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PRICKLE1-Related Disorders

Mario Mastrangelo, MD, PhD,[1] Caterina Caputi, MD,[1] Dario Esposito, MD,[1] and Vincenzo Leuzzi, MD[1]

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Summary

Clinical characteristics

Individuals with biallelic *PRICKLE1*-related disorders typically present with progressive myoclonus epilepsy (PME) with ataxia characterized by myoclonic seizures (lightning-like jerks), generalized convulsive seizures, varying degrees of neurologic regression mainly presenting with ataxia, and mild cognitive impairment or normal cognition. Onset of symptoms is between ages five and ten years. Action myoclonus may affect the limbs or bulbar muscles, while spontaneous myoclonus may occasionally involve facial muscles. Dysarthria may also be an early feature of this condition. The main seizure types are myoclonic or tonic-clonic with frequent nocturnal occurrence.

Individuals with heterozygous *PRICKLE1* pathogenic variants have presented with non-PME seizures (isolated myoclonic seizures, juvenile myoclonic epilepsy), myoclonic epilepsy, developmental delay, intellectual disability, autism spectrum disorder, and/or central nervous system malformations.

Diagnosis/testing

The diagnosis of a *PRICKLE1*-related disorder is established in a proband with suggestive findings and biallelic or heterozygous pathogenic variant(s) in *PRICKLE1* identified by molecular genetic testing.

Management

Treatment of manifestations: Occupational therapy, psychomotricity/physical therapy, and speech therapy for ataxia and neurodevelopmental impairment; adaptive devices as needed to maintain or improve independence in mobility and feeding; anti-seizure medications as needed, such as valproic acid, clonazepam, zonisamide, and levetiracetam.

Surveillance: Neurologic examination every six months; developmental assessment and evaluation of school performance and emotional status every six to 12 months as needed based on age.

Author Affiliation: 1 Child Neurology and Psychiatry Unit, Department of Human Neuroscience, Sapienza Università di Roma, Rome, Italy; Email: mario.mastrangelo@uniroma1.it; Email: caterina.caputi@uniroma1.it; Email: dario.esposito@uniroma1.it; Email: vincenzo.leuzzi@uniroma1.it.

Agents/circumstances to avoid: Phenytoin, carbamezapine, oxycarbazpine, gabapentin, pregabalin, tiagabine, and vigabatrin may worsen myoclonic seizures.

Genetic counseling

PRICKLE1-related PME with ataxia is associated with biallelic homozygous or compound heterozygous *PRICKLE1* pathogenic variants and inherited in an autosomal recessive manner. *PRICKLE1*-related phenotypes associated with a heterozygous *PRICKLE1* pathogenic variant are inherited in an autosomal dominant manner.

- **Autosomal recessive inheritance.** If both parents of a proband with *PRICKLE1*-related PME with ataxia are known to be heterozygous for a *PRICKLE1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial *PRICKLE1* pathogenic variants.
- **Autosomal dominant inheritance.** An individual with an autosomal dominant *PRICKLE1*-related disorder may have the disorder as the result of a *de novo* pathogenic variant or a pathogenic variant inherited from a parent. Each child of an individual with a heterozygous *PRICKLE1* pathogenic variant has a 50% chance of inheriting the pathogenic variant.

Once the *PRICKLE1* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *PRICKLE1*-related disorders are possible.

GeneReview Scope

Table. *PRICKLE1*-Related Disorders: Included Phenotypes

Phenotype	Cause
Progressive myoclonic epilepsy (PME) with ataxia (epilepsy, progressive myoclonic 1B [EPM1B])	Biallelic *PRICKLE1* pathogenic variants
• Non-PME seizures • Myoclonic seizures, developmental delay, mild intellectual disability, & autism spectrum disorder • Distal symmetric polyneuropathy • Central nervous system malformations	Heterozygous *PRICKLE1* pathogenic variants

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

Diagnosis

Suggestive Findings

***PRICKLE1*-related progressive myoclonus epilepsy (PME) with ataxia should be suspected** in a child or adolescent with the following:

- Myoclonic seizures (lightning-like jerks)
- Generalized convulsive seizures
- Varying degrees of cognitive decline and motor impairment especially presenting with ataxia
- Family history consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Autosomal dominant transmission or absence of a known family history does not preclude the diagnosis.

Heterozygous *PRICKLE1*-related disorders should be considered in individuals with any combination of the following features:

- Seizures
- Developmental delay / intellectual disability
- Autism spectrum disorder
- Central nervous system malformations

Establishing the Diagnosis

The diagnosis of **a *PRICKLE1*-related disorder is established** in a proband with suggestive findings and biallelic or heterozygous pathogenic (or likely pathogenic) variant(s) in *PRICKLE1* 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) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

The **current preferred approach to genetic testing** is use of a multigene panel including *PRICKLE1* and other genes of interest (see Differential Diagnosis). 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.

An **alternative approach to genetic testing** in an individual with PME is to perform molecular genetic testing for Unverricht-Lundborg disease and Lafora disease first because both are more common than *PRICKLE1*-related disorders. If pathogenic variants are not identified, *PRICKLE1* sequence analysis may be considered.

Table 1. Molecular Genetic Testing Used in *PRICKLE1*-Related Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
PRICKLE1	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. 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.

Clinical Characteristics

Clinical Description

PRICKLE1-Related Progressive Myoclonus Epilepsy

Individuals with biallelic *PRICKLE1* pathogenic variants typically present with progressive myoclonus epilepsy (PME). The clinical hallmarks of *PRICKLE1*-related PME include ataxia, action myoclonus, and seizures.

- **Ataxia** onset is typically around age four to five years, although ataxia has been reported as early as age 15 months. Gait disturbance is common, with a remarkable action tremor that generally impairs the development of motor skills. While ataxia often precedes epilepsy, an epileptic encephalopathy with onset of seizures at age ten months followed by ataxia at age 18 months was reported in one individual. Ataxia is often progressive, with individuals requiring assistive devices or becoming wheelchair bound [Mastrangelo et al 2018].
- **Action myoclonus** may affect the limbs or bulbar muscles, sometimes with spontaneous myoclonus of facial muscles. Myoclonic jerks occur in the first phases of movement and usually remit within seconds, even with sustained movement [El-Shanti et al 2006]. A co-occurring action tremor may worsen motor performance.
- **Seizures** can be myoclonic or tonic-clonic and are often nocturnal. Atonic seizures and focal motor seizures with impaired awareness have also been reported. Seizure onset is usually after age four years (age range 4-10 years) with few individuals developing seizures in the first year of life. Electroencephalography may reveal generalized spike-wave, sharp slow-wave, or polyspike-wave discharges, while photosensitivity is rarely reported [Mastrangelo et al 2018].

Other neurologic features. Marked dysarthria may occur, and upgaze palsy has been described [Straussberg et al 2005]. Some individuals presented with signs of peripheral neuropathy.

- **Neurodegenerative and neurodevelopmental disorders.** In individuals with *PRICKLE1*-related PME, intellect is generally preserved or mildly impaired – this in contrast to other causes of PME, in which cognitive decline is severe and generally occurs early. Developmental and cognitive profile are likely influenced by seizure severity, although systematic neurodevelopmental assessments have been performed in only a small number of affected individuals. Algahtani et al [2019] reported a female at age 35 years who developed myoclonic epilepsy at age 12 years, in whom cognitive and motor decline occurred several years after the onset of seizures.
- **Neuroimaging.** Brain MRI has yielded unremarkable results in most individuals with *PRICKLE1*-related PME who have undergone head imaging.

Heterozygous *PRICKLE1*-Related Disorders

Individuals with heterozygous *PRICKLE1* pathogenic variants have presented with the following phenotypes:

- Non-PME seizures including isolated myoclonic seizures and juvenile myoclonic epilepsy [Tao et al 2011]
- Myoclonic seizures, developmental delay, mild intellectual disability, and autism spectrum disorder [Todd & Bassuk 2018]
- Distal symmetric polyneuropathy consistent with Charcot-Marie-Tooth disease [Pehlivan et al 2016]
- Central nervous system malformations: myelomeningocele, tethered cord, hydrocephalus, diastematomyelia, caudal agenesis, Chiari type II malformation, agenesis of the corpus callosum, ventriculomegaly, and polymicrogyria [Bosoi et al 2011, Bassuk & Sherr 2015]. Note: Neuronal migration disorders have been observed in animal models with both heterozygous and homozygous variants of *PRICKLE1* orthologs [Bassuk & Sherr 2015].

Prognosis

No longitudinal data on the natural history of *PRICKLE1*-related disorders are available. Seizure severity may affect outcome, but neurologic deterioration appears to be independent of epilepsy in most individuals. One individual died at age 17 years from disease complications (falls and infection); another affected family member is alive at age 40 years [El-Shanti et al 2006]. A male with biallelic *PRICKLE1* pathogenic variants died at age 23 years with refractory status epilepticus and respiratory failure [Hata et al 2019].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

Prevalence for *PRICKLE1*-related PME with ataxia is not known. To date, four large families of Middle Eastern descent and a few other, unrelated individuals with *PRICKLE1*-related PME have been reported [Algahtani et al 2019].

Fewer than 50 individuals have been described with heterozygous *PRICKLE1*-related disorders, including nonsyndromic epilepsy, autism, and central nervous system malformations [Mastrangelo et al 2018].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic or heterozygous germline pathogenic variant(s) in *PRICKLE1*.

Differential Diagnosis

Progressive myoclonic epilepsy (PME). This term covers a large and varied group of disorders characterized by myoclonus, generalized tonic-clonic seizures, and progressive neurologic deterioration. This group includes the following disorders that should be excluded before considering *PRICKLE1*-related PME with ataxia: EPM1 (Unverricht-Lundborg disease); PME, Lafora type; several forms of neuronal ceroid lipofuscinoses; myoclonus epilepsy with ragged-red fibers (MERRF); EPM3 (non-neuronal ceroid lipofuscinosis *KCTD7*-related PME); and types I and II sialidoses (see Table 2).

Table 2. Disorders of Interest in the Differential Diagnosis of *PRICKLE1*-Related Progressive Myoclonus Epilepsy with Ataxia

Gene(s)	Disorder	MOI	Key Features
CLN3 *CLN5* *CLN6* *CLN8* *CTSD* *CTSF* *DNAJC5* *GRN* *KCTD7* *MFSD8* *PPT1* *TPP1*	Neuronal ceroid lipofuscinoses (OMIM PS256730)	AR (AD) [1]	A subset of lysosomal storage disorders classified into infantile, late-infantile, juvenile, & adult forms based on age of onset. All forms typically incl progressive visual deterioration, cognitive impairment, motor impairment (incl ataxia & spasticity), & myoclonic seizures w/early-onset photosensitivity on EEG, also at very low frequencies.

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Key Features
CSTB [2]	EPM1 (Unverricht-Lundborg disease)	AR	Neurodegenerative disorder characterized by onset age 6-15 yrs, stimulus-sensitive myoclonus, & tonic-clonic epileptic seizures. Some yrs after onset, ataxia, incoordination, intentional tremor, & dysarthria develop. Persons w/EPM1 may show emotional lability & depression. Seizures are usually well controlled by ASM, but myoclonic jerks are progressive, action activated, & treatment resistant.
EPM2A *NHLRC1*	PME, Lafora type	AR	Focal occipital seizures presenting as transient blindness or visual hallucinations & fragmentary, symmetric, or generalized myoclonus in previously healthy persons at age 8-19 yrs. Generalized tonic-clonic seizures, atypical absence seizures, atonic seizures, & focal seizures w/impaired awareness may occur. Frequency & intractability of seizures ↑ w/disease course; status epilepticus is common. Cognitive decline becomes apparent at or soon after seizure onset. Dysarthria & ataxia appear early, spasticity later. Emotional disturbance & confusion are common in early stages & followed by dementia.
GOSR2	EPM6 (OMIM 614018)	AR	Ataxia w/onset in 1st yrs of life, followed by action myoclonus & seizures later in childhood. Loss of independent walking occurs in 2nd decade. Cognition is not usually affected, but mild memory difficulties may be seen in 3rd decade.
KCNC1	EPM7 (OMIM 616187)	AD	Severe progressive myoclonus & infrequent tonic-clonic seizures in 1st or 2nd decade of life. Ataxia may have early onset & most persons become wheelchair bound after adolescence; some may have cognitive deterioration.
KCTD7	EPM3 (*KCTD7*-related PME) w/o intracellular inclusions (OMIM 611726)	AR	Characterized by the same hallmarks of PME (i.e., epilepsy, action myoclonus, progressive ataxia, & neurocognitive deterioration) as neuronal ceroid lipofuscinosis. This condition, however, is not assoc w/lysosomal storage on ultrastructural analysis of a skin biopsy.
MT-TF *MT-TI* *MT-TK* *MT-TL1* *MT-TP* *MT-TS1* *MT-TS2*	MERRF	Mat	Multisystem disorder characterized by myoclonus (often 1st symptom) followed by generalized epilepsy, ataxia, weakness, exercise intolerance, & dementia. Onset of symptoms may occur from childhood to adulthood, after normal early development. Common findings are ptosis, hearing loss, short stature, optic atrophy, cardiomyopathy, cardiac dysrhythmias such as Wolff-Parkinson-White syndrome, & peripheral neuropathy.
NEU1	Sialidosis, types I & II (OMIM 256550)	AR	Characterized by deficiency of neuraminidase, w/2 main types: sialidosis type I usually becomes apparent in 2nd decade of life w/myoclonus, distinctive cherry-red macules, visual & gait impairments, & seizures; sialidosis type II is usually more severe, w/infanitle onset, cherry-red macules, facial dysmorphisms, skeletal malformations, & mild cognitive disability.
SCARB2	Action myoclonus – renal failure syndrome	AR	PME & renal failure; in some instances, kidneys are not involved. Manifestations are usually evident between age 10 & 20 yrs. Neurologic manifestations (which appear before, simultaneously, or after renal manifestations) begin w/tremor at rest (exacerbated by fine motor activities) & progress to involuntary, action-activated myoclonic jerks that involve bulbar, proximal, & distal limb muscles; involuntary spontaneous myoclonic jerks; & generalized tonic-clonic seizures. Sensorimotor peripheral neuropathy & sensorineural hearing loss can be observed. [3]

AD = autosomal dominant; AR = autosomal recessive; ASM = anti-seizure medication; EPM = epilepsy, progressive myoclonic; Mat = maternal; MERRF = myoclonus epilepsy with ragged-red fibers; MOI = mode of inheritance; PME = progressive myoclonic epilepsy

1. Except for *DNAJC5*-related neuronal ceroid lipofuscinosis (which is inherited in an autosomal dominant manner), neuronal ceroid lipofuscinoses are inherited in an autosomal recessive manner.

2. EPM1 is caused by either biallelic abnormal CCC-CGC-CCC-GCG dodecamer repeat expansions in *CSTB* or compound heterozygosity for a *CSTB* dodecamer repeat expansion and a *CSTB* sequence variant.

3. See also Genetic Steroid-Resistant Nephrotic Syndrome Overview.

Ataxia. Individuals initially displaying only ataxia should be evaluated for hereditary ataxia (see Hereditary Ataxia Overview) and periodically examined to determine if they have developed epilepsy, action myoclonus, neurocognitive deterioration, and/or other features consistent with the types of PME included in Table 2.

Other presentations. The differential diagnosis of individuals presenting with seizures, developmental delay / intellectual disability, autism spectrum disorder, and/or central nervous system malformations is extensive. Selected disorders that may be of interest are summarized in the following OMIM Phenotypic Series:

- Autosomal Dominant Intellectual Developmental Disorder
- Autosomal Recessive Intellectual Developmental Disorder
- Nonsyndromic X-Linked Intellectual Developmental Disorder
- Syndromic X-Linked Intellectual Developmental Disorder
- Autism, Susceptibility to
- Epilepsy, Familial Adult Myoclonic
- Epilepsy, Familial Focal, with Variable Foci
- Epilepsy, Familial Temporal Lobe
- Epilepsy, Generalized, with Febrile Seizures Plus
- Epilepsy, Idiopathic Generalized
- Epilepsy, Juvenile Absence
- Epilepsy, Myoclonic Juvenile
- Epilepsy, Nocturnal Frontal Lobe
- Epilepsy, Progressive Myoclonic

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *PRICKLE1*-related disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *PRICKLE1*-Related Disorders

System/Concern	Evaluation	Comment
Neurologic	• Neurologic eval • EEG	• To evaluate progression of motor & cognitive impairment • To monitor efficacy of ASM
Ataxia	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Genetic counseling	By genetics professionals [1]	• To inform affected persons & their families re nature, MOI, & implications of *PRICKLE1*-related disorders • To facilitate medical and personal decision making

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	To improve quality of live, social integration, & family networking

ADL = activities of daily living; ASM = anti-seizure medication; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *PRICKLE1*-Related Disorders

Manifestation/Concern	Treatment	Considerations/Other
Ataxia & neurodevelopment	• OT, psychomotricity/PT, & speech therapy • Consider adaptive devices to maintain/improve independence in mobility & feeding.	
Seizures	• ASM incl valproic acid, clonazepam, zonisamide, & levetiracetam; valproate was particularly helpful in one family. [1] • Education of parents/caregivers [2]	Valproate levels are affected by several drugs & serum valproate concentration should be closely monitored; if side effects such as nausea, vomiting, hair loss, or tremor occur, consider switching to an extended-release formulation that allows for more stable serum levels.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. El-Shanti et al [2006]
2. 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.

Surveillance

Table 5. Recommended Surveillance for Individuals with *PRICKLE1*-Related Disorders

System/Concern	Evaluation	Frequency
Neurologic	Neurologic exam & assessment for new onset or changes in seizures	Every 6 mos
Development	• Developmental assessment incl speech, walking (mobility), coordination, & handwriting • Eval of school performance & emotional status	Every 6-12 mos (depending on age)

Agents/Circumstances to Avoid

Avoid the following drugs, which could worsen myoclonic seizures:

- Phenytoin [Eldridge et al 1983]
- Carbamezapine and oxycarbazepine [National Organization for Rare Disorders 1990]
- Gabapentin, pregabalin, tiagabine, and vigabatrin [National Institute for Health and Care Excellence 2016]

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an affected individual to identify as early as possible those who would benefit from institution of treatment and preventive measures.

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: No clinical trials are currently ongoing for *PRICKLE1*-related disorders.

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

PRICKLE1-related progressive myoclonus epilepsy (PME) with ataxia is associated with biallelic homozygous or compound heterozygous *PRICKLE1* pathogenic variants and inherited in an autosomal recessive manner.

PRICKLE1-related phenotypes associated with heterozygous *PRICKLE1* pathogenic variants (e.g., non-PME seizures, myoclonic epilepsy with neurodevelopmental features, polyneuropathy, and central nervous system malformations) are inherited in an autosomal dominant manner.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an individual with *PRICKLE1*-related PME with ataxia are presumed to be heterozygous for a *PRICKLE1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *PRICKLE1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.

Sibs of a proband

- If both parents of a proband with *PRICKLE1*-related PME with ataxia are known to be heterozygous for a *PRICKLE1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being

affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial *PRICKLE1* pathogenic variants.
- To date, the heterozygous sibs of individuals with *PRICKLE1*-related PME with ataxia have been asymptomatic. However, further data are needed to determine if the pathogenic variants associated with *PRICKLE1*-related PME with ataxia can also be associated with manifestations in heterozygous individuals.

Offspring of a proband. Because of the early onset and rapid deterioration, individuals with *PRICKLE1*-related PME with ataxia typically do not reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a *PRICKLE1* pathogenic variant.

Heterozygote detection. Heterozygote testing for at-risk relatives requires prior identification of the *PRICKLE1* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- An individual with an autosomal dominant *PRICKLE1*-related disorder may have the disorder as the result of a *de novo* pathogenic variant or a pathogenic variant inherited from a parent.
- 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 and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - 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.
- The family history of some individuals diagnosed with an autosomal dominant *PRICKLE1*-related disorder 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 has the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.

Because reduced penetrance has been suggested in autosomal dominant *PRICKLE1*-related disorders [Algahtani et al 2019], sibs who inherit a *PRICKLE1* pathogenic variant may or may not be affected.

- If the *PRICKLE1* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *PRICKLE1* 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 an autosomal dominant *PRICKLE1*-related disorder because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a heterozygous *PRICKLE1* pathogenic variant 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 has the *PRICKLE1* pathogenic variant, the parent's family members may be at risk.

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.

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, are heterozygous, or are at risk of being heterozygous.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PRICKLE1* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for *PRICKLE1*-related disorders are possible.

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.

- **American Epilepsy Society**
  aesnet.org
- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  ataxia.org.uk
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: ageorgousis@ataxia.org.uk
  euroataxia.org
- **National Ataxia Foundation**
  Phone: 763-553-0020

Email: naf@ataxia.org
ataxia.org

- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Epilepsy and Seizures

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. PRICKLE1-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PRICKLE1	12q12	Prickle-like protein 1	PRICKLE1 database	PRICKLE1	PRICKLE1

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 PRICKLE1-Related Disorders (View All in OMIM)

608500	PRICKLE PLANAR CELL POLARITY PROTEIN 1; PRICKLE1
612437	EPILEPSY, PROGRESSIVE MYOCLONIC, 1B; EPM1B

Molecular Pathogenesis

PRICKLE1 encodes a nuclear membrane receptor called prickle homolog 1 (Pk). This protein is likely a regulator of the Wnt noncanonic planar cell polarity (PCP) pathway, implicated in the nuclear trafficking of the transcription repressors REST (RE-1 silencing transcription factor) / NRSF (neuron-restrictive silencer factor) and REST4. The Wnt/PCP pathway is crucial in the regulation of gastrulation movements and neurulation and Pk is thought to be essential for organ formation and proper function of the primary cilia. Primary cilia are hair-like structures protruding from the cell surface that sense and transduce many extracellular signals to influence processes, such as cell proliferation and polarity and neuronal growth during embryonic development [Liu et al 2013].

Mechanism of disease causation. *PRICKLE1*-related epileptogenesis may be correlated with: (1) impairment of calcium-mediated signaling in different brain regions, especially the cortex, thalamus, and hippocampus; (2) impairment of microtubule-associated vesicle transport of neurotransmitter; and (3) dysregulation of neurite outgrowth and neuronal connectivity [Mastrangelo et al 2018].

The alterations of neuronal signaling and networking cascades in which *PRICKLE1* is involved may result in dysfunction of RE-1 silencing transcription factor or ubiquitin-specific peptidase 9 X-linked, which may contribute to cognitive decline [Mastrangelo et al 2018].

Chapter Notes

Author Notes

Mario Mastrangelo, MD, PhD
Caterina Caputi, MD

Dario Esposito, MD
Vincenzo Leuzzi, MD

Unit of Child Neurology and Psychiatry
Department of Human Neuroscience
Sapienza Università di Roma
Referring Center for Rare and Complex Neurologic and Neurometabolic Pediatric Diseases

Department of Human Neuroscience web page

Unit of Child Neurology and Psychiatry web page

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Author History

Alexander G Bassuk, MD, PhD; University of Iowa (2009-2022)
Caterina Caputi, MD (2022-present)
Dario Esposito, MD (2022-present)
Mark H Fox, MD; University of Iowa (2009-2022)
Vincenzo Leuzzi, MD (2022-present)
Mario Mastrangelo, MD, PhD (2022-present)

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