic) with bilateral ICA occlusion (**Fig. 15**).[131-133]

Genetic causes are poorly understood and largely limited to individual case reports or small series (COL4A1, PIK3CA, LAMB1, CEP55, TUBA1A).[134-138] These may in fact be phenocopies that correspond to severe manifestations of genetic encephaloclastic insults. The only well-characterized genetic condition is Fowler syndrome, caused by biallelic pathogenic variants in the FLVCR2 gene, This presents as hydranencephaly (secondary to proliferative vasculopathy) and multiple pterygia characterized by joint contractures and webbing (resulting in fetal akinesia deformation sequence).[139,140]

Maximal Hydrocephalus

Unlike hydranencephaly, in hydrocephalus there is an intact cortical mantle that is simply compressed by the dilated ventricular system. Etiologies of pediatric hydrocephalus include congenital malformations such as aqueductal stenosis, Chiari malformation, or Blake pouch cyst; tumors; infection/inflammation; and hemorrhage associated with prematurity or coagulopathy. The level of obstruction can be within the ventricular system (obstructive, noncommunicating) or at the level of arachnoid granulations (nonobstructive, communicating). "Dangling" choroid plexus may be seen floating dependently within the enlarged lateral ventricles. In severe hydrocephalus, ventricular diverticula can outpouch and herniate over dural reflections, including the falx cerebri and tentorium cerebelli. Surgical CSF diversion and/or correction of the inciting etiology will allow for parenchymal reexpansion (**Fig. 16**).[141,142]

Etiologies of congenital hydrocephalus are extremely broad, including both sporadic and genetic conditions. It is important to evaluate the underlying cause and identify any

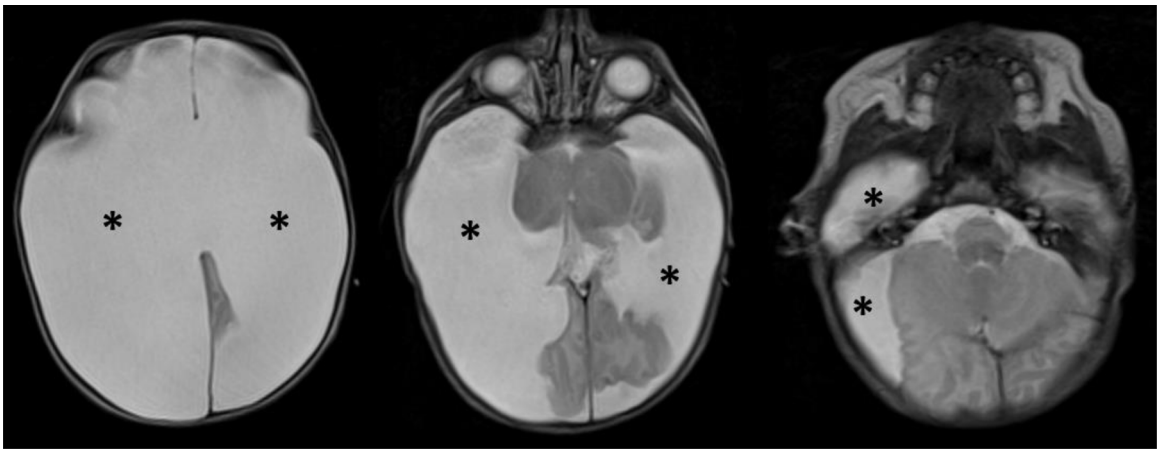

Figure 15 Hydranencephaly. Supratentorial transmantle porencephaly with near-complete absence of supratentorial brain parenchyma (asterisks). A small amount of posterior cerebrum, basal ganglia, and cerebellum are preserved.

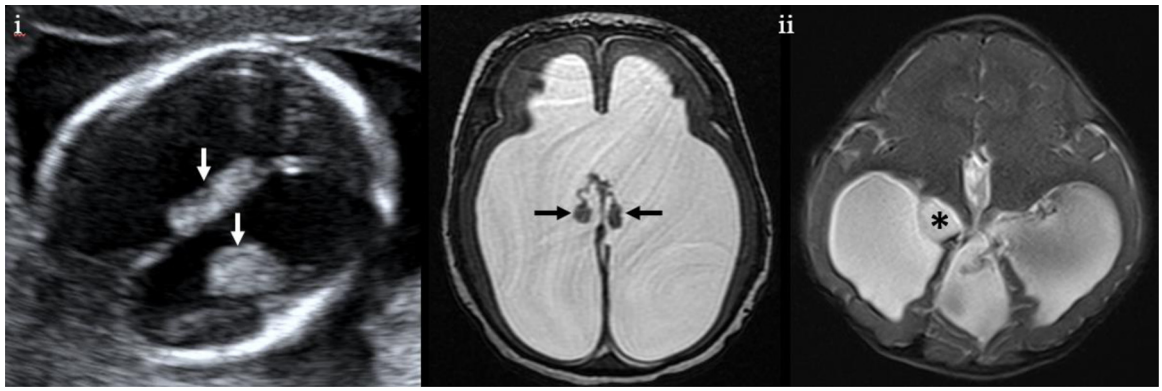

Figure 16 Maximal hydrocephalus. Fetal head ultrasound (i) shows ventriculomegaly with dependently dangling choroid plexus (white arrows). Postnatal MRI (ii) with floating choroid (black arrows) and thinned cortical mantle compressed against the inner table. Right atrial diverticulation (asterisk) extends over the tentorium cerebelli.

brain malformations that can direct appropriate genetic testing.[143-150]

Encephalomalacia

Encephalomalacia is observed with later (at least third trimester) acquired brain injuries, at which time the astroglia have matured and proliferated. Brain injuries are thus associated with greater parenchymal gliosis involving scarring, septations, and wall irregularity (Fig. 17).[151,152]

Although cystic encephalomalacia was historically considered to be sporadic, more recent reports describe certain genetic mimics of neonatal hypoxic-ischemic injury. For example, sulfur metabolism defects and Molybdenum Cofactor Deficiency (MoCD) can demonstrate fetal/neonatal cystic encephalomalacia. One form of MoCD has an approved treatment, making early diagnosis crucial. When this condition is under consideration, rapid ES or GS in parallel with biochemical studies is indicated. Empiric trials of therapy while awaiting confirmation may also be considered.[153,154]

Migrational Lesions

Malformations of cortical development (MCDs) are caused by abnormalities of neural migration. Depending on the underlying mechanism, a vast array of morphological abnormalities can result with focal, segmental, or diffuse patterns. We cover major classes of MCDs related to undermigration, overmigration, and organization.

Gray Matter Heterotopia

Gray matter heterotopia refers to collections of normal gray matter in abnormal locations. Periventricular or subependymal heterotopia results from early neural disruption at the level of the ventricular ependyma, resulting in complete failure of outward migration. Subcortical or columnar heterotopia refers to a partially or fully transmantle mass of gray matter ("pseudotumor"), which can integrate blood vessels and CSF (Fig. 18).[6,155-160] Band heterotopia indicates undermigration, which will be discussed in the Lissencephaly-Pachygyria section. Leptomeningeal heterotopia indicates

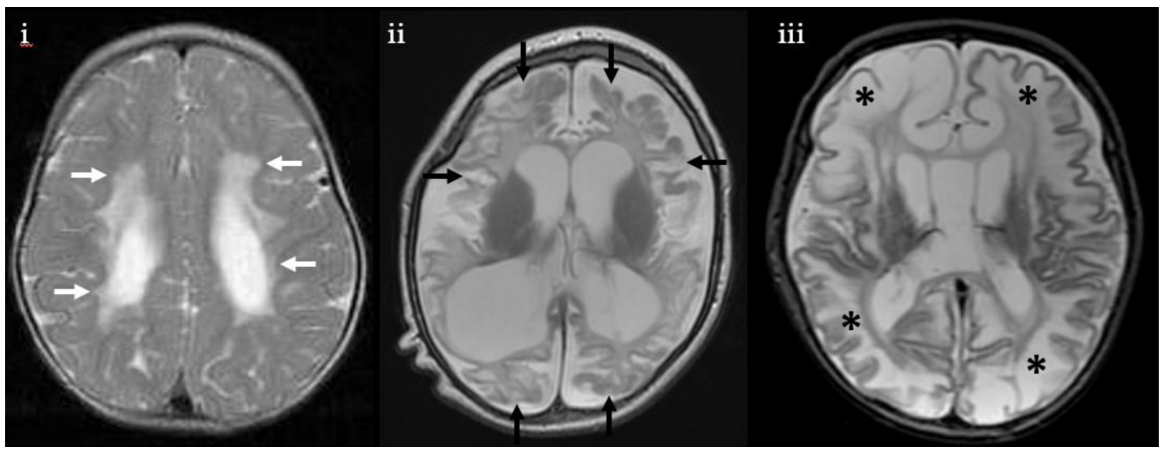

Figure 17 Encephalomalacia. Preterm brain injury (i) with wedge-shaped periventricular white matter hyperintensities (arrows). Term brain injury (ii) with global volume loss and ulegyria preferentially affecting the deep cerebral sulci. Severe hypoxic-ischemic injury (iii) with developing multifocal cystic encephalomalacia (asterisks).

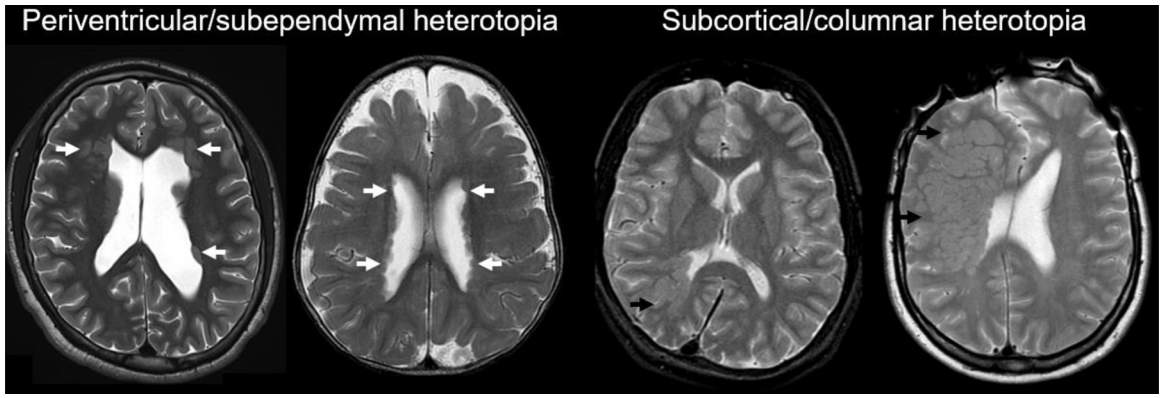

Figure 18 Gray matter heterotopia. Periventricular or subbependymal heterotopia can be focal or diffuse (white arrows). Subcortical or columnar heterotopia demonstrates a pseudotumor appearance (white arrows) with mass effect and swirling/infolding of cortical vessels.

overmigration, which will be discussed in the Cobblestone Cortex section.

In practice, the most common finding is periventricular nodular heterotopia (PVNH), with multiple nodules of grey matter studding the lateral ventricles. PVNH can occur in isolation or be associated with other brain and body malformations. PVNH has been reported in conjunction with numerous different CNVs. The most common mutation affects the cytoskeletal protein filamin A (FLNA), which shows X-linked inheritance with variable expressivity. When a child tests positive for FLNA, it is not uncommon to discover an affected mother as well.[161,162] Heterotopia can also be seen in association with various chromosomal aberrations and genetic conditions.[163-170]

Lissencephaly-Pachygyria

Previously termed "classic" or "type I" lissencephaly, the lissencephaly spectrum now includes various degrees of undermigration. From most to least severe, these are classified as agyria (absent gyri), pachygyria (broad gyri), and subcortical band heterotopia (SBH). The fetal brain starts out with a rudimentary "figure 8" gyral pattern and simplified cortical architecture, then subsequently folds and organizes from the second trimester through postnatal life. Partial lissencephaly presents with thin underfolded cortex (molecular layer), subcortical cell-sparse zone (white matter), and thick heterotopic gray matter (trapped neuronal cell bodies). Band heterotopia is a milder condition with thicker and more normally folded cortex with thinner bands of subcortical gray matter (**Fig. 19A**).[6,156-160,171-173]

The severity and gradient of lissencephaly depend on the specific molecular pathogenesis. Classic Miller-Dieker syndrome is seen with LIS1 mutations, giving rise to posterior pachygyria and abnormal facies.[174,175] Double cortex (DCX) is an X-linked gene that produces anterior pachygyria and band heterotopia.[176,177] Norman-Roberts syndrome is seen with RLN or VLDRL mutations, yielding severe cerebellar hypoplasia with ataxia (**Fig. 19B**).[178,179]

Prior authors have proposed a general approach to prioritize genes for analysis and prognosticate clinical outcomes.[180-182] Given the enormous advances in sequencing capacity since the original publications, it is probably sufficient to recognize that a case is on the lissencephaly spectrum, and select an appropriate panel or pursue ES. The main exception is recognition of a possible case of Miller-Dieker syndrome due to a large deletion of at least PAFAH1B1 and YWHAE, detectable by microarray or even classical karyotype in some cases.

Cobblestone Cortex

Previously known as "cobblestone" or "type II" lissencephaly, the cobblestone cortex is now understood to represent a completely separate group of disorders related to overmigration.[6,156-160] Defects in the pial basement membrane (glia limitans) result in failed cytoskeletal attachments with disorganized and uncontrolled migration into the subpial and subarachnoid spaces. On imaging, the cortex can appear variably irregular, with gap size determining the overall morphology. Large glial gaps produce a pachygyria-like ("piano-key") appearance, while smaller gaps yield a polymicrogyria-like appearance. In the posterior fossa, cerebellar migration is guided by external granule cells that adhere to the basement membrane. The characteristic peripheral cerebellar cysts actually represent subarachnoid CSF inclusions engulfed by dysplastic leptomeningeal tissue.[183-186] Additional imaging features can include brainstem kinking, pontocerebellar hypoplasia, and hypomyelination reflective of diffusely disordered development (**Fig. 20**).[187-189]

There are two major considerations in the genetic evaluation of cobblestone cortex. The first is the co-occurrence of muscle and/or eye diseases, caused by alpha-dystroglycanopathies including muscle-eye-brain disease, Fukuyama muscular dystrophy, and Walker-Warburg syndrome.[190-197] The second is awareness that the earlier literature conflated cobblestoning with polymicrogyria and/or lissencephaly. Indeed, The HPO still indexes cobblestoning as 'Type II lissencephaly (HP:0007260).[5]

Polymicrogyria

Polymicrogyria (PMG) refers to multiple small and irregular cerebral gyri. Currently, PMG is classified as an abnormality

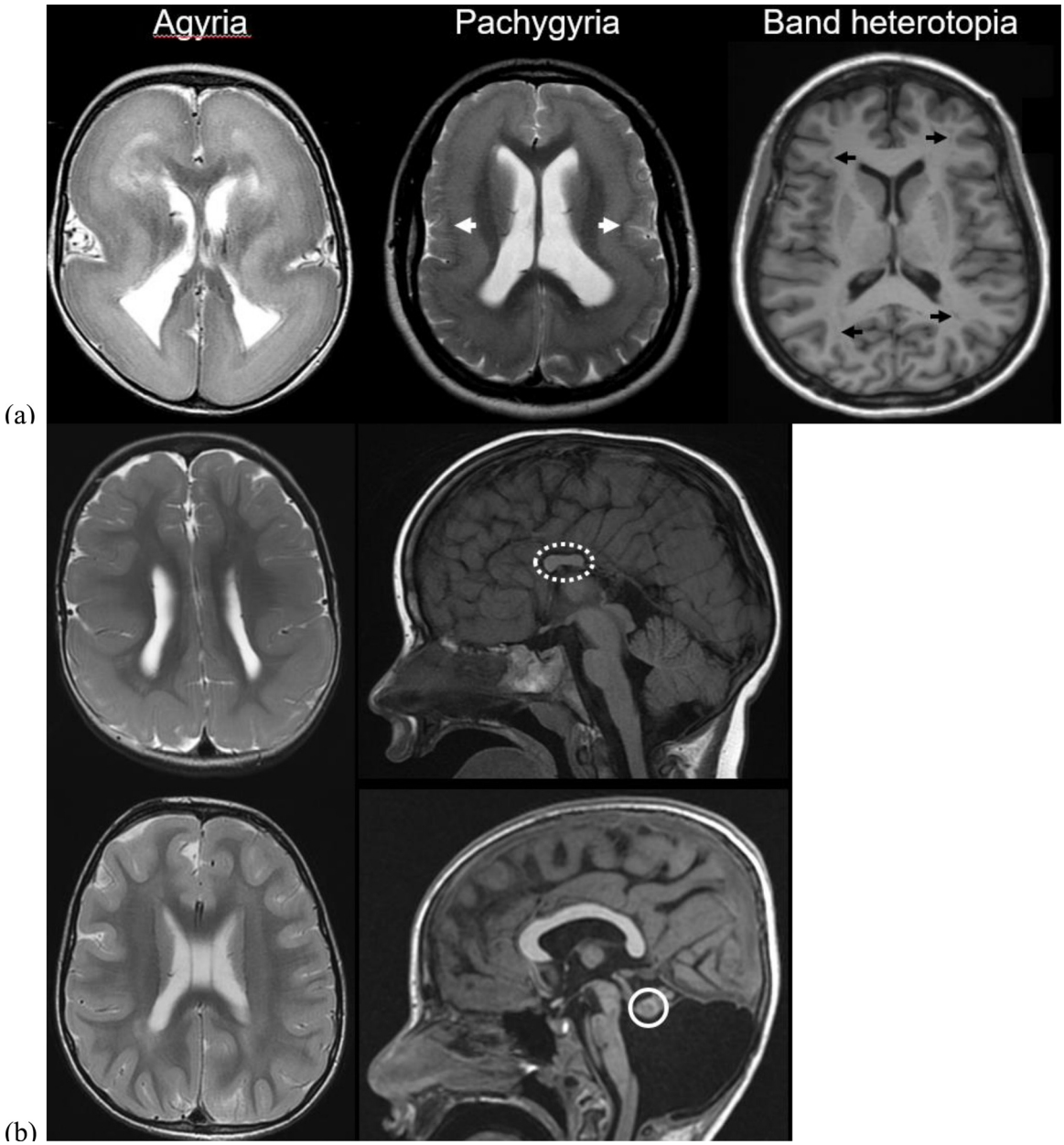

Figure 19 Lissencephaly-pachygyria on postnatal imaging. (A) Classic lissencephaly spectrum. Agyria refers to complete lissencephaly with "figure 8" brain showing absent gyration and simplified cortical layers. Pachygyria or "thick cortex" represents partial lissencephaly with thin underfolded cortex, subcortical cell-sparse zone, and thick subcortical gray matter (white arrows). Band heterotopia designates thicker and more normally folded cortex with thinner bands of subcortical gray matter (black arrows). (B) Variant lissencephaly with callosal hypogenesis (dotted oval) and cerebellar hypoplasia (solid circle).

of late neuronal migration and early cortical organization. Optimal imaging evaluation requires high-resolution multiplanar technique, since low-resolution studies may suffer from volume averaging. On conventional MRI field strengths, the appearance of PMG can vary between thin irregular, deep sawtooth, and thick palisaded morphologies (**Fig. 21**).[198-201] On ultra-high-field imaging, the appearance of PMG is much more uniform due to the ultrahigh spatial resolution.[202,203]

PMG shows tremendous variation in pathogenesis, distribution, and histologic features, with the HPO describing over 200 associated genes.[5,6,156-160] PMG is also described in early destructive congenital infections (eg, cytomegalovirus, Zika virus).[204,205] Of note, the PIK3CA-related overgrowth syndromes (PROS) arise from somatic mutations that may not be detected by blood testing. One characteristic overgrowth phenotype is MPPH, megalencephaly-polydactyly-polymicrogyria-hydrocephalus syndrome. With suspected overgrowth disorders, testing of affected tissue (eg, cheek swab, skin biopsy) is preferable to sequencing on blood, and targeted assays may be required.[206-212]

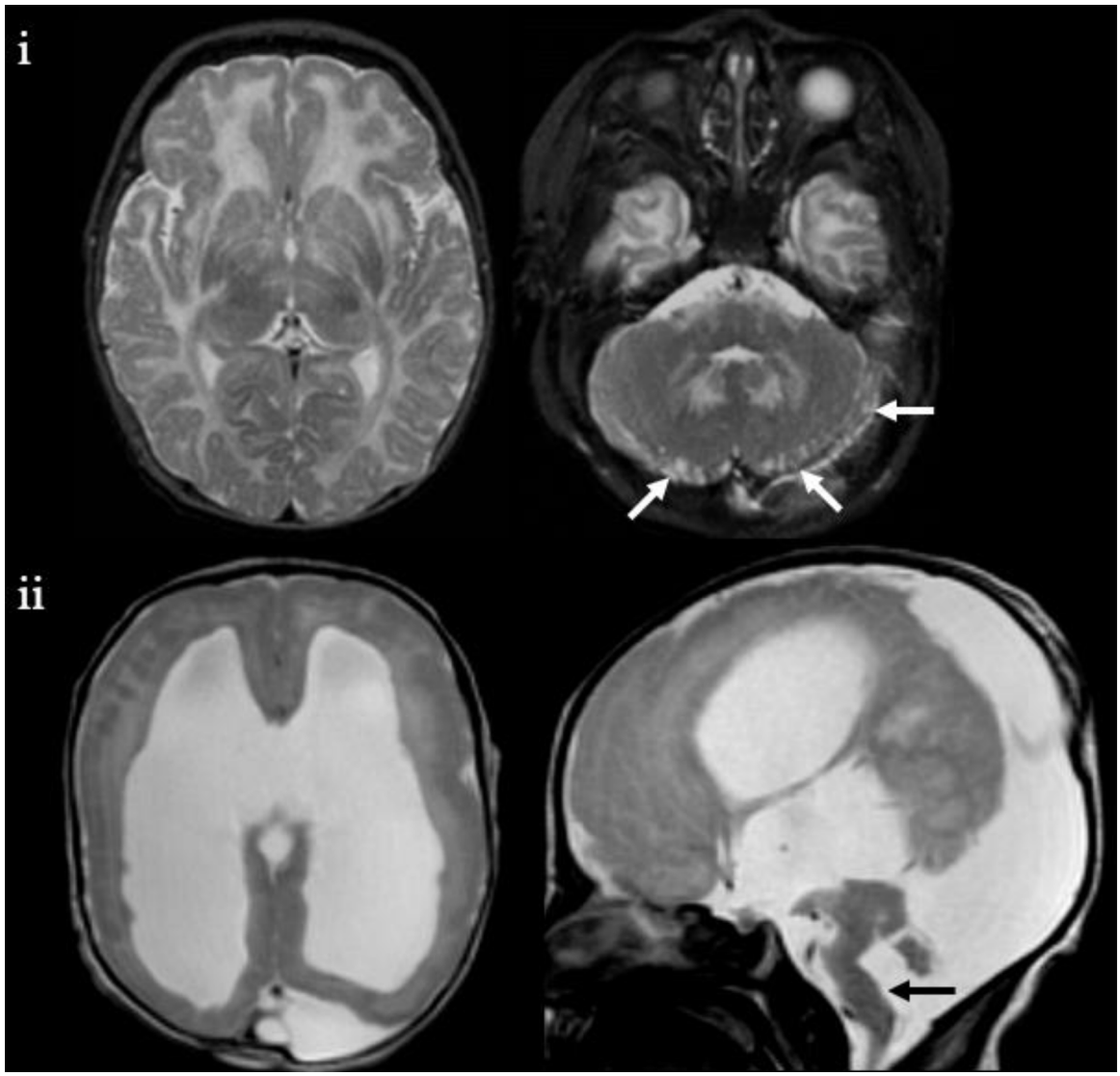

Figure 20 Cobblestone cortex. Dystroglycanopathy (i) with fine cobblestone cortex, white matter signal abnormality, and peripheral cerebellar cysts (white arrows). Walker-warburg syndrome (ii) with coarse "piano-key" cortex, periventricular nodular heterotopia, and Z-shaped brainstem (black arrow).

Megalencephaly

Megalencephaly (MEG) refers to hamartomatous brain overgrowth with disorganized migration, proliferation, and differentiation. Anatomic distribution can be segmental (lobar, quadrantic, hemispheric) or diffuse. Affected regions show regional parenchymal enlargement and disorganization, which can include accelerated and disorganized myelination, loss of gray-white distinction, abnormal brain folding, and other migrational abnormalities. There can be regional cutaneous stigmata, as well as soft tissue and bone overgrowth (**Fig. 22**).[6,156-160]

Overgrowth pathways have already been discussed in the setting of PMG, and can also manifest with megalencephaly. Most causal variants are either mosaic or de novo, rather than inherited.[206-212] A recently described autosomal recessive condition is STRADA-related MEG.[213,214] Aside from this, the major pathways to consider are AKT3, PIK3CA, PIK3R2, CCND2, PTEN, and mTOR, which may be distinguished clinically based on extra-CNS findings. Given the high burden of de novo and/or mosaic variants, targeted approaches are likely to be more productive than untargeted testing in blood. The one exception to this is the detection of large scale AKT3 deletions, which are still best detected by microarray.[215,216]

Focal Cortical & Miscellaneous Dysplasias

Focal cortical dysplasias are localized MCDs and represent the most common etiology of medically refractory epilepsy in children. The ILAE (International League Against Epilepsy) classification is based on histologic rather than radiologic criteria. FCD I is characterized by abnormal cortical lamination, which is radial in type Ia, tangential in Ib, and both in Ic. FCD II (Taylor dysplasia) has the best surgical

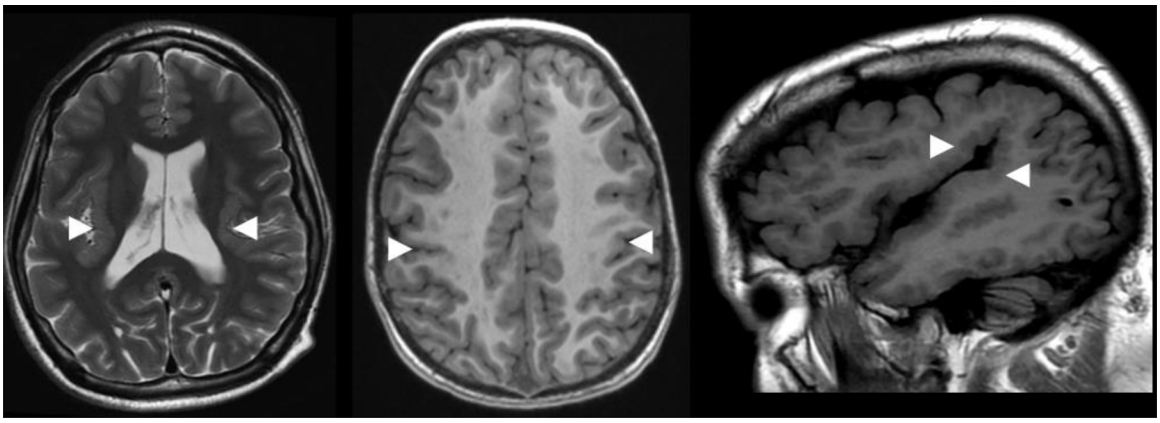

Figure 21 Polymicrogyria. Bilateral perisylvian cortical irregularity (arrowheads) with broad shallow Sylvian fissures and prominent overlying subarachnoid spaces.

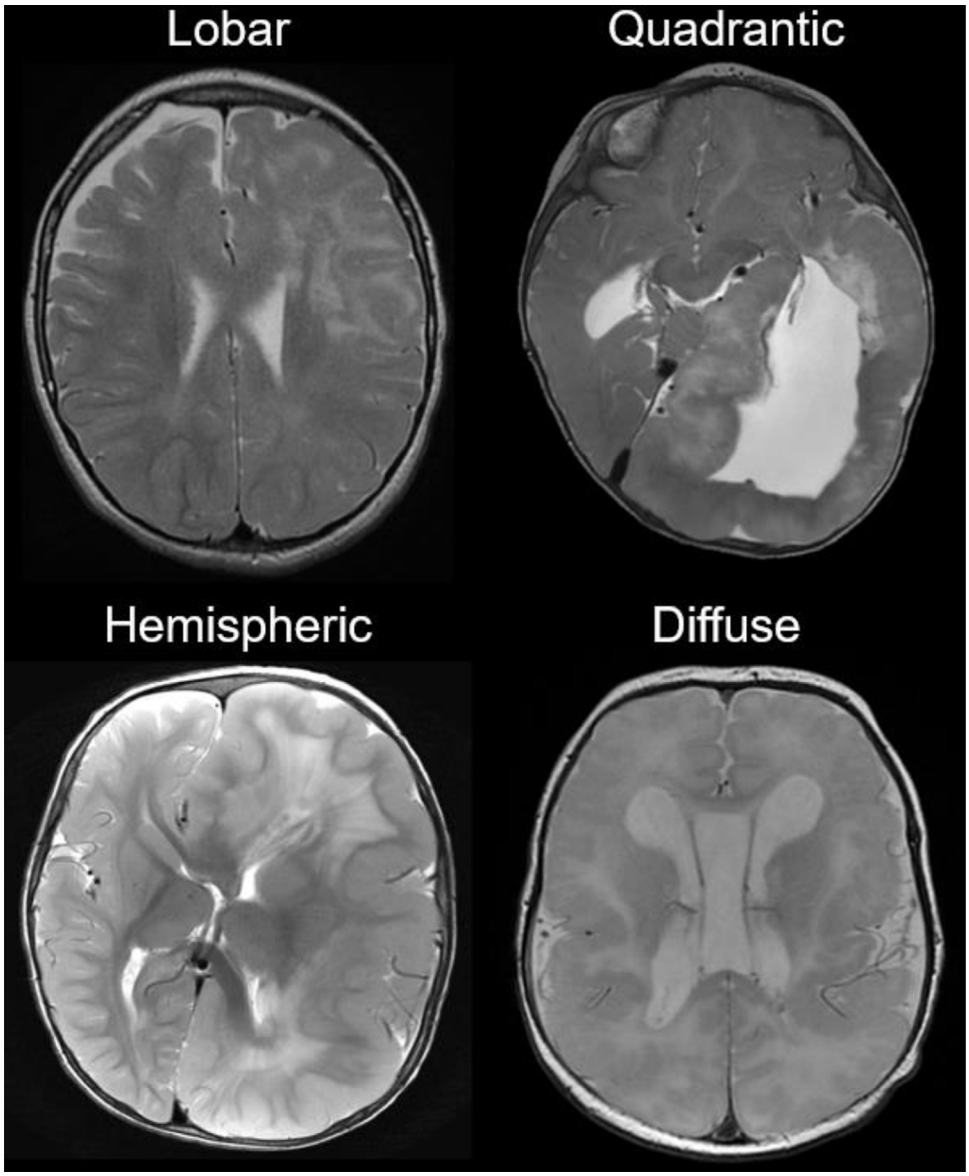

Figure 22 Megalencephaly. Depending on developmental timing of genetic mutation, brain overgrowth of the brain can be diffuse or segmental (eg, lobar, quadrantic, hemispheric).

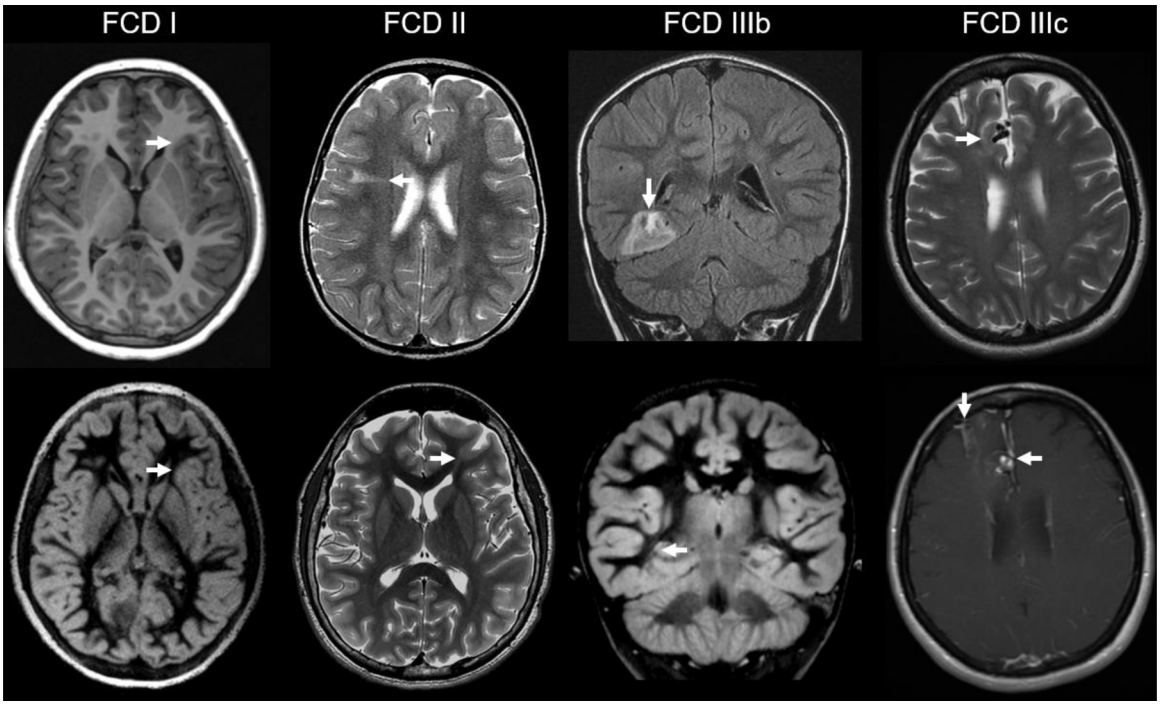

Figure 23 Focal cortical dysplasias. FCD I can be very subtle or occult on imaging, showing subtle gray-white blurring and dysgyria (arrows). FCD II is characterized by a transmantle signal abnormality (arrows) tracking to the bottom of an abnormal sulcus. FCD IIIb refers to dysplasia (arrows) associated with a low-grade tumor, such as dysembryoplastic neuroepithelial tumor. FCD IIIc indicates dysplasia associated with a vascular malformation (arrows).

prognosis, due to the typically localized imaging with a classic trasnmantle or "bottom of the sulcus" dysplasia. Type IIa contains only dysmorphic neurons, while type IIb also contains balloon progenitor cells with increased epileptogenic potential. FCD III refers to lesions with "dual" or concurrent pathology associated with dysplasia. Type IIIa is seen

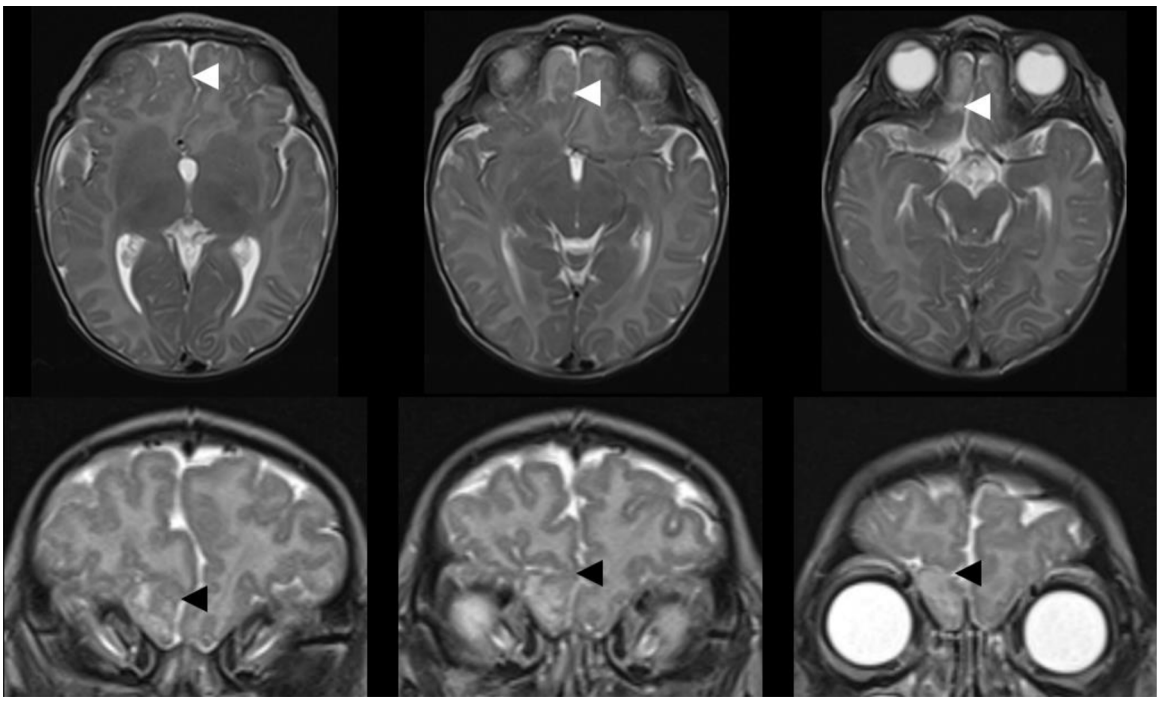

Figure 24 Sublobar dysplasia. Right anterior gyrus rectus (white arrowheads) demonstrates anomalous signal and folding pattern, connected to normal brain by a thin isthmus (black arrowheads).

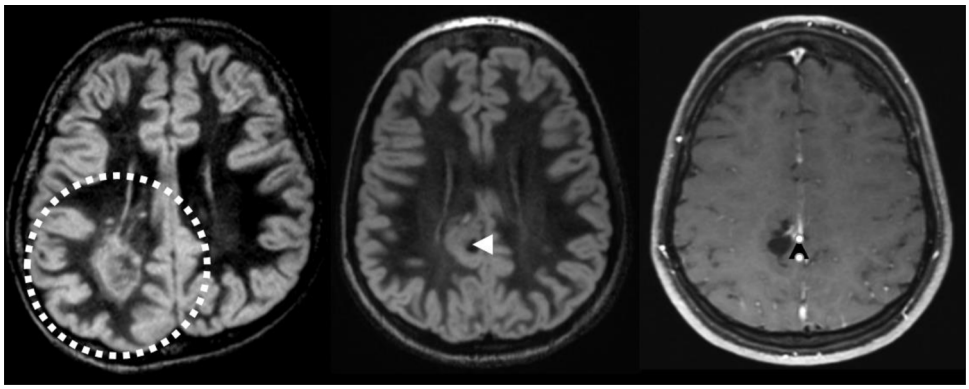

Figure 25 Compound dysplasia. Right posterior quadrant overgrowth (dotted circle) includes polymicrogyria, periventricular heterotopia, gliosis, cortical dysplasia (white arrowhead), and vascular dysplasia (black arrowhead) in a developmental distribution.

with hippocampal sclerosis, IIIb with glioneuronal tumor, IIIc with vascular malformation, and IIId with developmental insult (trauma, ischemia, infection) (Fig. 23).[6,156-160,217,218]

Optimal imaging diagnosis of FCD requires 3D high-resolution sequences to identify aberrant cortical folding (dysgyria), loss of gray-white distinction, and abnormal white matter signal (dysmyelination). Diagnosis during fetal MRI is nearly impossible, given the inherently low-resolution and motion-degraded sequences. In infants with incomplete myelination, underdeveloped white matter can also obscure underlying dysplasias. Therefore, a negative early brain MRI with continued clinical suspicion for structural abnormality merits a follow-up MRI later in life to increase the likelihood of epileptogenic focus detection.

Genetically, FCDs are an interesting subset of disorders because they are frequently targeted for surgical resection in treatment-refractory epilepsy, allowing detailed study of the mosaic tissue. FCD II shows somatic mTOR variants,[219,220] while FCD 1 is heterogeneous with 30% of cases linked to disorders of glycosylation from biallelic variants in SLC35A2.[221-223] It has been suggested that paired genome-wide sequencing of brain tissue and blood would be necessary to increase diagnostic yield in FCDs.[224,225]

Overall, the classification of MCDs continues to evolve, and certain cases defy conventional taxonomic classification. Sublobar dysplasia is a rare malformation that involves part of a cerebral lobe, separated from the rest of the brain by deep cortical infolding and a thin connecting isthmus (Fig. 24).[226-228] Other complex or compound dysplasias may display features of multiple malformations, in a transmantle or segmental distribution suggesting migrational origin (Fig. 25).[229,230]

Tubulinopathies

Tubulinopathies encompass a diverse spectrum of malformations linked to defects of microtubules, which are critically involved in regulating neural development and migration. The constellation of findings reflects global developmental disruption, with panmigrational abnormalities encompassing many of the previously described pathways. Imaging features can include central or diffuse pachygyria (undermigration) or polymicrogyria (overmigration), callosal and cerebellar hypogenesis, and ventriculomegaly. Highly specific findings are underdevelopment of the anterior limbs of internal capsules, dysmorphic basal ganglia including fused caudate and putamina, and hooked frontal horns. Imaging abnormalities are typically asymmetric, reflecting the inherent dynamic instability of microtubule energetics. This is a key distinction from other genetic encephalopathies, which tend to be relatively symmetric (Fig. 26).[231-234]

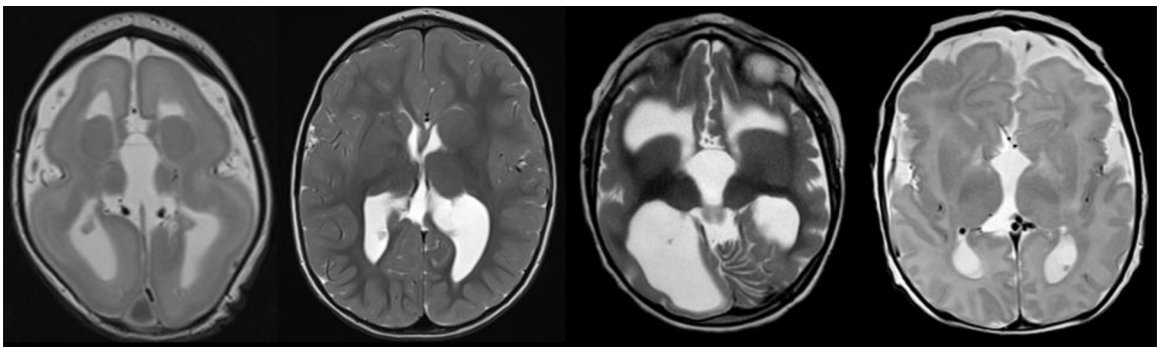

Figure 26 Tubulinopathies. Panmigrational defects with asymmetric pachygyria and polymicrogyria, dysmorphic basal ganglia, hypoplastic anterior limbs of internal capsules, and ventriculomegaly.

Tubulinopathies have been linked to variants in the alpha, beta, and gamma subtypes (TUBA1A, TUBB2B and TUBB3).[6,156-160] However, imaging features can overlap broadly with other disorders, such that molecular diagnosis is best pursued with either a very broad brain malformations panel or ES/GS. The burden of CNVs is sufficiently low that it is appropriate to proceed directly to sequencing if imaging is highly suggestive.[235,236]

Conclusion

Congenital brain malformations reflect developmental disruptions at various stages of development. The clinical presentation is nonspecific and can include developmental delay, hypotonia, and/or epilepsy. An integrated diagnostic approach includes radiologic phenotyping and directed genetic testing, and necessitates multidisciplinary collaboration between neurologists, radiologists, and geneticists. In this article, we provide an overview of clinical workflow for fetal/postnatal neuroimaging and genetic testing. Our simplified imaging-based etiologic classification includes malformative, destructive, and migrational abnormalities. For the various radiologic ontologies, key neuroimaging features can be linked to embryology and molecular pathogenesis.

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