U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Brock S, Dobyns WB, Jansen A. *PAFAH1B1*-Related Lissencephaly / Subcortical Band Heterotopia. 2009 Mar 3 [Updated 2021 Mar 25]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

PAFAH1B1-Related Lissencephaly / Subcortical Band Heterotopia

Synonym: *LIS1*-Related Lissencephaly / Subcortical Band Heterotopia

Stefanie Brock, MD,[1] William B Dobyns, MD,[2] and Anna Jansen, MD, PhD[3]

Created: March 3, 2009; Updated: March 25, 2021.

Summary

Clinical characteristics

PAFAH1B1-related lissencephaly / subcortical band heterotopia (SBH) comprises a spectrum of severity. Affected newborns typically have mild-to-moderate hypotonia, feeding difficulties, and poor head control. During the first years, neurologic examination typically demonstrates poor visual tracking and response to sounds, axial hypotonia, and mild distal spasticity that can transition over time to more severe spasticity. Seizures occur in more than 90% of individuals with lissencephaly and often include infantile spasms. Seizures are often drug resistant, but even with good seizure control, the best developmental level achieved (excluding the few individuals with partial lissencephaly) is the equivalent of about age three to five months. In individuals with *PAFAH1B1*-related lissencephaly/SBH, developmental delay ranges from mild to severe. Other findings in *PAFAH1B1*-related lissencephaly/SBH include feeding issues and aspiration (which may result in need for gastrostomy tube placement), progressive microcephaly, and occasional developmental regression.

Diagnosis/testing

The diagnosis of *PAFAH1B1*-related lissencephaly/SBH is established in a proband with a heterozygous pathogenic variant in *PAFAH1B1* identified by molecular genetic testing.

Management

Treatment of manifestations: Standard treatment with anti-seizure medication based on the specific seizure type and frequency; polytherapy with valproic acid and lamotrigine appears most effective in reducing drug-resistant seizures; placement of a gastrostomy tube for those with failure to thrive, dysphagia, and/or recurrent aspiration

Author Affiliations: 1 Department of Pathology, Universitair Ziekenhuis Brussel; Neurogenetics Research Group, Vrije Universiteit, Brussels, Belgium; Email: stefanie.brock@uzbrussel.be. 2 Department of Pediatrics (Genetics), University of Minnesota, Minneapolis, Minnesota; Email: wbdobyns@umn.edu. 3 Pediatric Neurology Unit, Department of Pediatrics, Universitair Ziekenhuis Brussel; Neurogenetics Research Group, Vrije Universiteit, Brussels, Belgium; Email: anna.jansen@uzbrussel.be.

pneumonia; treatment with stool softeners, prokinetics, osmotic agents, or laxatives for constipation; standard treatment for developmental delay/intellectual disability, spasticity, visual impairment, and hearing loss.

Surveillance: At each visit: measure growth parameters and evaluate nutrition status and safety of oral intake; monitor for signs and symptoms of constipation, aspiration, and respiratory insufficiency; monitor those with seizures as clinically indicated; assess for new manifestations, such as unusual spells or developmental regression; assessment of developmental progress and educational needs; assessment of mobility and self-help skills. Annually or as clinically indicated: ophthalmologic and audiologic evaluations.

Genetic counseling

Individuals diagnosed with isolated *PAFAH1B1*-related lissencephaly/SBH typically have the disorder as the result of a *de novo* genetic alteration (an intragenic *PAFAH1B1* pathogenic variant or, rarely, a chromosome rearrangement that disrupts *PAFAH1B1*). In rare families, an individual with *PAFAH1B1*-related lissencephaly/SBH has the disorder as the result of autosomal dominant inheritance of a *PAFAH1B1* pathogenic variant from a parent. If the intragenic *PAFAH1B1* pathogenic variant identified in the proband is not identified in either parent, the recurrence risk for a future pregnancy is slightly greater than that of the general population because of the possibility of parental germline mosaicism. If a parent of a proband is known to have the intragenic *PAFAH1B1* pathogenic variant or a balanced translocation that disrupts *PAFAH1B1*, the recurrence risk is 50% with each future pregnancy. Once the causative genetic alteration has been identified in the proband, prenatal testing may be offered to parents of an affected child because of the recurrence risk associated with the possibility of parental mosaicism or a balanced chromosome rearrangement.

GeneReview Scope

PAFAH1B1-Related Lissencephaly / Subcortical Band Heterotopia: Included Phenotypes [1]
• Isolated lissencephaly sequence (ILS) • Subcortical band heterotopia (SBH)

1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

Note: This chapter on *PAFAH1B1*-related lissencephaly / subcortical band heterotopia (SBH) excludes Miller-Dieker syndrome. The term "Miller-Dieker syndrome" is frequently used to refer to individuals with larger deletions of 17p13.3 that include both *PAFAH1B1* and *YWHAE* (a region of about 1.3 Mb harboring many genes) (see Genetically Related Disorders).

Suggestive Findings

PAFAH1B1-related lissencephaly/SBH **should be suspected** in individuals with the following clinical and MRI findings.

Clinical features (nonspecific)

- Generalized hypotonia
- Abnormal arching (opisthotonus) in infants transitioning to bilateral spastic cerebral palsy in older individuals
- Central visual impairment
- Developmental delay, intellectual disability, psychomotor delay, speech and language delay

- Behavioral difficulties
- Epilepsy ranging from infantile spasms to severe drug-resistant epilepsy
- Nonspecific dysmorphic features (See Clinical Description.)

  Note: Dysmorphic features are rare in individuals with intragenic pathogenic variants or intragenic deletions of *PAFAH1B1* and are more commonly seen in those with larger deletions that include *PAFAH1B1* and adjacent genes (see Genetically Related Disorders).

MRI findings (specific) (See Figure 1.)

- **Lissencephaly,** characterized by absent or abnormally broad cerebral gyri with abnormally thick cerebral cortex (10-20 mm; normal: 3-4 mm) [Di Donato et al 2017]
- **Subcortical band heterotopia,** characterized by either a symmetric or an asymmetric subcortical band of heterotopic gray matter restricted to the parietal and occipital lobes with a posterior-to-anterior gradient

Establishing the Diagnosis

The diagnosis of *PAFAH1B1*-related lissencephaly/SBH **is established** in a proband with a heterozygous pathogenic (or likely pathogenic) variant in *PAFAH1B1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *PAFAH1B1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability typically begins with chromosomal microarray analysis (CMA).

Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *PAFAH1B1*) that cannot be detected by sequence analysis.

If CMA is not diagnostic, molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires clinical suspicion of a particular genetic cause, based on the clinical and imaging phenotype. This also implies that the clinician is familiar with rare disorders such as lissencephaly/SBH. In contrast, genomic testing can be used when clinical findings are nonspecific, as this does not require preliminary suspicion of a defined genetic cause. Because the phenotype of lissencephaly/SBH is broad, individuals with the distinctive MRI findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with lissencephaly and/or epileptic encephalopathy are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and imaging findings suggest the diagnosis of *PAFAH1B1*-related lissencephaly/SBH, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *PAFAH1B1* may be considered to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing

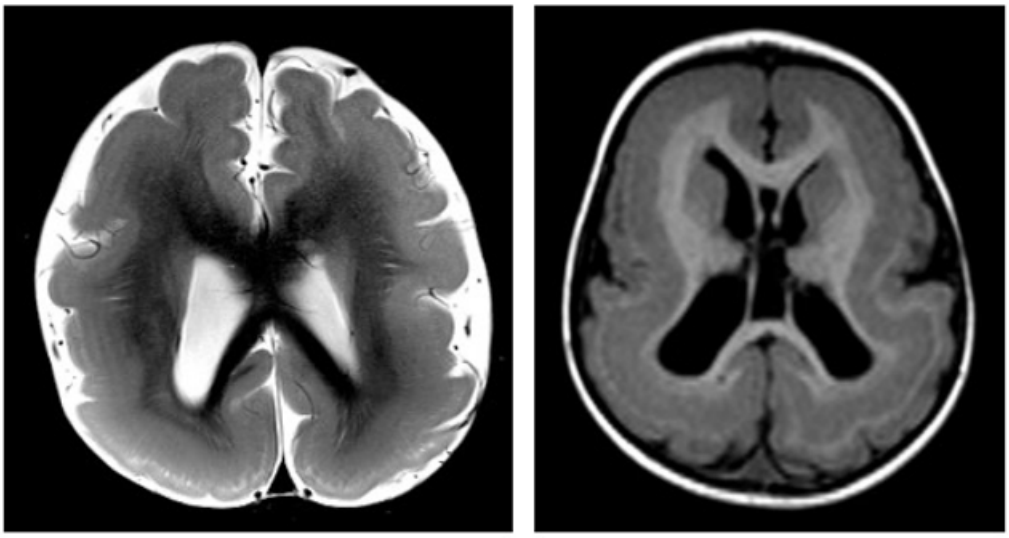

Figure 1. Left panel – axial T_2-weighted MRI image illustrating diffuse agyria-pachygyria with posterior-to-anterior (p>a) gradient. Right panel – axial T_1-weighted MRI image illustrating diffuse subcortical band heterotopia with posterior-to-anterior (p>a) gradient. Both are caused by a pathogenic variant in *PAFAH1B1*.

method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to consider gene-targeted deletion/duplication analysis to detect exon-level deletions or duplications.

- **A multigene panel** that includes *PAFAH1B1* and other genes of interest (see Differential Diagnosis) is likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Karyotype.** If the features are highly suggestive of *PAFAH1B1*-related lissencephaly/SBH but the above testing is nondiagnostic, a chromosome analysis (karyotype) may be considered. Rarely, affected individuals have a balanced reciprocal translocation disrupting *PAFAH1B1*. Note: Balanced chromosome translocations cannot be detected using chromosomal microarray analysis.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by lissencephaly, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *PAFAH1B1*-Related Lissencephaly/SBH

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method
PAFAH1B1	Sequence analysis [4]	77% [5]
	Gene-targeted deletion/duplication analysis [6]	23% [5]
	Karyotype [7]	Rare

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. As currently defined, Miller-Dieker syndrome (MDS) is associated with deletions that include both *PAFAH1B1* and *YWHAE* (a region of about 1.3 Mb harboring many genes) in 17p13.3 [Pilz et al 1998, Cardoso et al 2003] (see Genetically Related Disorders).
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Saillour et al [2009], Di Donato et al [2018]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Cardoso et al [2003] that include both *PAFAH1B1* and *YWHAE*) may not be detected by these methods.
7. Rarely, affected individuals have a balanced reciprocal translocation disrupting *PAFAH1B1*, which may not be detectable through either sequence analysis or gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

Together, isolated lissencephaly sequence (ILS) and subcortical band heterotopia (SBH) comprise the "agyria-pachygyria-band" spectrum of cortical malformations that are caused by deficient neuronal migration during embryogenesis. The term lissencephaly refers to a "smooth brain" with absent (agyria) or abnormally wide gyri (pachygyria).

To date, almost 200 individuals have been identified with an intragenic pathogenic variant in *PAFAH1B1* [De Vita et al 2018, Di Donato et al 2018] causative of ILS and SBH. The following description of the phenotypic features associated with this condition is based on these reports.

Neurologic

Affected newborns may appear normal or may have mild-to-moderate hypotonia, feeding difficulties, and poor head control. During the first years, neurologic examination typically demonstrates poor visual tracking and response to sounds, axial hypotonia, and mild distal spasticity. Infants often demonstrate abnormal arching (opisthotonus). Later, distal spasticity becomes more prominent, although axial hypotonia remains. Affected individuals may develop moderate spastic quadriplegia and scoliosis.

ILS. Seizures occur in more than 90% of individuals with ILS, with onset usually in the first two years of life (mean onset age: 5 months) [Saillour et al 2009, Herbst et al 2016]. Approximately 80% of affected individuals have infantile spasms, although EEG does not always show the typical hypsarrhythmia pattern.

- Epileptic encephalopathies typically evolve from infantile spasms (West syndrome) to Lennox-Gastaut syndrome of mixed epilepsy with a slow spike-and-wave pattern on EEG.
- Some children with ILS have characteristic EEG changes, including diffuse high-amplitude fast rhythms that are considered to be highly specific for this malformation [Quirk et al 1993].

After the first months of life, most children have mixed seizure disorders including persisting infantile spasms, focal motor and generalized tonic seizures, and atypical absence, atonic, and myoclonic seizures [Herbst et al 2016].

Seizures are drug resistant in more than 65% of affected individuals. While polytherapy with lamotrigine and valproic acid can reduce the number of daily seizures effectively, two thirds of affected individuals continue to experience daily seizures [Herbst et al 2016].

SBH. Seizures typically occur in the first decade and are often drug resistant [Bahi-Buisson & Guerrini 2013, Herbst et al 2016].

Neurodevelopment

Prior to the onset of seizures, most infants have mild delay in development and mild hypotonia.

ILS. Onset of infantile spasms may be associated with a decline in function:

- The developmental prognosis is poor for most individuals with ILS.
- Even with good seizure control, the best developmental level achieved (excluding the few individuals with partial lissencephaly) is the equivalent of about age three to five months.
- Affected individuals may achieve rolling over, limited creeping, and, very rarely, sitting. Few individuals have been reported to be able to walk with support.
- Visual tracking is variable among affected individuals, with a subset achieving normal visual interactions while other do not achieve visual tracking.
- With poor seizure control, children with ILS may function at or below the level of a newborn. Regression of acquired functioning due to poor seizure control has been reported [Sicca et al 2003].
- A few individuals with less severe (grade 4) lissencephaly (see Neuroimaging), especially partial posterior lissencephaly or pachygyria, have a better developmental outcome [Leventer et al 2001].

SBH. Developmental delay (ranging from mild to severe) has been seen in all of the limited number of individuals reported with SBH [Saillour et al 2009, Herbst et al 2016].

Growth

At birth, the occipitofrontal circumference is typically normal (between the mean and -2 SD). However, postnatal head growth is slow; most children develop microcephaly by age one year. The remainder of the growth parameters are often normal.

Feeding

Some have difficulty with feeding, and transient elevations in bilirubin in neonates are likely related to feeding difficulties. Feeding often improves during the first few months of life, but typically worsens again with seizure onset during the first year of life, and then again at several years of age for various reasons.

- Poor feeding in newborns is usually managed by nasogastric tube feedings, as the feeding problems often improve during the first weeks of life (see Management, Treatment of Manifestations).
- However, feeding often worsens again with intercurrent illnesses and with advancing age and size. At least 50% of children with *PAFAH1B1*-related lissencephaly (but not *PAFAH1B1*-related SBH) eventually have a gastrostomy tube placed for feeding issues.
- Individuals with low central tone frequently develop constipation; this is not specific to those with *PAFAH1B1*-related lissencephaly / subcortical band heterotopia.

Respiratory

Children with lissencephaly have poor control of their airway, which predisposes them to aspiration pneumonia, the most common terminal event. This is not typically seen in those with SBH.

Visual Impairment

Poor or absent visual interaction and limited visual-perceptual and eye-hand abilities have been reported in a subset of affected individuals, likely secondary to the severe cortical malformations [Leventer et al 2001, Mineyko et al 2010, de Wit et al 2011].

Neuroimaging

In 2017, the imaging criteria for lissencephaly/SBH with a defined monogenic cause were revised. This classification system subdivides lissencephaly/SBH into 21 recurring patterns in order to aid clinicians in predicting the most likely genetic cause based on imaging features. Criteria to stratify lissencephaly/SBH are based on the anteroposterior gradient, grade of severity, cortical thickness and appearance, and associated non-cortical brain malformations [Di Donato et al 2017].

Imaging criteria for lissencephaly and subcortical band heterotopia in general [Di Donato et al 2017]. Note: This is not specific to *PAFAH1B1*-related lissencephaly/SBH.

Gradient of gyral malformation:

- Diffuse
- Anterior more severe than posterior (a>p)
- Posterior more severe than anterior (p>a)
- Temporal more severe than posterior and p>a

Grade of gyral malformation:

- SBH partial
- SBH diffuse
- LIS partial pachygyria
- LIS diffuse pachygyria
- LIS agyria-pachygyria
- LIS diffuse agyria

Cortical thickness & appearance:

- Simplified gyration overlying SBH
- Thin undulating
- Thin variable dysgyria
- Thin w/enlarged lateral ventricles & thin mantle
- Thick classic

Non-cortical brain malformations:

- Basal ganglia dysgenesis
- Complete or partial agenesis (dysgenesis) of corpus callosum
- Tectal hyperplasia
- Brain stem hypoplasia & dysgenesis
- Cerebellar hypoplasia (either diffuse or vermis predominant)

Applying the above **imaging criteria** allows correlation of major imaging features with the expected clinical outcome (although exceptions may exist, especially in those with severe epilepsy). The clinical severity of lissencephaly/SBH **in general** is characterized based on the criteria presented in Table 2 [Di Donato et al 2017]. Note: This is not specific to *PAFAH1B1*-related lissencephaly/SBH.

Table 2. Clinical Severity of Lissencephaly and Subcortical Brain Heterotopia in General

Grade	Subtypes	Imaging Pattern	Typical Clinical Outcome
1 (mild)	1-1	Partial SBH a>p or p>a	Borderline-to-moderate ID, seizures of variable severity; survival into adulthood expected
	1-2	Diffuse thin SBH (<10 mm)	
	1-3	Partial pachygyria a>p or p>a	
	1-4	Isolated "thin" or undulating LIS	
2 (moderate)	2-1	Diffuse thick SBH (>10 mm)	Moderate-to-severe ID, severe language impairment, seizures often poorly controlled; life expectancy may be ↓, although many survive to adulthood.
	2-2	Mixed pachygyria-SBH	
	2-3	Diffuse pachygyria a>p or p>a	
3 (severe)	3-1	Mixed pachygyria-agyria	Profound ID, poorly controlled seizures, short survival typical: mortality rate ~50% by age 10 yrs w/normal cerebellum; much higher w/cerebellar hypoplasia
	3-2	Diffuse agyria	
	3-3	Agyria w/cerebellar hypoplasia	

a = anterior; ID = intellectual disability; LIS = lissencephaly; p = posterior; SBH = subcortical band heterotopia

ILS. ILS consists of variable lissencephaly (grades 2-3, 3-1, or 3-2 in Table 2). Other associated brain MRI findings in the most common ("classic") form of lissencephaly:

- Enlarged lateral ventricles, especially posteriorly
- Mild hypoplasia of the corpus callosum (the anterior portion often appears flattened)
- Cavum septi pellucidi et vergae
- Normal brain stem and cerebellum in most individuals, mild cerebellar vermis hypoplasia in a few

SBH

- In *PAFAH1B1*-related SBH, the subcortical bands are restricted to the parietal and occipital lobes (diffuse or frontal predominant SBH are associated with mutation of *DCX* [see *DCX*-Related Disorders]).
- The gyral pattern is normal or demonstrates mildly simplified shallow sulci; a normal cortical ribbon is present.

Prognosis

In general, life expectancy in individuals with lissencephaly due to any cause is related to the severity of the malformation on neuroimaging [de Wit et al 2011].

- **ILS.** In individuals with ILS, approximately 50% live to age ten years, and very few reach age 20 years. Cause of death is usually pneumonia or status epilepticus. The oldest known individual lived to age 30 years.

  These estimates apply only to individuals with typical lissencephaly affecting the entire brain (the large majority of those with lissencephaly); Shi et al [2019] reported a mildly affected individual with grade 4b lissencephaly who was still alive at age 49 years.

- **SBH.** In general, affected individuals live into adult life. No reliable data regarding life span exist; it is likely to be shortened in those with severe intellectual disability, intractable epilepsy, or both.

Genotype-Phenotype Correlations

ILS

- Most individuals with a telomeric deletion including the 5' end of *PAFAH1B1* have grade 2 to 3 lissencephaly.
- The vast majority of individuals with intragenic deletions and duplications of *PAFAH1B1* have grade 3 lissencephaly [Haverfield et al 2009].
- Most individuals with a deletion of the 3' end of *PAFAH1B1* have grade 3 to 4 lissencephaly [Chong et al 1997; Author, unpublished data].
- Intragenic pathogenic variants in *PAFAH1B1* usually result in ILS grade 3 or 4.
    - Intragenic pathogenic variants that predict premature termination of the PAFAH1B1 protein tend to result in a more severe lissencephaly phenotype than missense variants in *PAFAH1B1* [Cardoso et al 2000, Leventer et al 2001, Cardoso et al 2002].
    - Pathogenic variants near the beginning of the gene in the coiled-coil domain that result in truncation/deletion may cause a more severe lissencephaly phenotype than similar variants that occur in other downstream regions of the gene [Cardoso et al 2000, Cardoso et al 2002].

Note: These generalizations notwithstanding, severity of the phenotype does not always appear to correspond to location and type of pathogenic variant, as a more severe phenotype has been observed in some individuals with pathogenic missense variants and more severe grades (2 and 3) of lissencephaly have been observed in individuals with truncation/deletion variants in the coiled-coil domain toward the 3' end of *PAFAH1B1* [Uyanik et al 2007].

SBH

- Two *PAFAH1B1* pathogenic missense variants, one frameshift variant, and somatic mosaicism for a *PAFAH1B1* missense, nonsense, in-frame, and splice site variant have been identified in nine individuals with a milder imaging phenotype consisting of posterior-predominant SBH [Pilz et al 1999, D'Agostino et al 2002, Sicca et al 2003, Uyanik et al 2007, Mineyko et al 2010, Pagnamenta et al 2012, Damiano et al 2017, González-Morón et al 2017].
- Somatic mosaicism for a *PAFAH1B1* deletion results in a variable clinical phenotype, ranging from mild to severe developmental delay.
- Seizures are intractable in most affected individuals and can cause regression of the developmental stage.

Prevalence

Classic lissencephaly from any cause is rare. Birth prevalence is estimated to range from 11.7 to 40 per million births [personal communication with Metropolitan Atlanta Congenital Defects Program Personnel, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, 2002]. Even the latter is likely to be an underestimate, as the CDC program ascertains only hospitalized children in the first several years of life.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with intragenic germline pathogenic variants in *PAFAH1B1*.

Miller-Dieker syndrome (MDS) is the term used for individuals with larger deletions of 17p13.3 that include at least *PAFAH1B1* and *YWHAE*, often with deletion of other contiguous genes. The most severely affected individuals with MDS have large cytogenetically visible deletions of 17p13.3 and unbalanced chromosome rearrangements associated with duplication of another chromosome segment.

Affected individuals typically have severe lissencephaly (grade 1-2) (see Table 2), characteristic facial changes, other more variable malformations, and severe neurologic and developmental abnormalities [Dobyns et al 1991, Cardoso et al 2003]. The facial changes consist of tall and prominent forehead, bitemporal narrowing, short nose with anteverted nares, protuberant vermilion of the upper lip with downturned corners of the mouth, and small jaw. Other malformations seen on occasion include omphalocele and congenital heart defects.

The developmental prognosis is poor for all children with MDS. Death occurs within the first two years in many children, and only a few reach age ten years. The oldest known individual with MDS died at age 17 years.

17p13.3 duplications. 17p13.3 duplications involving *PAFAH1B1* are referred to as class II duplications (contrasting with class I duplications, which do not include *PAFAH1A1*). Clinically, individuals with class II duplications present with mild-to-severe developmental and psychomotor delay, hypotonia, and growth restriction. Seizures are less common than in ILS. Brain malformations include hypoplasia/dysgenesis of the corpus callosum, mild cerebellar volume loss, and mildly reduced brain volume, often with a posterior-to-anterior gradient, as well as microcephaly. One affected individual with bilateral perisylvian polymicrogyria has been reported [Stutterd et al 2020]. Associated malformations of other organs are rarely present. Nonspecific facial dysmorphic features can be seen in individuals with microduplications including *PAFAH1B1*, but are rare in those with ILS/SBH.

Differential Diagnosis

The greatest difficulty in the diagnosis of lissencephaly and subcortical band heterotopia (SBH) is recognizing the malformation. Lissencephaly is subdivided into several types depending on gradient and grade of gyral malformation and cortical thickness [Di Donato et al 2017].

Several different cortical malformations that are sometimes mistaken for lissencephaly have been described, including severe congenital microcephaly with reduced number of gyri, cobblestone malformations as seen in Walker-Warburg and other syndromes, polymicrogyria, and polymicrogyria-like variants associated with pathogenic variants of tubulin genes. This leads to inefficient molecular testing and incorrect diagnosis and counseling.

Clinical features can help distinguish children who have lissencephaly from those who have other brain malformations. Children with lissencephaly usually have normal or slightly small OFC at birth (>-3 SD) and diffuse hypotonia except for mildly increased tone at the wrists and ankles. Children with severe congenital (i.e., primary) microcephaly and gyral abnormalities have smaller birth OFC (≤-3 SD) and may be hypotonic or spastic. Infants with polymicrogyria, especially when the frontal lobes are involved, frequently have spastic quadriparesis. Brain imaging (preferably by MRI) and/or neuropathologic examination during autopsy is necessary to confirm a diagnosis of lissencephaly.

Classic Lissencephaly

The differential diagnosis of classic lissencephaly is summarized in Table 3. These disorders are distinguished by mode of inheritance, grade and gradient of lissencephaly or SBH (see Clinical Description, Neuroimaging), presence of other congenital anomalies, clinical features, and results of molecular genetic testing.

Table 3. Genes of Interest in the Differential Diagnosis of Classic Lissencephaly

Gene	Disorder	MOI	Gradient of LIS or SBH [1, 2]	Features Differentiating Disorder from *PAFAH1B1* Malformations
PAFAH1B1	***PAFAH1B1* malformations** [3]	**AD**	**p>a**	
ACTB *ACTG1*	Baraitser-Winter cerebrofrontofacial syndrome	AD	a>p	Trigonocephaly; shallow orbits; ptosis; colobomas of the iris, choroid, or both; DD, LIS, & epilepsy in some persons; malformations of other organ systems
APC2	Cortical dysplasia complex, w/other brain malformations 10 (OMIM 618677)	AR	p>a	Severe DD, epilepsy, cortical dysplasia or LIS, thin CC, heterotopias
CDK5	CDK5 lissencephaly (OMIM 616342)	AD	Diffuse	Early lethal course. Agyria, agenesis of CC, cerebellar & pontine hypoplasia; facial dysmorphisms; arthrogryposis multiplex
CRADD	ID w/variant lissencephaly (OMIM 614499)	AR	a>p	↑ head circumference / megalencephaly, "thin" LIS
DCX	*DCX*-related disorders	XL	a>p	SBH in females, LIS in males. SBH is far more commonly caused by mutation of *DCX* than *PAFAH1BA*.
DYNC1H1	*DYNC1H1* pachygyria (OMIM 614563)	AD	a>p or p>a	Microcephaly, agyria, or polymicrogyria; abnormal CC, dysmorphic basal ganglia, brain stem / cerebellar hypoplasia
KIF2A	Cortical dysplasia, complex, w/other brain malformations 3 (OMIM 615411)	AD	p>a	Microcephaly; spastic paraplegia, LIS, SBH, hypoplastic CC
KIF5C	*KIF5C* pachygyria (OMIM 615282)	AD	a>p or p>a	Nonspecific facial dysmorphism possible, mild LIS
NDE1	Lissencephaly 4 (w/microcephaly) (OMIM 614019)	AR	Diffuse	Severe microcephaly w/SGP, microlissencephaly
RELN	Lissencephaly 2 (OMIM 257320)	AR	NA	Facial dysmorphisms, LIS, cerebellar & hippocampal hypoplasia/dysplasia
TUBA1A	*TUBA1A* malformations (See Tubulinopathies Overview.)	AD	p>a	Broad phenotypic spectrum of dysgyria ± assoc brain malformations (e.g., cerebellar hypoplasia, agenesis of CC). Can be indistinguishable from *PAFAH1B1* phenotype, esp in persons w/*TUBA1A* variant c.1204C>T (p.Arg402Cys).
TUBB2B	*TUBB2B* malformations (See Tubulinopathies Overview.)	AD	p>a	Dysgyria, SBH, hypoplasia CC, cerebellum w/o brain stem hypoplasia, dysmorphic basal ganglia
TUBG1	*TUBG1* malformations (See Tubulinopathies Overview.)	AD	p>a	Dysgyria, w/o hypoplastic CC, cerebellum w/o brain stem hypoplasia, w/o dysmorphic basal ganglia
VLDLR	*VLDLR* cerebellar hypoplasia	AR	a>p	LIS, cerebellar & hippocampal hypoplasia/ dysplasia

a = anterior; AD = autosomal dominant; AR = autosomal recessive; CC = corpus callosum, DD = developmental delay; ID = intellectual disability; LIS = lissencephaly; MOI = mode of inheritance; NA = not available; p = posterior; SBH = subcortical band heterotopia; SGP = simplified gyral pattern

1. See Clinical Description, Neuroimaging, **Imaging criteria for lissencephaly and subcortical band heterotopia in general**.

2. In severe classic lissencephaly or SBH the gradient may be difficult to discern.

3. Topic of this *GeneReview*; included for reference

Lissencephaly with Agenesis of the Corpus Callosum

Lissencephaly with agenesis of the corpus callosum is typically associated with pathogenic variants in *ARX*. Pathogenic variants in *ARX* cause X-linked lissencephaly with abnormal genitalia (XLAG; OMIM 300215). The XLAG phenotype in severely affected individuals with a 46,XY karyotype differs significantly from the phenotype associated with pathogenic variants in either *PAFAH1B1* or *DCX*. XLAG is characterized by congenital or postnatal microcephaly, neonatal-onset intractable epilepsy, poor temperature regulation, chronic diarrhea, and abnormal genitalia [Kato et al 2004].

Females who are heterozygous for an *ARX* pathogenic variant may be asymptomatic or may present with variable clinical features including: developmental delay, intellectual disability (55% of heterozygous females), learning disabilities, and behavioral abnormalities. Seizures were reported in 64% of affected females who also presented with intellectual disability [Mattiske et al 2017]. Brain imaging often shows agenesis of the corpus callosum, although lissencephaly has not been reported [Marsh et al 2009].

Tubulin-Related Dysgyria

Cortical malformations resembling lissencephaly and caused by mutation of an α-tubulin (*TUBA1A* or *TUBA8*), β-tubulin (*TUBB2A*, *TUBB2B*, *TUBB3*, *TUBB* [*TUBB5*]), or γ-tubulin (*TUBG1*) gene are referred to as tubulin-related dysgyria. Tubulinopathies often cause associated brain malformations including hypoplasia/agenesis of the corpus callosum, dysmorphic basal ganglia, and hypoplasia of the cerebellar vermis and brain stem (see Tubulinopathies Overview). Affected individuals present with variable degrees of developmental delay and often with epilepsy [Romaniello et al 2019]. Of note, the p.Arg402Cys variant in *TUBA1A* results in an agyria-pachygyria (posterior more severe than anterior on imaging) phenotype that is highly similar to that caused by pathogenic variants in *PAFAH1B1* [Bahi-Buisson et al 2014].

Cobblestone Cortical Malformation (Lissencephaly) Syndromes

The cobblestone cortical malformation (lissencephaly) syndromes (Walker-Warburg syndrome, muscle-eye-brain disease, and Fukuyama congenital muscular dystrophy) differ clinically in a number of ways, including the frequent presence of ventriculomegaly, white matter changes, and cerebellar hypoplasia, multiple different eye anomalies, and congenital muscular dystrophy manifested by hypotonia and elevated serum creatine kinase concentrations.

Management

No consensus management recommendations for *PAFAH1B1*-related lissencephaly / subcortical band heterotopia (SBH) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PAFAH1B1*-related lissencephaly/SBH, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *PAFAH1B1*-Related Lissencephaly / Subcortical Band Heterotopia

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To incl head circumference
Neurologic	Neurologic eval	• To incl brain MRI [1] • Consider EEG if seizures are a concern.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in those w/dysphagia &/or aspiration risk.
Respiratory	Eval of respiratory status	
Eyes [2]	Ophthalmologic eval	To assess for ↓ vision, abnormal ocular movement, strabismus
Hearing [3]	Audiologic eval	Assess for hearing loss.
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support/resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADL = activities of daily living; EEG = electroencephalogram; OT = occupational therapy; PT = physical therapy
1. Brain MRI should be interpreted carefully to provide as much prognostic information as possible. Although most affected individuals have severe-to-profound intellectual disability, a minority have less extensive lissencephaly that results in moderate intellectual disability, and a few have limited malformations that allow near-normal development. In the latter, the lissencephaly or SBH is typically less severe and less extensive on MRI. The resolution of brain CT scan is usually not sufficient to make this distinction.
2. Although ophthalmologic issues are not a primary feature of *PAFAH1B1*-related lissencephaly/SBH, assessment of vision in an individual with significant developmental delay and or brain malformation is often recommended.
3. Although hearing loss is not a primary feature of *PAFAH1B1*-related lissencephaly/SBH, assessment of hearing in an individual with significant developmental delay and or brain malformation is often recommended.

Treatment of Manifestations

Parents seem best able to deal with this severe disorder when accurate information regarding the prognosis is given as soon as possible after the diagnosis is recognized. For those with severe lissencephaly, it is usually appropriate to discuss limitations of care, such as "do not resuscitate" orders, in the event of severe illnesses.

Table 5. Treatment of Manifestations in Individuals with *PAFAH1B1*-Related Lissencephaly / Subcortical Band Heterotopia

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM based on specific seizure type & frequency by experienced neurologist	• A large majority of affected persons have seizures, incl frequent infantile spasms, which can be difficult to control. • Polytherapy w/valproic acid & lamotrigine appears most effective in ↓ drug-resistant seizures, but 2/3 of affected persons continue to have daily seizures. [1] • Treat seizures promptly & aggressively, as poor seizure control frequently results in ↓ in function & health. [2] • Education of parents/caregivers [3]
Poor weight gain / Failure to thrive / Aspiration	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding &/or respiratory issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia, incl episodes of aspiration pneumonia
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Visual impairment	Standard therapy per ophthalmologist	
Hearing impairment	Standard therapy per audiologist	
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; DD = developmental delay; FTT = failure to thrive; ID = intellectual disability; OT = occupational therapy; PT = physical therapy

1. Herbst et al [2016]

2. Poor seizure control worsens feeding (increasing the likelihood that a gastrostomy tube will be needed) and increases the risk for pneumonia. Overall development can be delayed or impaired through uncontrolled seizures.

3. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant special educators and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized

education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve

coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Surveillance

Table 6. Recommended Surveillance for Individuals with *PAFAH1B1*-Related Lissencephaly / Subcortical Band Heterotopia

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for constipation.	
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl unusual spells or developmental regression. [1]	
Development	Monitor developmental progress & educational needs.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	
Eyes	Ophthalmologic eval	Annually or as clinically indicated
Hearing	Audiologic eval	

OT = occupational therapy; PT = physical therapy
1. If present, a neurology consultation should be performed and an EEG considered.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

PAFAH1B1-related lissencephaly / subcortical band heterotopia (SBH) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Note: Genetic counseling for the families of individuals diagnosed with Miller-Dieker syndrome is not addressed in this section (see Genetically Related Disorders).

Risk to Family Members

Parents of a proband

- Individuals diagnosed with isolated *PAFAH1B1*-related lissencephaly/SBH typically have the disorder as the result of a *de novo* genetic alteration (an intragenic *PAFAH1B1* pathogenic variant or, rarely, a chromosome rearrangement that disrupts *PAFAH1B1*).
- In rare families, an individual with *PAFAH1B1*-related lissencephaly/SBH has the disorder as the result of a *PAFAH1B1* pathogenic variant inherited from a parent. Maternal vertical transmission of a *PAFAH1B1* pathogenic variant has been reported in three unrelated families:
  - A boy with ILS (with posterior more severe than anterior gradient) and epilepsy inherited a *PAFAH1B1* missense variant from his mother who presented with similar clinical features [De Vita et al 2018].
  - Two girls with severe intellectual disability, epilepsy, and anterior-predominant lissencephaly and calcifications of the basal ganglia were born to a mother also presenting with anterior-predominant lissencephaly (the affected daughters and their mother were all heterozygous for the same missense variant in *PAFAH1B1*, which was absent in unaffected family members [Shi et al 2019]).
  - A boy who presented with ILS/SBH inherited a *PAFAH1B1* missense variant from his mother, who was mosaic for the missense variant [Mineyko et al 2010].
- Molecular genetic testing for the intragenic *PAFAH1B1* pathogenic variant identified in the proband is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling. (If the proband has a chromosome rearrangement that disrupts *PAFAH1B1*, chromosome analysis [a karyotype] is recommended for the parents of the proband.)
- If the genetic alteration identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

    * If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic and germline mosaicism for the variant and may be mildly affected [Mineyko et al 2010].

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is known to have the intragenic *PAFAH1B1* pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If a parent of the proband has a structural chromosome rearrangement involving *PAFAH1B1*, the risk to sibs is increased and depends on the specific chromosome rearrangement.
- If the proband has a known *PAFAH1B1* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Mineyko et al 2010].
- If the parents have not been tested for the *PAFAH1B1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected

parents are still presumed to be at increased risk for *PAFAH1B1*-related lissencephaly/SBH because of the possibility of the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *PAFAH1B1*-related lissencephaly/SBH has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *PAFAH1B1* genetic alteration, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *PAFAH1B1* genetic alteration has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Fetal ultrasound examination. Prenatal testing by level 2 ultrasound examination does **NOT** detect lissencephaly, as normal fetal brains have a smooth surface until late in gestation.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Lissencephaly Information Page
- **American Epilepsy Society**
  www.aesnet.org
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. PAFAH1B1-Related Lissencephaly / Subcortical Band Heterotopia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PAFAH1B1	17p13.3	Platelet-activating factor acetylhydrolase IB subunit beta	PAFAH1B1 database	PAFAH1B1	PAFAH1B1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for PAFAH1B1-Related Lissencephaly / Subcortical Band Heterotopia (View All in OMIM)

601545	PLATELET-ACTIVATING FACTOR ACETYLHYDROLASE, ISOFORM 1B, ALPHA SUBUNIT; PAFAH1B1
607432	LISSENCEPHALY 1; LIS1

Molecular Pathogenesis

Platelet-activating factor acetylhydrolase IB subunit alpha (PAFAH1B1) is highly conserved among species. The main functional domains of this protein are a LisH motif at the N terminus and a coiled-coil region, which are important for protein dimerization. Seven WD40 repeats at the C terminus are necessary for protein-protein interactions [Cardoso et al 2000, Reiner 2013].

The PAFAH1B1 protein has several functions. PAFAH1B1 forms a trimeric complex with the PAFAH1B2 and PAFAH1B3 proteins to regulate the level of platelet-activating factor in the brain [Albrecht et al 1996, Bix & Clark 1998]. Additionally, PAFAH1B1 interacts directly with tubulin proteins and indirectly with microtubulin-associated proteins (MAP), such as dynein, DCX, or NDE1, to facilitate cytoskeleton organization during mitotic spindle cell orientation. Normal interaction of PAFAH1B1 with microtubules and MAPs is also crucial for interkinetic motility, nucleokinesis, and radial and tangential migration of neurons [Markus et al 2020].

Proliferation of neuronal progenitors and astrocytes has been shown to be impaired in individuals with pathogenic variants in *PAFAH1B1*. Additionally, cortical layering is disturbed due to abnormal migration of neuronal precursors from the ventricular and subventricular zone to the cortical plate during cortical development [Reiner & Sapir 2013].

Mechanism of disease causation. Loss of function

***PAFAH1B1*-specific laboratory technical considerations.** There are two alternative transcripts (5.5 kb and 7.5 kb) that differ in the length at their respective 3' UTR regions; both transcripts are expressed ubiquitously [Hattori et al 1994, Lo Nigro et al 1997]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Chapter Notes

Author Notes

Stefanie Brock: researchportal.vub.be

William B Dobyns: med.umn.edu

Anna Jansen: researchportal.vub.be, @jansen_ac

Author History

Stefanie Brock, MD (2021-present)
Soma Das, PhD; University of Chicago (2009-2021)
William B Dobyns, MD (2009-present)
Anna Jansen, MD, PhD (2021-present)

Revision History

- 25 March 2021 (ma) Comprehensive update posted live
- 14 August 2014 (me) Comprehensive update posted live
- 3 March 2009 (me) Review posted live
- 22 August 2008 (wd) Original submission

References

Literature Cited

Albrecht U, Abu-Issa R, Rätz B, Hattori M, Aoki J, Arai H, Inoue K, Eichele G. Platelet-activating factor acetylhydrolase expression and activity suggest a link between neuronal migration and platelet-activating factor. Dev Biol. 1996;180:579–93. PubMed PMID: 8954729.

Bahi-Buisson N, Guerrini R. Diffuse malformations of cortical development. Handb Clin Neurol. 2013;111:653–65. PubMed PMID: 23622213.

Bahi-Buisson N, Poirier K, Fourniol F, Saillour Y, Valence S, Lebrun N, Hully M, Bianco CF, Boddaert N, Elie C, Lascelles K, Souville I, Beldjord C, Chelly J, et al. The wide spectrum of tubulinopathies: what are the key features for the diagnosis? Brain. 2014;137:1676–700. PubMed PMID: 24860126.

Bix GJ, Clark GD. Platelet-activating factor receptor stimulation disrupts neuronal migration In vitro. J Neurosci. 1998;18:307–18. PubMed PMID: 9412509.

Cardoso C, Leventer RJ, Dowling JJ, Ward HL, Chung J, Petras KS, Roseberry JA, Weiss AM, Das S, Martin CL, Pilz DT, Dobyns WB, Ledbetter DH. Clinical and molecular basis of classical lissencephaly: mutations in the LIS1 gene. Hum Mutat. 2002;19:4–15. PubMed PMID: 11754098.

Cardoso C, Leventer RJ, Matsumoto N, Kuc JA, Ramocki MB, Mewborn SK, Dudlicek LL, May LF, Mills PL, Das S, Pilz DT, Dobyns WB, Ledbetter DH. The location and type of mutation predict malformation severity in isolated lissencephaly caused by abnormalities within the LIS1 gene. Hum Mol Genet. 2000;9:3019–28. PubMed PMID: 11115846.

Cardoso C, Leventer RJ, Ward HL, Toyo-Oka K, Chung J, Gross A, Martin CL, Allanson J, Pilz DT, Olney AH, Mutchinick OM, Hirotsune S, Wynshaw-Boris A, Dobyns WB, Ledbetter DH. Refinement of a 400-kb critical region allows genotypic differentiation between isolated lissencephaly, Miller-Dieker syndrome, and other phenotypes secondary to deletions of 17p13.3. Am J Hum Genet. 2003;72:918–30. PubMed PMID: 12621583.

Chong SS, Pack SD, Roschke AV, Tanigami A, Carrozzo R, Smith AC, Dobyns WB, Ledbetter DH. A revision of the lissencephaly and Miller-Dieker syndrome critical regions in chromosome 17p13.3. Hum Mol Genet. 1997;6:147–55. PubMed PMID: 9063734.

D'Agostino MD, Bernasconi A, Das S, Bastos A, Valerio RM, Palmini A, Costa da Costa J, Scheffer IE, Berkovic S, Guerrini R, Dravet C, Ono J, Gigli G, Federico A, Booth F, Bernardi B, Volpi L, Tassinari CA, Guggenheim

MA, Ledbetter DH, Gleeson JG, Lopes-Cendes I, Vossler DG, Malaspina E, Franzoni E, Sartori RJ, Mitchell MH, Mercho S, Dubeau F, Andermann F, Dobyns WB, Andermann E. Subcortical band heterotopia (SBH) in males: clinical, imaging and genetic findings in comparison with females. Brain. 2002;125:2507–22. PubMed PMID: 12390976.

Damiano JA, Do H, Ozturk E, Burgess R, Kalnins R, Jones NC, Dobrovic A, Berkovic SF, Hildebrand MS. Sensitive quantitative detection of somatic mosaic mutation in "double cortex" syndrome. Epileptic Disord. 2017;19:450–5. PubMed PMID: 29258966.

De Vita D, Mei D, Rutigliano D, Bartalucci N, Cinnante CM, Parrini E, Dilena R, Guerrini R. Familial dominant epilepsy and mild pachygyria associated with a constitutional LIS1 mutation. Am J Med Genet A. 2018;176:2808–12. PubMed PMID: 30144370.

de Wit MC, de Rijk-van Andel J, Halley DJ, Poddighe PJ, Arts WF, de Coo IF, Mancini GM. Long-term follow-up of type 1 lissencephaly: survival is related to neuroimaging abnormalities. Dev Med Child Neurol. 2011;53:417–21. PubMed PMID: 21410694.

Di Donato N, Chiari S, Mirzaa GM, Aldinger K, Parrini E, Olds C, Barkovich AJ, Guerrini R, Dobyns WB. Lissencephaly: expanded imaging and clinical classification. Am J Med Genet A. 2017;173:1473–88. PubMed PMID: 28440899.

Di Donato N, Timms AE, Aldinger KA, Mirzaa GM, Bennett JT, Collins S, Olds C, Mei D, Chiari S, Carvill G, Myers CT, Rivière JB, Zaki MS, Gleeson JG, Rump A, Conti V, Parrini E, Ross ME, Ledbetter DH, Guerrini R, Dobyns WB, et al. Analysis of 17 genes detects mutations in 81% of 811 patients with lissencephaly. Genet Med. 2018;20:1354–64. PubMed PMID: 29671837.

Dobyns WB, Curry CJ, Hoyme HE, Turlington L, Ledbetter DH. Clinical and molecular diagnosis of Miller-Dieker syndrome. Am J Hum Genet. 1991;48:584–94. PubMed PMID: 1671808.

González-Morón D, Vishnopolska S, Consalvo D, Medina N, Marti M, Córdoba M, Vazquez-Dusefante C, Claverie S, Rodríguez-Quiroga SA, Vega P, Silva W, Kochen S, Kauffman MA. Germline and somatic mutations in cortical malformations: molecular defects in Argentinean patients with neuronal migration disorders. PLoS One. 2017;12:e0185103. PubMed PMID: 28953922.

Hattori M, Adachi H, Tsujimoto M, Arai H, Inoue K. Miller-Dieker lissencephaly gene encodes a subunit of brain platelet-activating factor acetylhydrolase. Nature. 1994;370:216–8. PubMed PMID: 8028668.

Haverfield EV, Whited AJ, Petras KS, Dobyns WB, Das S. Intragenic deletions and duplications of the LIS1 and DCX genes: a major disease-causing mechanism in lissencephaly and subcortical band heterotopia. Eur J Hum Genet. 2009;17:911–8. PubMed PMID: 19050731.

Herbst SM, Proepper CR, Geis T, Borggraefe I, Hahn A, Debus O, Haeussler M, von Gersdorff G, Kurlemann G, Ensslen M, Beaud N, Budde J, Gilbert M, Heiming R, Morgner R, Philippi H, Ross S, Strobl-Wildemann G, Muelleder K, Vosschulte P, Morris-Rosendahl DJ, Schuierer G, Hehr U. LIS1-associated classic lissencephaly: a retrospective, multicenter survey of the epileptogenic phenotype and response to antiepileptic drugs. Brain Dev. 2016;38:399–406. PubMed PMID: 26494205.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Kato M, Das S, Petras K, Kitamura K, Morohashi K, Abuelo DN, Barr M, Bonneau D, Brady AF, Carpenter NJ, Cipero KL, Frisone F, Fukuda T, Guerrini R, Iida E, Itoh M, Lewanda AF, Nanba Y, Oka A, Proud VK, Saugier-Veber P, Schelley SL, Selicorni A, Shaner R, Silengo M, Stewart F, Sugiyama N, Toyama J, Toutain A, Vargas AL, Yanazawa M, Zackai EH, Dobyns WB. Mutations of ARX are associated with striking pleiotropy and consistent genotype-phenotype correlation. Hum Mutat. 2004;23:147–59. PubMed PMID: 14722918.

Leventer RJ, Cardoso C, Ledbetter DH, Dobyns WB. LIS1 missense mutations cause milder lissencephaly phenotypes including a child with normal IQ. Neurology. 2001;57:416–22. PubMed PMID: 11502906.

Lo Nigro C, Choong CS, Smith AC, Dobyns WB, Carrozzo R, Ledbetter DH. Point mutations and an intragenic deletion in LIS1, the lissencephaly causative gene in isolated lissencephaly sequence and Miller-Dieker syndrome. Hum Mol Genet. 1997;6:157–64. PubMed PMID: 9063735.

Markus SM, Marzo MG, McKenney RJ. New insights into the mechanism of dynein motor regulation by lissencephaly-1. Elife. 2020.:9.

Marsh E, Fulp C, Gomez E, Nasrallah I, Minarcik J, Sudi J, Christian SL, Mancini G, Labosky P, Dobyns W, Brooks-Kayal A, Golden JA. Targeted loss of Arx results in a developmental epilepsy mouse model and recapitulates the human phenotype in heterozygous females. Brain. 2009;132:1563–76. PubMed PMID: 19439424.

Mattiske T, Moey C, Vissers LE, Thorne N, Georgeson P, Bakshi M, Shoubridge C. An emerging female phenotype with loss-of-function mutations in the aristaless-related homeodomain transcription factor ARX. Hum Mutat. 2017;38:548–55. PubMed PMID: 28150386.

Mineyko A, Doja A, Hurteau J, Dobyns WD, Das S, Boycott KM. A novel missense mutation in LIS1 in a child with subcortical band heterotopia and pachygyria inherited from his mildly affected mother with somatic mosaicism. J Child Neurol. 2010;25:738–41. PubMed PMID: 19808989.

Pagnamenta AT, Lise S, Harrison V, Stewart H, Jayawant S, Quaghebeur G, Deng AT, Murphy VE, Sadighi Akha E, Rimmer A, Mathieson I, Knight SJ, Kini U, Taylor JC, Keays DA. Exome sequencing can detect pathogenic mosaic mutations present at low allele frequencies. J Hum Genet. 2012;57:70–2. PubMed PMID: 22129557.

Pilz DT, Kuc J, Matsumoto N, Bodurtha J, Bernadi B, Tassinari CA, Dobyns WB, Ledbetter DH. Subcortical band heterotopia in rare affected males can be caused by missense mutations in DCX (XLIS) or LIS1. Hum Mol Genet. 1999;8:1757–60. PubMed PMID: 10441340.

Pilz DT, Macha ME, Precht KS, Smith AC, Dobyns WB, Ledbetter DH. Fluorescence in situ hybridization analysis with LIS1 specific probes reveals a high deletion mutation rate in isolated lissencephaly sequence. Genet Med. 1998;1:29–33. PubMed PMID: 11261426.

Quirk JA, Kendall B, Kingsley DP, Boyd SG, Pitt MC. EEG features of cortical dysplasia in children. Neuropediatrics. 1993;24:193–9. PubMed PMID: 8232776.

Reiner O. LIS1 and DCX: implications for brain development and human disease in relation to microtubules. Scientifica (Cairo). 2013;2013:393975. PubMed PMID: 24278775.

Reiner O, Sapir T. LIS1 functions in normal development and disease. Curr Opin Neurobiol. 2013;23:951–6. PubMed PMID: 23973156.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Romaniello R, Zucca C, Arrigoni F, Bonanni P, Panzeri E, Bassi MT, Borgatti R. Epilepsy in tubulinopathy: personal series and literature review. Cells. 2019;8:669. PubMed PMID: 31269740.

Saillour Y, Carion N, Quelin C, Leger PL, Boddaert N, Elie C, Toutain A, Mercier S, Barthez MA, Milh M, Joriot S, des Portes V, Philip N, Broglin D, Roubertie A, Pitelet G, Moutard ML, Pinard JM, Cances C, Kaminska A, Chelly J, Beldjord C, Bahi-Buisson N. LIS1-related isolated lissencephaly: spectrum of mutations and relationships with malformation severity. Arch Neurol. 2009;66:1007–15. PubMed PMID: 19667223.

Shi CH, Zhang S, Yang ZH, Liu YT, Li YS, Li Z, Hu ZW, Xu YM. Identification of a novel PAFAH1B1 missense mutation as a cause of mild lissencephaly with basal ganglia calcification. Brain Dev. 2019;41:29–35. PubMed PMID: 30100227.

Sicca F, Kelemen A, Genton P, Das S, Mei D, Moro F, Dobyns WB, Guerrini R. Mosaic mutations of the LIS1 gene cause subcortical band heterotopia. Neurology. 2003;61:1042–6. PubMed PMID: 14581661.

Stutterd CA, Francis D, McGillivray G, Lockhart PJ, Leventer RJ. Polymicrogyria associated with 17p13.3p13.2 duplication: Case report and review of the literature. Eur J Med Genet. 2020;63:103774. PubMed PMID: 31585183.

Uyanik G, Morris-Rosendahl DJ, Stiegler J, Klapecki J, Gross C, Berman Y, Martin P, Dey L, Spranger S, Korenke GC, Schreyer I, Hertzberg C, Neumann TE, Burkart P, Spaich C, Meng M, Holthausen H, Adès L, Seidel J, Mangold E, Buyse G, Meinecke P, Schara U, Zeschnigk C, Muller D, Helland G, Schulze B, Wright ML, Kortge-Jung S, Hehr A, Bogdahn U, Schuierer G, Kohlhase J, Aigner L, Wolff G, Hehr U, Winkler J. Location and type of mutation in the LIS1 gene do not predict phenotypic severity. Neurology. 2007;69:442–7. PubMed PMID: 17664403.

License