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TBC1D24-Related Disorders

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Summary

Clinical characteristics

TBC1D24-related disorders comprise a continuum of features that were originally described as distinct, recognized phenotypes:

- DOORS syndrome (*d*eafness, *o*nychodystrophy, *o*steodystrophy, mental *r*etardation, and *s*eizures). Profound sensorineural hearing loss, onychodystrophy, osteodystrophy, intellectual disability / developmental delay, and seizures
- Familial infantile myoclonic epilepsy (FIME). Early-onset myoclonic seizures, focal epilepsy, dysarthria, and mild-to-moderate intellectual disability
- Progressive myoclonus epilepsy (PME). Action myoclonus, tonic-clonic seizures, progressive neurologic decline, and ataxia
- Early-infantile epileptic encephalopathy 16 (EIEE16). Epileptiform EEG abnormalities which themselves are believed to contribute to progressive disturbance in cerebral function
- Autosomal recessive nonsyndromic hearing loss, DFNB86. Profound prelingual deafness
- Autosomal dominant nonsyndromic hearing loss, DFNA65. Slowly progressive deafness with onset in the third decade, initially affecting the high frequencies

Diagnosis/testing

The diagnosis of a *TBC1D24*-related disorder is established in an individual with biallelic *TBC1D24* pathogenic variants when the mode of inheritance is autosomal recessive (i.e., DOORS syndrome, FIME, PME, EIEE16, and DFNB86), and in an individual with a heterozygous *TBC1D24* pathogenic variant when the mode of inheritance is autosomal dominant (DFNA65).

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Management

Treatment of manifestations: Hearing aids or cochlear implants as needed for hearing loss; early educational intervention and physical, occupational, and speech therapy for developmental delay; symptomatic pharmacologic management for seizures; routine management of visual impairment and renal and cardiac anomalies.

Surveillance: Neurology evaluations with EEGs depending on seizure frequency and/or progression of clinical manifestations; yearly audiologic evaluation to assess for possible progression of hearing loss and/or the efficacy of hearing aids; yearly dental evaluation.

Agents/circumstances to avoid: Excessive ambient noise, which may exacerbate hearing loss in heterozygotes for a *TBC1D24* pathogenic variant that causes DFNA65.

Evaluation of relatives at risk: Molecular genetic testing for the familial *TBC1D24* pathogenic variant(s) in older and younger sibs of a proband in order to identify as early as possible those who would benefit from early treatment of seizures and/or hearing loss.

Genetic counseling

Most *TBC1D24*-related disorders are inherited in an autosomal recessive manner (DOORS syndrome, FIME, PME, EIEE16, and DFNB86). For autosomal recessive inheritance: at conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives requires prior identification of the *TBC1D24* pathogenic variants in the family. Prenatal testing is possible for a pregnancy at increased risk if the *TBC1D24* pathogenic variants have been identified in an affected family member.

GeneReview Scope

TBC1D24-Related Disorders: Included Phenotypes [1]
• DOORS syndrome • Familial infantile myoclonic epilepsy (FIME) • Progressive myoclonus epilepsy (PME) • Early-infantile epileptic encephalopathy 16 (EIEE16) • Autosomal recessive nonsyndromic hearing loss, DFNB86 • Autosomal dominant nonsyndromic hearing loss, DFNA65

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

TBC1D24-related disorders comprise a continuum of recognized phenotypes:

- DOORS syndrome (*d*eafness, *o*nychodystrophy, *o*steodystrophy, mental *r*etardation, and *s*eizures)
- Familial infantile myoclonic epilepsy (FIME)
- Progressive myoclonus epilepsy (PME)
- Early-infantile epileptic encephalopathy 16 (EIEE16)
- Autosomal recessive nonsyndromic hearing loss (DFNB86)
- Autosomal dominant nonsyndromic hearing loss (DFNA65)

No formal diagnostic criteria have been published for any of the*TBC1D24*-related disorders.

Suggestive Findings

A *TBC1D24*-related disorder **should be suspected** in individuals with the following features of the recognized phenotypes that comprise a phenotypic continuum. (Information on additional features appears in Clinical Characteristics).

DOORS syndrome

- *D*eafness (profound sensorineural hearing loss)
- *O*nychodystrophy (short/absent nails)
- *O*steodystrophy (short phalanges)
- Intellectual disability / developmental delay (formerly known as mental *r*etardation)
- *S*eizures
- 2-oxoglutaric aciduria

Familial infantile myoclonic epilepsy (FIME). Early-onset myoclonic seizures

Progressive myoclonus epilepsy (PME). Action myoclonus, tonic-clonic seizures, progressive neurologic decline, and ataxia

Early-infantile epileptic encephalopathy 16 (EIEE16)

- Early-onset seizures (unresponsive to medication) that can include myoclonic seizures or malignant migrating partial seizures of infancy
- Extrapyramidal signs (e.g., dystonia), hemiparesis, and/or autonomic signs
- Neurologic deterioration and early death
- Progressive diffuse cerebral atrophy

Autosomal recessive nonsyndromic hearing loss, DFNB86. Prelingual nonsyndromic sensorineural deafness (See Deafness and Hereditary Hearing Loss Overview.)

Autosomal dominant nonsyndromic hearing loss, DFNA65. Adult-onset nonsyndromic sensorineural deafness (See Deafness and Hereditary Hearing Loss Overview.)

Establishing the Diagnosis

The diagnosis of a *TBC1D24*-related disorder **is established** in a proband by identification of (Table 1):

- Biallelic pathogenic variants in *TBC1D24* on molecular genetic testing when the mode of inheritance is autosomal recessive (i.e., DOORS syndrome, FIME, PME, EIEE16, and DFNB86);
- A heterozygous *TBC1D24* pathogenic variant when the mode of inheritance is autosomal dominant (DFNA65).

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *TBC1D24* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

  Note: (1) The diagnostic yield appears to be highest in individuals with all five typical features of DOORS syndrome [Campeau et al 2014]. (2) The proportion of epilepsy caused by pathogenic variants in *TBC1D24* appears to be small, and clinically distinctive signs and symptoms have not yet been identified.

- **A multigene panel** that includes *TBC1D24* and other genes of interest (see Differential Diagnosis) may be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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.

- **More comprehensive genomic testing** (when available) including exome sequencing, mitochondrial sequencing, and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  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 *TBC1D24*-Related Disorders

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
TBC1D24	Sequence analysis [3]	• DOORS syndrome: 9/18 families w/all 5 major features [4] • FIME: rare [5, 6] • PME: rare [5, 7] • EIEE16: rare [5, 8] • DFNB86: rare [5, 9] • DFNA65: rare [5, 10]
	Gene-targeted deletion/duplication analysis [11]	Unknown [12]
Unknown [13]		

EIEE = early-infantile epileptic encephalopathy; FIME = familial infantile myoclonic epilepsy; PME = progressive myoclonus epilepsy

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. 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.

4. Campeau et al [2014]

5. Although a significant proportion of individuals with this phenotype have a genetic etiology, *TBC1D24* is a rare cause.

6. Three families reported [Corbett et al 2010, Falace et al 2010, Afawi et al 2013]

7. One family reported [Muona et al 2015]

8. Three families reported [Guven & Tolun 2013, Milh et al 2013, Lozano et al 2016]; one individual in a cohort of 359 individuals with epileptic encephalopathy [de Kovel et al 2016]

9. Recessive deafness; five families reported [Rehman et al 2014, Bakhchane et al 2015]

10. Dominant deafness; two families reported [Azaiez et al 2014, Zhang et al 2014]

11. 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.

12. No data on detection rate of gene-targeted deletion/duplication analysis are available.

13. Genetic heterogeneity for DOORS syndrome is likely. Exome analysis in some of these families did not reveal a commonly mutated gene [Campeau et al 2014], but an extension of this study is ongoing.

Clinical Characteristics

Clinical Description

While initial reports suggested specific phenotypes associated with pathogenic variants in *TBC1D24*, several recent publications suggest that the features represent a phenotypic spectrum ranging from a mild form of familial infantile myoclonic epilepsy (FIME) to a combination of epilepsy with variable other features, to DOORS syndrome [Balestrini et al 2016]. Features seen in individuals with biallelic *TBC1D24* pathogenic variants who do not have DOORS syndrome include parkinsonism [Banuelos et al 2017], ataxia, dysarthria, axial hypotonia, hearing loss, visual impairment, mild dysmorphic facial features, developmental delay or intellectual disability, and microcephaly [Balestrini et al 2016].

DOORS Syndrome

The five major features of DOORS syndrome are profound sensorineural hearing loss, onychodystrophy, osteodystrophy, intellectual disability / developmental delay, and seizures [James et al 2007, Campeau et al 2014].

The sensorineural hearing loss is often profound and prelingual. Some have benefited from cochlear implants.

The onychoosteodystrophy affects the hands and feet equally. Small or absent nails (onychodystrophy) and hypoplastic terminal phalanges (osteodystrophy) are noted in most individuals. A triphalangeal thumb is present in one third of affected individuals.

The intellectual disability (previously referred to as mental retardation) can vary significantly in degree but is often severe [Balestrini et al 2016]. The motor and language skills were most delayed in two children where such details are available [Nomura et al 2009, Girish et al 2011]. One child had autism spectrum disorder [Nomura et al 2009].

Seizures, present in most individuals with DOORS syndrome, usually start in the first year of life. The seizures are more often generalized tonic-clonic, but myoclonic, partial, and absence seizures also occur. Occasionally their frequency or severity increases. In several instances, the seizures have been difficult to control even with multiple antiepileptic medications, and have led to status epilepticus and death.

On MRI hyperintense T_2-weighted signal anomalies may be observed in the cerebellar hemispheres and the frontal region [Campeau et al 2014].

Nonspecific dysmorphic features. A wide nasal base and a bulbous nose are the most common facial dysmorphisms. Other findings in a minority of individuals include narrow forehead, narrow or high arched palate, broad alveolar ridge, short frenulum, and nevus simplex on the glabella and nose.

Other. In individuals with DOORS syndrome the additional anomalies noted are the following:

- Microcephaly in one third of individuals
- Other cranial anomalies (sagittal craniosynostosis in 1 individual; frontal bossing, trigonocephaly, or brachycephaly in several other affected individuals)
- Dental anomalies (delayed eruption, wide spacing, and abnormal shape, size, and number)
- Congenital heart defects (double outlet right ventricle)
- Skeletal anomalies (e.g., calcaneal deformities)
- Hypothyroidism
- Renal and urinary tract anomalies (e.g., hydronephrosis, nephrocalcinosis) [Campeau et al 2014]
- Elevated levels of urinary 2-oxoglutaric acid, which can fluctuate between normal and elevated over time [Patton et al 1987, van Bever et al 2007, Campeau et al 2014]
- Visual impairment in six of 14 individuals [Balestrini et al 2016]

- Peripheral neuropathy in one individual with confirmed *TBC1D24* pathogenic variants [Balestrini et la 2016] and three individuals who either did not undergo genetic testing or in whom no *TBC1D24* pathogenic variant was identified

Familial Infantile Myoclonic Epilepsy (FIME)

FIME is characterized by early-onset myoclonic seizures.

Findings include focal epilepsy, dysarthria, mild-to-moderate intellectual disability, and cortical thickening and cerebellar atrophy with high T_2-weighted and FLAIR on MRI (in 4 sibs of an Israeli Arab family [Corbett et al 2010, Afawi et al 2013]).

Intellect may be normal: all seven members of an Italian family who had FIME and biallelic *TBC1D24* pathogenic variants also had normal intelligence. Six had normal brain MRI and one had periventricular nodular heterotopia [Zara et al 2000, de Falco et al 2001, Falace et al 2010].

Progressive Myoclonus Epilepsy (PME)

PME is characterized by action myoclonus, tonic-clonic seizures, progressive neurologic decline, and ataxia.

For the child described with PME caused by biallelic pathogenic variants in *TBC1D24*, tonic seizures started at age 36 hours. Developmental delay with later regression was then noted. Myoclonus started at age eight months and tonic-clonic seizures at age 3.5 years. Ataxia, spasticity, supranuclear gaze palsy, and visual decline were also noted. Although the initial clinical diagnosis was of an epileptic encephalopathy, a florid PME pattern was apparent by age nine years [Muona et al 2015]. There were no digital anomalies or deafness [Sam Berkovic, MD, personal communication].

Early-Infantile Epileptic Encephalopathy 16 (EIEE16)

Epileptic encephalopathies are defined by the International League Against Epilepsy (ILAE) as conditions in which epileptiform EEG abnormalities themselves are believed to contribute to progressive disturbance in cerebral function [Engel 2001, Berg et al 2010].

Findings may include:

- Myoclonic epilepsy with episodic dystonia, hemiparesis, autonomic signs, and lethargy evolving to chronic dystonia, progressive diffuse cerebral atrophy, and early death (in 5 Turkish families [Duru et al 2010, Guven & Tolun 2013]);
- Malignant migrating partial seizures in infancy with progressive diffuse cerebral atrophy of the gray matter (sparing the posterior fossa) and early death (in 2 French sibs [Milh et al 2013]).

Autosomal Recessive Nonsyndromic Hearing Loss, DFNB86

Findings observed include profound prelingual deafness with hearing thresholds above 90 dB for all test frequencies (in 2 consanguineous Pakistani families; 1 affected family member and 1 individual with a heterozygous *TBC1D24* pathogenic variant also had seizures [Rehman et al 2014]) (see Deafness and Hereditary Hearing Loss Overview).

Autosomal Dominant Nonsyndromic Hearing Loss, DFNA65

Findings include slowly progressive deafness with onset in the third decade, initially affecting the high frequencies (in 1 Chinese family [Zhang et al 2014] and in a family of European descent [Azaiez et al 2014]) (see Deafness and Hereditary Hearing Loss Overview).

Heterozygotes, in the context of autosomal recessive disease. Two unrelated individuals with generalized tonic-clonic seizures and biallelic pathogenic *TBC1D24* variants both had a family history of hearing loss, but the relatives with hearing loss were not tested for a heterozygous *TBC1D24* pathogenic variant. In one family, the affected individual's brother had hearing loss and in the other family the affected individual's maternal grandmother had hearing loss [Balestrini et al 2016].

Increasing evidence points to an elevated susceptibility to seizure disorders in apparently unaffected individuals who have a heterozygous *TBC1D24* pathogenic variant (i.e., a "carrier") as compared to the population frequency estimated at seven per 1,000 individuals.

- In a family with autosomal recessive hearing loss, an individual with a heterozygous pathogenic p.Asp70Tyr variant developed seizures starting at age three years [Rehman et al 2014].
- A family history of seizures was also reported in two families with DOORS syndrome, including a mother who was heterozygous for a c.1008delT variant with absence seizures in childhood [Campeau et al 2014] and a heterozygous father [Balestrini et al 2016, supplemental material].
- Family history was positive in an additional five families with *TBC1D24* pathogenic variants; family members were unavailable for sequencing [Stražišar et al 2015, Balestrini et al 2016, supplemental material].
- Finally, in a family with an atypical neurologic phenotype in the proband, both the affected individual's mother and her brother had seizures in childhood and adolescence, respectively. Both were confirmed to have a heterozygous novel pathogenic variant (p.Pro135Leu) [Banuelos et al 2017].

Genotype-Phenotype Correlations

The *TBC1D24* pathogenic variants that cause DOORS syndrome, FIME, EIEE16, DFNB86, and DFNA65 are located throughout the gene; no pattern has emerged to date. Most pathogenic variants causing one phenotype have not been demonstrated to cause the others, either within the same family or in different families. However, a heterozygous frameshift variant (c.1008delT) coupled with another pathogenic variant affecting the other *TBC1D24* allele was identified in four affected individuals, two with DOORS and one sib pair with EIEE16 and early death.

In general, loss-of-function variants (frameshift, nonsense, or splice site) are associated with a more severe epilepsy phenotype with drug resistance and early death, except when the loss-of-function variant is located in the last exon. Pathogenic missense variants in or before the TBC domain are also associated with a higher risk of lethality.

The diagnosis of DOORS does not allow for a prediction of the epilepsy type [Balestrini et al 2016]. The location of new pathogenic variants cannot yet be used to predict a phenotype. This may change as more pathogenic variants are identified.

Nomenclature

The acronym "DOOR syndrome" was coined in 1975 [Cantwell 1975]. Subsequently, Qazi & Nangia [1984] suggested adding an S (DOORS syndrome) because of the seizures present in most individuals. Other terms used for this condition include digito-reno-cerebral syndrome [Eronen et al 1985] and Eronen syndrome [Le Merrer et al 1992].

EIEE16 has also been referred to as malignant migrating partial seizures of infancy (MMPSI) [Milh et al 2013], which is also known as epilepsy of infancy with migrating focal seizures.

Prevalence

The prevalence of *TBC1D24*-related disorders is very low. Fewer than 50 families with DOORS syndrome are known, and fewer than five each for the other *TBC1D24*-related disorders. A targeted sequencing study of a cohort of 359 individuals with epileptic encephalopathy identified one person with biallelic *TBC1D24* variants [de Kovel et al 2016].

Genetically Related (Allelic) Disorders

All the phenotypes known to be associated with pathogenic variants in *TBC1D24* are included in this *GeneReview*.

Differential Diagnosis

DOORS Syndrome

Table 2. Disorders to Consider in the Differential Diagnosis of DOORS Syndrome

Differential Diagnosis Disorder	Gene(s)	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/DOORS syndrome	Distinguishing from DOORS syndrome
Coffin-Siris syndrome (See also *ARID1B*-Related Disorder.)	*ARID1A* *ARID1B* *SMARCA4* *SMARCB1* *SMARCE1* *SOX11*	AD [1]	ID/DD, aplastic or hypoplastic nails & terminal phalanges, seizures	Variably seen: coarse face, generalized hypertrichosis, scoliosis (some), gingival overgrowth (some), & 5th finger hypoplasia
Dominant deafness-onychodystrophy syndrome (OMIM 124480)	*ATP6V1B2*	AD	Congenital sensorineural deafness, onychodystrophy	Dental anomalies (conical, hypoplastic teeth) (some); absence of ID/DD & seizures
Nicolaides-Baraitser syndrome	*SMARCA2*	AD [1]	Severe ID/DD, seizures	Coarse face, prominent finger joints & broad distal phalanges, scoliosis (some)
Temple-Baraitser syndrome (OMIM 611816)	*KCNH1*	AD [1]	Severe ID/DD, seizures, nail hypoplasia/aplasia limited to 1st rays (thumb, great toe)	Broad and proximally implanted thumbs, long great toes
Zimmermann-Laband syndrome (OMIM 135500 and 616455)	*KCNH1* *ATP6B1B2*	AD	Variable ID/DD, seizures in ZLS due to pathogenic variants in *KCNH1*, hypoplasia or aplasia of nails & terminal phalanges, hearing loss (some)	Coarse face, hypertrichosis, gingival overgrowth, scoliosis; no seizures in individuals w/ZLS caused by pathogenic variants in *ATP6B1B2*
Mabry syndrome (OMIM 239300)	*PIGV*	AR	Severe ID/DD, seizures, short terminal phalanges, and nail hypoplasia	Hyperphosphatasia; absence of 2-oxoglutaric aciduria & deafness
Kaufman oculocerebrofacial syndrome (OMIM 244450)	*UBE3B*	AR	ID/DD, hearing loss (some), microcephaly, nail dysplasia	Blepharophimosis; hypoplastic/absent terminal phalanges rarely seen
Fetal anticonvulsant syndrome	NA	NA	ID/DD, nail hypoplasia	Dental abnormalities w/delayed eruption, talipes equinovarus, otitis media w/ effusion; absence of hearing loss & seizures

AD = autosomal dominant; AR = autosomal recessive; ID/DD = intellectual disability / developmental delay; MOI = mode of inheritance; NA = not applicable; XL = X-linked

1. Pathogenic variants are typically (or always) *de novo*.

Table 3. Other Conditions with 2-Oxoglutaric Aciduria

Differential Diagnosis Disorder	Gene	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/*TBC1D24*-related disorders	Distinguishing from *TBC1D24*-related disorders
Combined D-2- and L-2-hydroxyglutaric aciduria (OMIM 615182)	*SLC25A1*	AR	Severe DD, seizures	Severe neonatal encephalopathy w/early death, no skeletal manifestations, ↑ D-2- & L-2-hydroxyglutaric acid
3-methylcrotonyl-CoA carboxylase 1 deficiency (OMIM 210200)	*MCCC1*	AR	2-oxoglutaric aciduria in 1 individual; ID, DD, seizures	Urinary excretion of 3-hydroxyisovalerate & 3-methylcrotonylglycine, metabolic decompensation
2-ketoglutarate dehydrogenase deficiency (OMIM 203740)	Unknown	AR	Elevated 2-oxoglutaric acid	Progressive neurodegenerative disorder; development initially normal

AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance

Familial Infantile Myoclonic Epilepsy (FIME) and Progressive Myoclonus Epilepsy (PME)

Table 4. Disorders to Consider in the Differential Diagnosis of *TBC1D24*-Related FIME and *TBC1D24*-Related PME

Differential Diagnosis Disorder	Gene(s)	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/*TBC1D24*-related FIME/PME	Distinguishing from *TBC1D24*-related FIME/PME
Juvenile myoclonic epilepsy (OMIM 254770)	*EFHC1*	AD	Myoclonic seizures, generalized tonic-clonic seizures	Typical 3-Hz polyspike EEG, normal intelligence, later mean age of onset (~10 yrs), myoclonic seizures (jerks) typically in the morning
Early-infantile myoclonic encephalopathy 3 (OMIM 609304)	*SLC25A22*	AR	Myoclonic refractory seizures, early onset age	Burst suppression on EEG, abnormal visual evoked potentials, spasticity
Unverricht-Lundborg disease	*CSTB*	AR	Generalized tonic-clonic seizures, myoclonic seizures	No or mild decline in intellectual performance, EEG always abnormal, later onset age
Progressive myoclonus epilepsy, Lafora type	*EPM2A* *NHLRC1*	AR	Generalized myoclonus and/or generalized tonic-clonic seizures	Progressive neurologic degeneration in previously healthy adolescents; Lafora bodies
Neuronal ceroid lipofuscinoses	*ATP13A2* *CLN3* *CLN5* *CLN6* *CLN8* *CTSD* *CTSF* *DNAJC5* *GRN* *KCTD7* *MFSD8* *PPT1* *TPP1*	AR [1]	Myoclonus, seizures	Progressive intellectual & motor deterioration w/vision loss

Table 4. continued from previous page.

Differential Diagnosis Disorder	Gene(s)	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/*TBC1D24*-related FIME/PME	Distinguishing from *TBC1D24*-related FIME/PME
MERRF	*MT-TF* *MT-TI* *MT-TK* *MT-TL1* *MT-TP*	Mat	Myoclonus, generalized epilepsy, hearing loss, ataxia	Normal early development, ragged-red fibers on muscle biopsy, lactic acidosis; cardiomyopathy in some
POLG-related disorders	*POLG*	AR AD	Myoclonus, seizures, ataxia	Variable phenotype that may incl ophthalmoplegia, neuropathy, liver dysfunction
SCN1A-related seizure disorders	*SCN1A*	AD	Myoclonic epilepsy, generalized tonic-clonic/ hemiclonic & focal seizures	Not assoc w/hearing loss
Action myoclonus-renal failure syndrome	*SCARB2*	AR	Progressive myoclonic epilepsy	Onset in late teens or early 20s w/tremors, proteinuria, & development of renal failure possible
PRICKLE1-related progressive myoclonus epilepsy with ataxia	*PRICKLE1*	AR	Myoclonic seizures, generalized convulsive seizures, ataxia	Normal intellect

AD = autosomal dominant; AR = autosomal recessive; Mat = maternal; MOI = mode of inheritance
1. Neuronal ceroid lipofuscinosis (NCL) is inherited in an autosomal recessive manner with the exception of adult NCL, which can be inherited in either an autosomal recessive or an autosomal dominant manner.

Early-Infantile Epileptic Encephalopathy (EIEE)

EIEE is a rare form of epilepsy in which affected children develop intractable seizures in the first weeks or months of life resulting in severe developmental disabilities or death in infancy.

EIEE is genetically heterogeneous. Causes can include the following:

- Rare copy number variations [Mefford et al 2011]
- Mutation of an individual gene that may be rare, with fewer than five affected families identified (e.g., *ST3GAL3* (EIEE15), *GNAO1* (EIEE17), or *SZT2* (EIEE18)
- Mutation of an individual gene that may affect hundreds of individuals (e.g., *SCN1A* (Dravet syndrome) [Brunklaus et al 2012]
- Metabolic causes of epileptic encephalopathies such as glycine encephalopathy, biotinidase deficiency, organic acidemias, cerebral folate deficiency, and pyridoxine-dependent epilepsy [Yu & Pearl 2013]

See Epileptic encephalopathy, early-infantile – OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Hereditary Hearing Loss and Deafness

For the differential diagnosis of hereditary hearing loss and deafness, see Hereditary Deafness and Hearing Loss Overview.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *TBC1D24*-related disorder, the following evaluations are recommended if they have not already been completed:

DOORS syndrome

- Audiology evaluation
- Ophthalmology evaluation
- Dental examination
- Otolaryngology consultation
- Echocardiogram
- Renal ultrasound examination
- Neurology consultation
- Consultation with a clinical geneticist and/or genetic counselor

FIME, PME, EIEE16, and ***TBC1D24*-related nonsyndromic deafness syndromes (DFNA65** and **DFNB86).** One should consider some of the above evaluations depending on the signs and symptoms, since clinical overlap between all *TBC1D24*-related conditions exists.

Treatment of Manifestations

Deafness. Consider hearing aids or cochlear implants as needed for hearing loss (see Hereditary Hearing Loss and Deafness Overview). Cochlear implants at age one have been beneficial in one individual with DOORS syndrome [Campeau et al 2014].

Visual impairment should be managed in the standard fashion.

Heart defects should be managed according to the anomalies detected.

Renal anomalies. Refer to an urologist or nephrologist, as indicated.

Seizures. Symptomatic pharmacologic management is warranted, as no controlled studies have compared the efficacy of different antiepileptic drugs in *TBC1D24*-related disorders. A variety of different antiepileptic agents have been used to achieve seizure control [Balestrini et al 2016].

The management of epilepsy in many genetic epilepsies is complex; general recommendations from the UK National Institute for Health and Care Excellence are available online.

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, and speech therapy. In the US, early intervention is a federally funded program available in all states.

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.

Ages 5-21 years

- In the US, an individualized education program (IEP) based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

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

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a 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 as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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

Communication issues. Consider evaluation for alternative means of communication (e.g., Augmentative and Alternative Communication [AAC]) for individuals who have expressive language difficulties.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications when necessary.

Surveillance

Neurology evaluations with EEGs are appropriate, depending on seizure frequency and/or progression of clinical manifestations. Individuals with epilepsy, irrespective of cause, should have periodic EKGs as interictal and ictal abnormalities may predispose to sudden unexplained death in epilepsy (SUDEP).

Perform yearly audiologic evaluation to assess for possible progression of hearing loss and/or the efficacy of hearing aids.

Yearly dental evaluation is appropriate.

Agents/Circumstances to Avoid

Heterozygotes for a *TBC1D24* pathogenic variant causing autosomal dominant deafness, DFNA65 should avoid excessive ambient noise as it may exacerbate hearing loss.

Evaluation of Relatives at Risk

Molecular genetic testing for the familial *TBC1D24* pathogenic variant(s) in older and younger sibs of a proband is appropriate in order to identify as early as possible those who would benefit from early treatment of seizures and/or deafness.

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

Pregnancy Management

In general, no information on specific prenatal presentations is available.

Polyhydramnios is often noted when a fetus has DOORS syndrome [James et al 2007]. A subsequent affected pregnancy in one family with DOORS syndrome was terminated due to an elevated nuchal translucency of 5.1 mm at 12 weeks' estimated gestational age [Balestrini et al 2016].

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

Most *TBC1D24*-related disorders (DOORS syndrome, FIME, PME, EIEE16, and DFNB86) are inherited in an autosomal recessive manner.

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *TBC1D24* pathogenic variant).
- Heterozygotes (carriers) are typically asymptomatic and are not at risk of developing an autosomal recessive *TBC1D24*-related disorder. It is possible that some heterozygotes (carriers) could have an elevated susceptibility to seizure disorders related to certain *TBC1D24* pathogenic variants, but genotype-phenotype correlation is lacking and no risk estimates are available.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Individuals with *TBC1D24*-related DOORS syndrome, *TBC1D24*-related PME, and EIEE16 have not reproduced.
- The offspring of an individual with a FIME or DFNB86 are obligate heterozygotes (carriers) for a pathogenic variant in *TBC1D24*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *TBC1D24* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *TBC1D24* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

The following points are noteworthy:

- Communication with individuals who are members of the Deaf community and who sign requires the services of a skilled interpreter.
- Members of the Deaf community may view deafness as a distinguishing characteristic and not as a handicap, impairment, or medical condition requiring a "treatment" or "cure," or to be "prevented."
- Many deaf people are interested in obtaining information about the cause of their own deafness, including information on medical, educational, and social services, rather than information about prevention, reproduction, or family planning. It is, therefore, important to ascertain and address the questions and concerns of the family/individual.
- The use of certain terms is preferred: probability or chance vs risk; deaf and hard-of-hearing vs hearing impaired. Terms such as "abnormal" should be avoided.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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, are carriers, or are at risk of being carriers.

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 *TBC1D24* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

- **American Epilepsy Society**
  www.aesnet.org
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Epilepsy Information Page

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. TBC1D24-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TBC1D24	16p13.3	TBC1 domain family member 24	TBC1D24 @ LOVD	TBC1D24	TBC1D24

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 TBC1D24-Related Disorders (View All in OMIM)

220500	DEAFNESS, ONYCHODYSTROPHY, OSTEODYSTROPHY, IMPAIRED INTELLECTUAL DEVELOPMENT, AND SEIZURES SYNDROME; DOORS
605021	MYOCLONIC EPILEPSY, FAMILIAL INFANTILE; FIME
613577	TBC1 DOMAIN FAMILY, MEMBER 24; TBC1D24
614617	DEAFNESS, AUTOSOMAL RECESSIVE 86; DFNB86
615338	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 16; DEE16
616044	DEAFNESS, AUTOSOMAL DOMINANT 65; DFNA65

Gene structure. Transcript variant 1 (NM_001199107.1) encodes the longest isoform, and is composed of eight exons, with exon 1 being noncoding. Exon 3 is spliced out in isoform 2 (encoded by transcript NM_020705.2), which is expressed predominantly in non-neural tissues [Guven & Tolun 2013]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants

Table 5. *TBC1D24* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.119G>T	p.Arg40Leu	NM_001199107.1 NP_001186036.1
c.208G>T	p.Asp70Tyr	
c.404C>T	p.Pro135Leu	
c.533C>T	p.Ser178Leu	
c.724C>T	p.Arg242Cys	
c.1008delT	p.His336GlnfsTer12	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. TBC1D24 is a Tre2–Bub2–Cdc16 (TBC) domain-containing RAB GTPase-activating protein, which catalyzes the hydrolysis of GTP by small GTPases, thus regulating the proper transport of intracellular vesicles. TBC1D24 is the only TBC/RabGAP protein with a TLDc domain (TBC, LysM, Domain catalytic) of unknown function but thought to be involved in oxidative stress resistance and perhaps to have some enzymatic activity.

TBC1D24 has been demonstrated to interact with ARF6 when both proteins are overexpressed in cell culture [Falace et al 2010, Falace et al 2014]. In *C. elegans*, C31H2.1 (a TBC1D24 ortholog) was implicated in synaptic function by an RNAi screen [Sieburth et al 2005]. In *Drosophila*, the ortholog Skywalker (Sky) facilitates endosomal trafficking in synaptic vesicles by facilitating GTP hydrolysis by Rab35, thus controlling synaptic vesicle rejuvenation and neurotransmitter release [Uytterhoeven et al 2011]. Analysis of the crystal structure of Sky identified a cationic pocket that is preserved in human TBC1D24. This pocket is necessary for binding to the lipid membrane via phosphoinositides phosphorylated at the 4 and 5 positions [Fischer et al 2016]. Whether human TBC1D24 is able to also facilitate Rab protein-mediated GTP hydrolysis remains to be determined.

Abnormal gene product. *TBC1D24*-related disorders that are inherited in an autosomal recessive manner are thought to be the result of reduced function or loss of function of TBC1D24. Abrogation of the cationic pocket by introducing two human pathogenic variants p.Arg40 and p.Arg242 led to impaired synaptic vesicle trafficking and seizures in *Drosophila* [Fischer et al 2016]. Functional studies of other causative variants are limited and to

date, no studies have been conducted examining the variant causing autosomal dominant hearing loss, p.Ser178Leu.

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Chapter Notes

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