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Tubulinopathies Overview

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Summary

The purpose of this overview is to:

1. Describe the clinical characteristics of tubulinopathies.
2. Review the genetic causes of tubulinopathies.
3. Review the differential diagnosis of tubulinopathies.
4. Provide an evaluation strategy to identify the genetic cause of a tubulinopathy in a proband (when possible).
5. Review general medical management of tubulinopathies.
6. Inform genetic counseling of family members of an individual with a tubulinopathy.

1. Clinical Characteristics of Tubulinopathies

Tubulinopathies (or tubulin-related cortical dysgenesis) comprise a wide and overlapping range of brain malformations as well as other clinical features caused by pathogenic variants in genes encoding different isotypes of tubulin [Romero et al 2018].

Brain Malformations

Lissencephaly ranges from a thickened cortex and complete absence of sulci (agyria) to a thickened cortex and a few shallow sulci (pachygyria) [Di Donato et al 2017].

- **Classic lissencephaly** is characterized by marked thickening of the cortex with a posterior-to-anterior gradient of severity (i.e., more severe involvement posteriorly [parietal and occipital lobes] than anteriorly [orbitofrontal and anterior temporal regions]). Most often, cerebellar structure is normal and the basal ganglia appear normal except that the anterior limb of the internal capsule is usually not visible.
- **Lissencephaly with cerebellar hypoplasia.** Some rare forms of lissencephaly are associated with a disproportionately small cerebellum.
- **Lissencephaly with agenesis of the corpus callosum.** The corpus callosum in living individuals is commonly dysmorphic (missing rostrum plus flat genu and anterior body), hypoplastic, or partially

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absent. In contrast, all prenatally diagnosed cases show complete agenesis (Figure 1 A-C and Figure 1 D-F).

- **Centrally predominant pachygyria** is characterized by pachygyria involving the insula and the frontal, temporal, and parietal opercula [Bahi-Buisson et al 2008]. All have abnormalities of the basal ganglia that appear as large round structures in which the caudate, putamen, and globus pallidus are indistinguishable. Hypoplasia of the anterior limbs of the internal capsule is a major feature. Common findings are vermian hypoplasia and brain stem hypoplasia. The corpus callosum is commonly dysmorphic or hypoplastic; less frequently, it is partially or completely absent (Figure 1 G-I).

Microlissencephaly refers to the most severe of the cortical dysplasias that combines extreme microcephaly and lissencephaly with hemispheres lacking primary fissures and olfactory sulci. Mainly diagnosed by prenatal MRI, findings at a median age of 25 weeks' gestation include microcephaly, absent-to-poorly operculized cortex, virtually no visible gyration, severe cerebellar hypoplasia, absent or severely hypoplastic basal ganglia, and usually complete agenesis of the corpus callosum. Associated malformations include pontocerebellar hypoplasia [Fallet-Bianco et al 2008, Lecourtois et al 2010, Fallet-Bianco et al 2014].

Dysgyria describes a cortex of normal thickness but with an abnormal gyral pattern characterized by abnormalities of sulcal depth or orientation: obliquely oriented sulci directed radially toward the center of the cerebrum and narrow gyri separated by abnormally deep or shallow sulci without imaging evidence of lissencephaly, pachygyria, cobblestone cortex, polymicrogyria, or other cortical abnormalities [Mutch et al 2016, Blumkin et al 2020]. This pattern tends to predominate in the perisylvian areas.

MRI reveals a "coarse" appearance with a thick cortex and irregular surfaces on both the pial and grey-white junction sides (Figure 1 J-L, Figure 2 A-F, Figure 3 D-I). Dysgyria can range in severity and distribution.

Note: Dysgyria was previously referred to as "simplified gyral pattern" or "polymicrogyria-like cortical dysplasia"; these terms are potentially confusing.

Basal ganglia, thalami, and corpus callosum. One of the key feature of tubulinopathies is dysmorphic basal ganglia. This pattern is usually asymmetric with bulbous appearance of the caudate and the thalami, with diffuse, branched or absent anterior limb of the internal capsule. The lateral ventricles have an irregular contour and abnormal rounding of the frontal horns likely related to the basal ganglia dysplasia.

The corpus callosum is variably affected, ranging from almost complete agenesis to normal.

Recognizable cerebellar and brain stem abnormalities. The most characteristic tubulinopathy-related cerebellar malformation is dysplasia of the superior cerebellum, especially the vermis (with "diagonal" folia – i.e., folia crossing the midline at an oblique angle). Less commonly, the vermis is hypoplastic with the anterior vermis more severely affected. The cerebellar hemispheres are either normal in size or mildly hypoplastic with mild asymmetry.

A large majority of affected individuals show brain stem hypoplasia that is usually asymmetric with a midline ventral indentation and asymmetric inferior and middle cerebellar peduncles [Oegema et al 2015].

Clinical Features of the Tubulinopathies

The clinical features of the tubulinopathies include motor and intellectual disabilities and epilepsy.

Motor and cognitive and impairments, present in almost all individuals with a tubulinopathy, correlate with the severity of brain malformations.

- Lissencephaly, microlissencephaly, and generalized severe dysgyria: spastic tetraplegia and virtually no voluntary motor control and absent eye contact
- Mild-to-moderate dysgyria: mild motor disability and intellectual disabilities

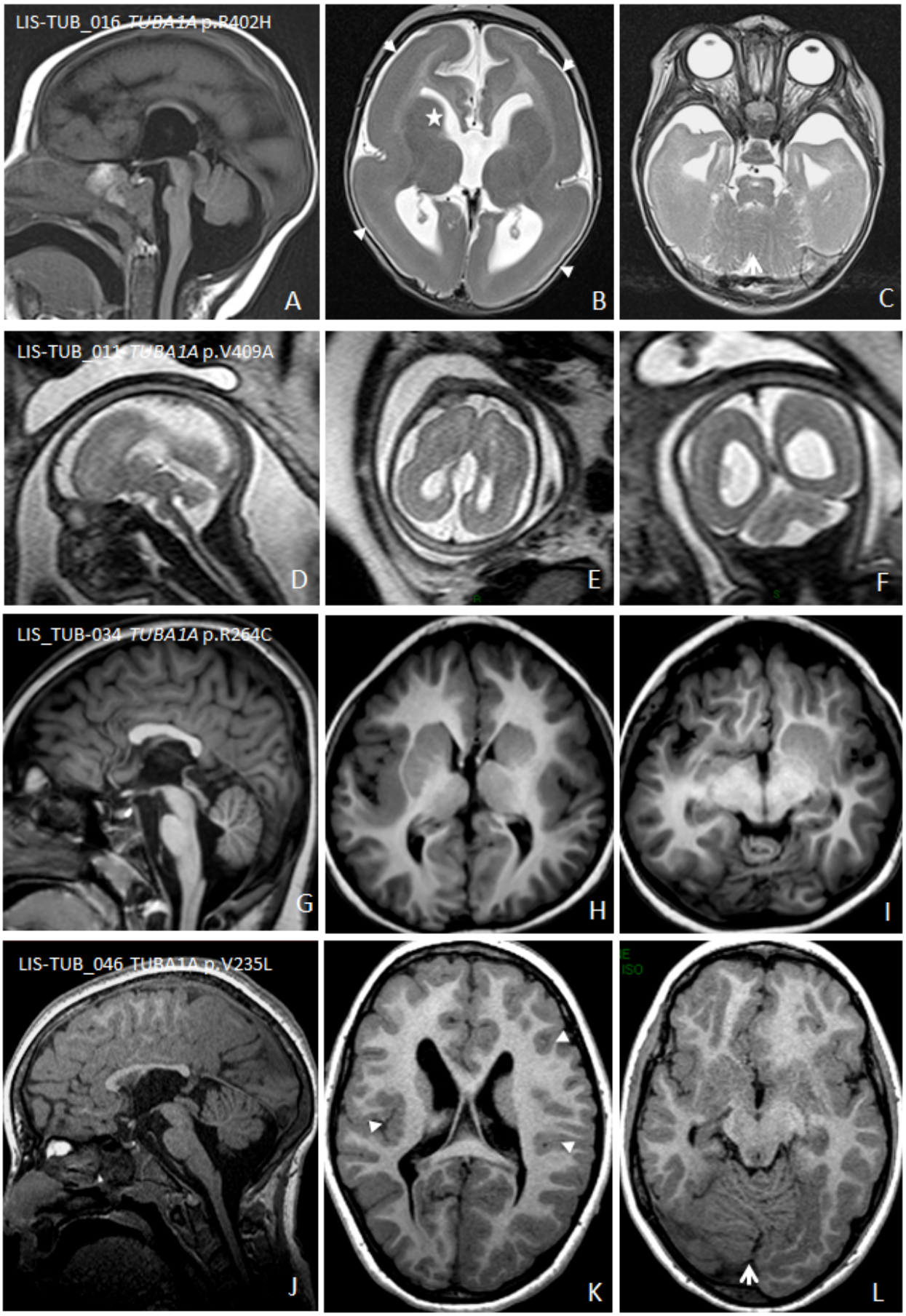

Figure 1. Representative images of *TUBA1A*-related tubulinopathies

A-C. Infant age four months with classic lissencephaly. Other features include dysmorphic corpus callosum, dysmorphic/dysplastic internal capsules, and hypoplasia of the cerebellar vermis.

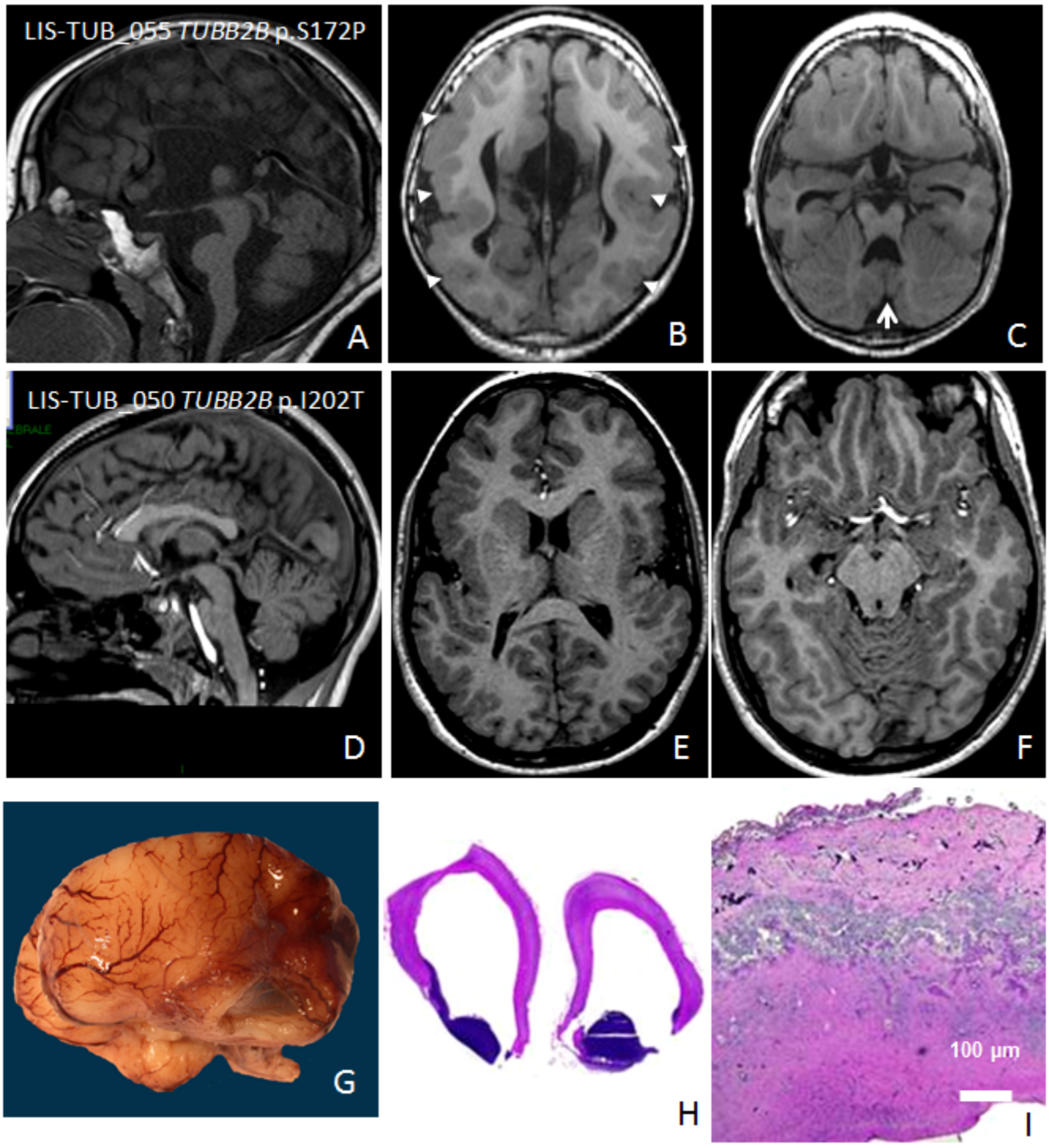

Figure 2. Representative images of *TUBB2B*-related tubulinopathies

A-C. Child age three years with cortical dysgyria resembling polymicrogyria. The cortex has a coarse appearance with excessively folded gyri (arrowheads in B). Cortical dysgyria resembling polymicrogyria is associated with complete agenesis of the corpus callosum (A). The basal ganglia are hypertrophic and fused; the lateral ventricles are dysmorphic (B). The cerebellar vermis is dysplastic (arrow in C).

D-F. Individual age 15 years with cortical dysgyria resembling polymicrogyria that appears to be typical with an irregular cortical surface or overfolded cortex aspect and irregularity at the grey-white interface (E). Cortical dysgyria resembling polymicrogyria appears mildly asymmetric and most severe over the central (mid- and posterior frontal, perisylvian, and anterior parietal) regions rather than over the posterior and frontal poles. The superior vermis is dysplastic (F).

G-I. Fetus at 27 weeks' gestation with microlissencephaly. Macroscopic view of the left hemisphere shows agyria with absent sylvian fissure and absent olfactory bulbs (G). Coronal section passing through the hemispheres shows a thin mantle with absence of the corpus callosum, internal capsule, and basal ganglia; enlarged ventricles; and voluminous germinal zones (H). There is diffuse disorganization of the cortical plate with massive overmigration of cells within the meningeal spaces (I).

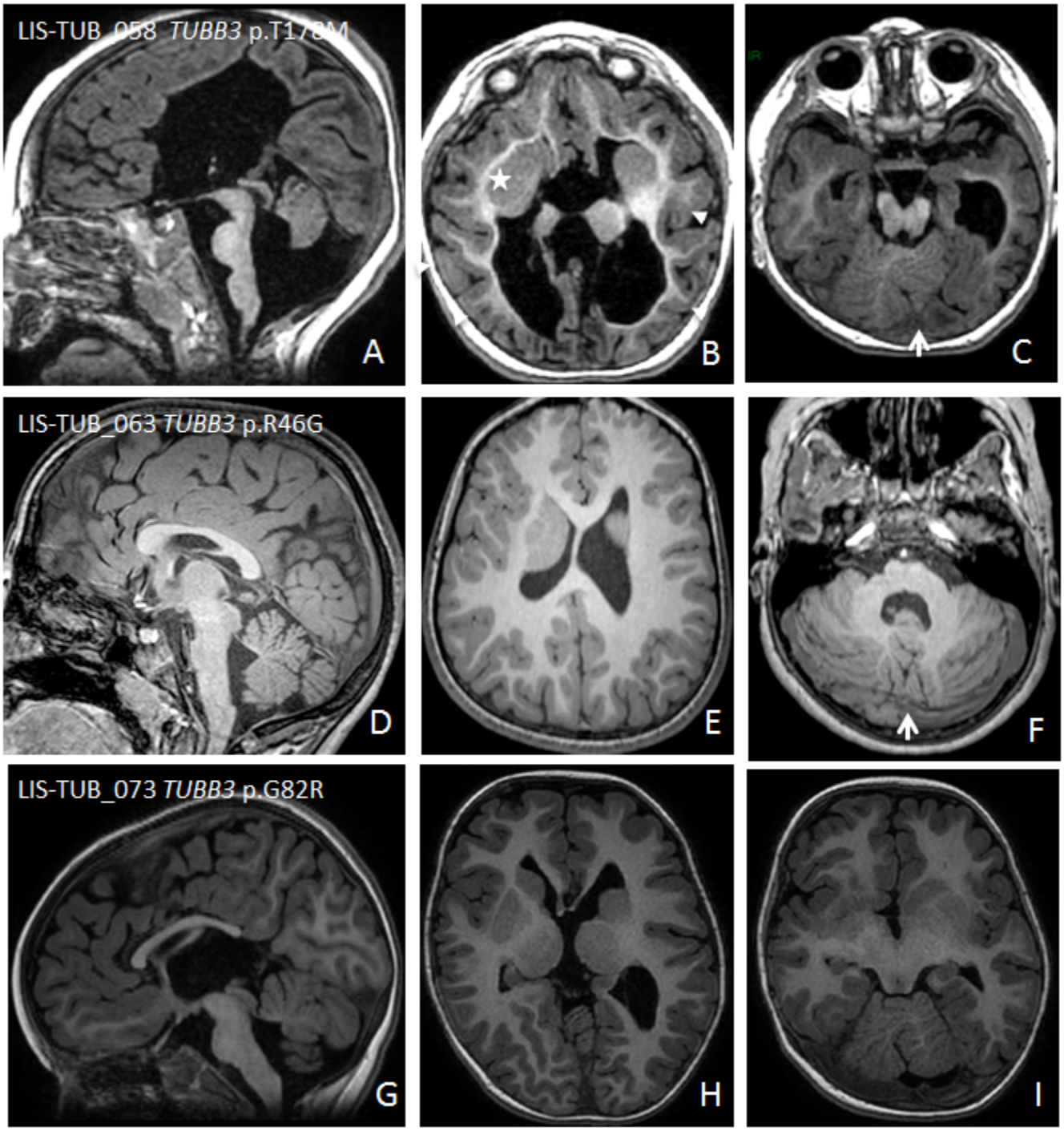

Figure 3. Representatives images of *TUBB3*-related tubulinopathies

A-C. Child age three years with diffuse cortical dysgyria. The cortex shows a coarse appearance, with excessively folded gyri (arrowhead in B). Associated malformations include complete agenesis of corpus callosum (A), pontocerebellar hypoplasia (A), and dysplasia of the cerebellar vermis (arrowhead in C). The basal ganglia are hypertrophic and fused (asterisks in B); the lateral ventricles are dysmorphic (B).

D-F. Child age 11 years; G-I. Child age three years. Both show gyral disorganization with multifocal dysplasia. In both individuals, the cortex has an abnormal appearance with poorly folded gyri, generalized undersulcation (mostly the ternary sulci) (D-F). The basal ganglia are malformed and the lateral ventricles are dysmorphic (E-H). The corpus callosum is hypoplastic (G). The cerebellar vermis is dysplastic (F-I).

While most affected individuals have severe-to-profound intellectual disability, a minority have less extensive cortical malformations that result in only moderate intellectual disability, and a few have limited malformations that allow near-normal cognitive abilities. In the latter instance, the cortical malformation is typically less severe and less extensive on MRI.

Epilepsy varies significantly among affected individuals and is not necessarily determined by the severity of the cortical malformation, the gene involved, or the causative pathogenic variant [Romaniello et al 2019]. However:

- Early epileptic encephalopathy (with or without infantile spasms) is common in lissencephaly and generalized severe dysgyria.
- Seizures are usually present in fewer than 30% of individuals with a simplified gyral pattern with the exception of the two individuals with *TUBB2A*-related tubulinopathy who had infantile spasms with hypsarrhythmia (i.e., West syndrome) [Cushion et al 2014].

Additional findings. Facial diplegia and strabismus suggestive of pseudobulbar palsy are often observed in central pachygyria and various forms of dysgyria [Bahi-Buisson et al 2008].

Prognosis. Individuals with the milder forms of tubulinopathies survive into adulthood, while those with the most severe forms may die at a young age as a result of complications such as seizures or pneumonia.

2. Genetic Causes of Tubulinopathies

The genetic causes of tubulinopathies and their associated complex cortical malformations are summarized in Table 1.

Table 1. Tubulinopathies: Molecular Genetics and Complex Cortical Malformations

Gene [1]	MOI	Complex Cortical Malformations					
		CL	Dysgyria	SGP	MLIS	Other	References
TUBA1A	AD	37%	12%	4% [2]	13%	Lissencephaly w/cerebellar hypoplasia (15%); predominantly central pachygyria (30%)	Kumar et al [2010], Bahi-Buisson et al [2014], Hebebrand et al [2019]
TUBB (*TUBB5*)	AD			3 persons		Range: SGP to focal polymicrogyria & microcephaly	Breuss et al [2012]
TUBB2A	AD			2 persons		Dysmorphic CC, normal gyral pattern, & basal ganglia	Cushion et al [2014]
TUBB2B	AD		87.5%	30%	9.4%	Lissencephaly w/agenesis of CC (3.1%); open-lip schizencephaly (1 person); CFEOM (1 family)	[Guerrini et al [2012], Romaniello et al [2012], Cushion et al [2013], Amrom et al [2014]
TUBB3	AD		90%	10%	1 person [3]	Brain stem & cerebellar vermian hypoplasia & basal ganglia dysmorphism; CFEOM	Poirier et al [2010], Tischfield et al [2010]
TUBG1	AD	2/3 persons				Predominantly posterior subcortical band heterotopia (1/3 persons)	Poirier et al [2013a], Brock et al [2018]

AD = autosomal dominant; AR = autosomal recessive; CC = corpus callosum; CFEOM = congenital fibrosis of the extraocular muscles; CL = classic lissencephaly; MLIS = microlissencephaly; MOI = mode of inheritance; SGP = simplified gyral pattern

1. Genes are in alphabetic order.

2. Dysgyria or cortical dysplasia resembling polymicrogyria [Jansen et al 2011, Cushion et al 2013, Poirier et al 2013b]

3. At the extreme severe end of the spectrum, only one fetus was reported with microlissencephaly and corpus callosum agenesis, severe brain stem and cerebellar hypoplasia, and dysmorphic basal ganglia [Poirier et al 2010] (Figure 3 A-C).

3. Differential Diagnosis of Tubulinopathies

Tubulinopathies need to be distinguished clinically from other brain malformations that may resemble them (Table 2).

Table 2. Differential Diagnosis of Tubulinopathies

Brain Malformation	Gene(s)	Disorder	MOI
Lissencephaly-pachygyria spectrum of cortical malformation (smooth cortex w/simplified gyration appearance)	*PAFAH1B1* (*LIS1*)	*PAFAH1B1*-related lissencephaly/subcortical band heterotopia)	AD
	ACTB *ACTG1*	Baraitser-Winter cerebrofrontofacial (BWCFF) syndrome	AD
Classic & atypical lissencephaly syndromes	*ARX*	X-linked lissencephaly 2 (OMIM 300215)	XL
	DCX	*DCX*-related disorders	XL
	DYNC1H1	*DYNC1H1*-related disorders [1]	AD
	PAFAH1B1 (*LIS1*)	*PAFAH1B1*-related lissencephaly/subcortical band heterotopia	AD
	PAFAH1B1 & *YWHAE* [2]	Miller-Dieker lissencephaly syndrome (OMIM 247200)	AD
	RELN	Lissencephaly 2 (OMIM 257320)	AR
	VLDLR	*VLDLR* cerebellar hypoplasia	AR
Cobblestone cortical malformation (lissencephaly) syndromes (frequently assoc w/hydrocephalus, dysmyelination, dysplastic cerebellum & brain stem hypoplasia, multiple eye anomalies, & congenital muscular dystrophy)	*ADGRG1* (*GPR56*)	Polymicrogyria	AR
	B3GALNT2 *B4GAT1* *CRPPA* (*ISPD*) *DAG1* *FKRP* *FKTN* *GMPPB* *LARGE1* *POMGNT1* *POMGNT2* *POMK* *POMT1* *POMT2* *RXYLT1* (*TMEM5*)	Walker-Warburg syndrome [3]	AR
	DAG1 *GMPPB* *LARGE1* *POMGNT1* *POMT1* *POMT2*	Muscle-eye-brain disease [3]	AR
	FKTN	Fukuyama congenital muscular dystrophy [3]	AR
Generalized dysgyria	*DYNC1H1*	*DYNC1H1*-related disorders [1]	AD
	NDE1	Lissencephaly 4 (OMIM 614019)	AR
	WDR62	Primary AR microcephaly 2	AR

Table 2. continued from previous page.

Brain Malformation	Gene(s)	Disorder	MOI
Polymicrogyria	*EOMES (TBR2)*	See OMIM 604615	AR
	KIF5C	Complex cortical dysplasia w/other brain malformations 2 (OMIM 615282)	AD
Microlissencephaly	*KATNB1*	Lissencephaly 6 w/microcephaly (OMIM 616212)	AR
	NDE1	Lissencephaly 4 (OMIM 614019)	AR
	WDR62	Primary AR microcephaly 2	AR
Microcephaly w/cortical malformations	*KIF2A*	Complex cortical dysplasia w/other brain malformations 3 (OMIM 615411)	AD

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. Mutation of *DYNC1H1* is associated with isolated polymicrogyria, nodular heterotopia, hypoplasia of the corpus callosum, abnormally shaped basal ganglia, and in some cases, evidence of peripheral neuropathy (see *DYNC1H1*-Related Disorders).
2. As currently defined, Miller-Dieker syndrome is associated with deletions that include both *PAFAH1B1 (LIS1)* and *YWHAE* (a region of ~1.3 Mb harboring many genes) in 17p13.3 [Pilz et al 1998, Cardoso et al 2003].
3. See Fukuyama Congenital Muscular Dystrophy: Table 3: Distinguishing Between the Major Phenotypes of the Alpha-Dystroglycanopathies: FCMD, MEBD, and WWS.

4. Evaluation Strategies to Identify the Genetic Cause of Tubulinopathy in a Proband

Establishing a specific genetic cause of a tubulinopathy:

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, family history, and molecular genetic testing.

Family history. A three-generation family history should be taken, with attention to relatives with manifestations of a tubulinopathy and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing.

Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **A multigene panel** that includes some or all of the genes listed in Table 1 is most 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **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.

5. General Medical Management of Tubulinopathies

A pediatric neurologist with expertise in the management of children with multiple disabilities and medically refractory epilepsy is recommended for long-term management.

Supportive management, including an individualized therapy plan that includes physical therapy to manage the complications of spasticity, occupational therapy, speech therapy, and vision therapy for oculomotor deficits and/or strabismus should begin at the time of diagnosis to ensure the best possible functionality and developmental outcome. Of note, it is appropriate to institute measures early on to manage potential complications of spasticity (e.g., joint contractures or reduced range of motion), which can increase the risk for decubitus ulcers as well as affect mobility and hygiene.

Those with congenital fibrosis of the extraocular muscles may require nonsurgical and/or surgical treatment.

Nutritional needs in infants with the more severe brain malformations (e.g., lissencephaly, generalized polymicrogyria) are usually managed by nasogastric tube feedings, followed by gastrostomy tube placement as needed.

Seizures are treated with anti-seizure medications based on the specific seizure type. In general, seizures should be treated promptly by specialists, as poor seizure control frequently worsens feeding and increases both the likelihood that a gastrostomy tube will be needed and the risk for aspiration.

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

For individuals with severe cortical malformations (lissencephalies, polymicrogyria-like cortical dysplasia, microlissencephaly), it is usually appropriate to discuss the level of care to be provided in the event of a severe intercurrent illness.

6. Genetic Counseling of Family Members of an Individual with a Tubulinopathy

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

Tubulinopathies caused by pathogenic variants in *TUBA1A*, *TUBB2A, TUBB2B*, *TUBB3*, *TUBB* (*TUBB5*), or *TUBG1* are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- More than 95% of individuals diagnosed with a tubulinopathy have a *de novo* pathogenic variant in *TUBA1A*, *TUBB2A*, *TUBB2B*, *TUBB3*, *TUBB* (*TUBB5*), or *TUBG1*.
- Rarely, an individual diagnosed with a tubulinopathy has an affected parent. These individuals generally have either a *TUBB3* or (less frequently) *TUBB2B* pathogenic variant.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant 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.* Maternal germline mosaicism has been reported in two families with multiple affected offspring [Zillhardt et al 2016]. 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.

      * A parent with somatic and germline mosaicism for a pathogenic variant may be mildly/minimally affected. While this situation is unusual, several groups have reported somatic mosaic pathogenic variants in genes encoding tubulin [Jamuar & Walsh 2014, Zillhardt et al 2016].
- The family history of some individuals diagnosed with a tubulinopathy may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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 affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the proband has a known tubulinopathy-related 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 [Poirier et al 2013a, Zillhardt et al 2016].
- If the parents have not been tested for the pathogenic variant identified in the proband but are clinically unaffected, the risk to the sibs of the proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for a tubulinopathy because of the possibility of the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a tubulinopathy has a 50% chance of inheriting the pathogenic variant.

Other family members

- The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.
- The risk to other family members appears to be low given that most probands with an autosomal dominant tubulinopathy have the disorder as a result of a *de novo* pathogenic variant.

Prenatal Testing and Preimplantation Genetic Testing

Once the tubulinopathy-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic 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.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **American Epilepsy Society**
  aesnet.org
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **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

Chapter Notes

Author Notes

Nadia Bahi-Buisson is a pediatric neurologist specializing in cortical malformations and fetal neurology. Her research at Imagine Institute focuses on the genetic and pathophysiologic bases of cortical malformations. She follows more than 100 patients with diffuse cortical malformations, and has consulted on more than 500 such cases. Dr Bahi-Buisson is involved in the European consortium on cortical malformations. This work is performed in collaboration with Chérif Beldjord, MD, PhD (director of the Laboratory of Biochemical Genetics – Cochin-Port-Royal).

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