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NLM Citation: Dyment D, Lines M, Innes AM. *TRPM3*-Related Neurodevelopmental Disorder. 2023 Feb 23. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

TRPM3-Related Neurodevelopmental Disorder

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Created: February 23, 2023.

Summary

Clinical characteristics

TRPM3-related neurodevelopmental disorder (*TRPM3*-NDD) is characterized by congenital hypotonia, developmental delay affecting motor and speech/language skills, mild-to-severe intellectual disability, seizures, ophthalmologic manifestations including strabismus, nystagmus, and refractive errors, and musculoskeletal manifestations (e.g., talipes equinovarus, hip dysplasia, scoliosis). Reported seizure types include febrile, absence, generalized tonic-clonic, infantile spasms, and atonic drops. Cerebellar atrophy may be seen on brain MRI.

Diagnosis/testing

The diagnosis of *TRPM3*-NDD is established in a proband with a heterozygous pathogenic variant in *TRPM3* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental and educational support; physical medicine and therapies for ataxia as needed; anti-seizure medications for epilepsy as needed; standard treatments for ophthalmologic manifestations, musculoskeletal manifestations, and hearing impairment; social work support and care coordination as needed.

Surveillance: Monitor developmental progress, educational needs, changes in neurologic manifestations, growth, feeding, behavioral issues, and family needs at each visit; ophthalmologic and hearing evaluation annually.

Genetic counseling

TRPM3-NDD is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Vertical transmission of a *TRPM3* pathogenic variant from an affected father to an affected son has been reported in one

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family to date. Each child of an individual with *TRPM3*-NDD has a 50% chance of inheriting the pathogenic variant. Once the *TRPM3* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

TRPM3-related neurodevelopmental disorder (*TRPM3*-NDD) **should be considered** in individuals with the following clinical and brain MRI findings.

Clinical findings

- Congenital hypotonia
- Developmental delay (DD)
- Intellectual disability (ID) of varying degrees of severity (mild to severe)
- Seizures (febrile, absence, generalized tonic-clonic, infantile spasms, atonic drops)
- Ophthalmologic findings (strabismus, nystagmus, refractive errors)
- Musculoskeletal features (talipes equinovarus, hip dysplasia and/or subluxation, scoliosis)

Imaging findings on brain MRI. Cerebellar atrophy

Family history is consistent with autosomal dominant inheritance. Absence of a known family history does not preclude the diagnosis, as vertical transmission of a *TRPM3* pathogenic variant (from an affected father to an affected son) has only been reported in one family to date [Burglen et al 2023].

Establishing the Diagnosis

The diagnosis of *TRPM3*-NDD **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *TRPM3* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variant. (2) Identification of a heterozygous *TRPM3* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with DD or an older individual with ID may begin with chromosomal microarray analysis (CMA). Other options include use of a multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *TRPM3*) is rarely useful and typically NOT recommended.

- **An ID or epilepsy multigene panel** that includes *TRPM3* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition in a person with a nondiagnostic CMA 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*. Of note, given the rarity of *TRPM3*-NDD, some panels for ID or epilepsy may not include this gene. (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** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID whereas some multigene panels may not. **Genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in *TRPM3*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
TRPM3	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

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. Kang et al [2021], Burglen et al [2023], and 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.
6. All pathogenic variants reported to date are gain-of-function *TRPM3* missense variants; thus, testing for deletion (haploinsufficiency) or duplication (overexpression) is not indicated.

Clinical Characteristics

Clinical Description

TRPM3-related neurodevelopmental disorder (*TRPM3*-NDD) is characterized by congenital hypotonia, developmental delay, intellectual disability, seizures, and ophthalmologic and musculoskeletal manifestations. To date, 28 individuals have been reported in the literature with a pathogenic variant in *TRPM3* [Dyment et al 2019, de Sainte Agathe et al 2020, Gauthier et al 2021, Kang et al 2021, Burglen et al 2023]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of *TRPM3*-Related Neurodevelopmental Disorder

Feature	Proportion of Persons w/Feature	Comment
Developmental delay	27/28	
Intellectual disability	22/24	Moderate to severe in 15 individuals
Congenital hypotonia	23/28	Typically mild
Seizures	14/28	Typically well controlled w/or w/o medication
Ophthalmologic findings	19/28	Most commonly strabismus
Musculoskeletal manifestations	14/28	Commonly talipes equinovarus, hip dysplasia, & scoliosis
Brain MRI abnormalities	13/26	Often nonspecific findings; cerebellar atrophy observed in 6/26

Developmental delay (DD) and intellectual disability (ID). DD is near universal in those with a pathogenic variant in *TRPM3*.

Infant feeding difficulties have been reported (four individuals) that included dysphagia and gastroesophageal reflux.

A significant proportion of individuals assessed at age two years and older had not attained independent steps (11/26; this includes two adults older than age 18 years). For those that are able to walk independently, the average age of first steps is three years (range: age 1-5 years).

Speech is often severely affected and approximately half of affected individuals do not have single words (13/24). For those using at least single words, first words were used at an average age of three years (range: age 1-5 years). Some individuals can use signs or aids to help with communication, and a minority of individuals can speak in short sentences.

ID is also common. When the extent of disability was assessed and reported, the majority had ID in the severe or moderate-to-severe range. Moderate and mild ID was reported in 4/22 and 1/22 individuals, respectively. Two individuals were reported to have cognitive ability in the "low-normal" range.

Other neurologic features

- **Congenital hypotonia** is often the first manifestation observed in a neonate, though it is often considered mild. The results of a muscle biopsy have been reported in one individual with *TRPM3*-NDD and was described as nondiagnostic [Lines et al 2022].
- **Increased pain tolerance** has been reported, anecdotally, by the parents of individuals with *TRPM3*-NDD [Dyment et al 2019]. Similarly, some individuals have an increased tolerance to heat (e.g., a preference for hot baths and no physical reaction to burns).
- **Athetoid or choreoathetoid movements** have been reported in 4/28 (14%) affected individuals and typically occur in infancy and resolve spontaneously.
- **Ataxia** has been reported in four individuals with subsequent neuroimaging showing cerebellar atrophy.

Epilepsy. Several seizure types have been reported (febrile, absence, generalized tonic-clonic, tonic, electrical status epilepticus during slow-wave sleep, and infantile spasms) with no single type being characteristic for the disorder. When reported, seizure onset varied from age nine months to seven years (average: age 3.4 years). Most individuals required one anti-seizure medication or no medication to attain seizure control. To date, one individual has been reported with a history of infantile spasms and Lennox-Gastaut syndrome refractory to treatment [Kang et al 2021]. EEG abnormalities are seen in 17/26 individuals.

Neurobehavioral and psychiatric manifestations. Features of autism spectrum disorder have been reported in 8/28 individuals including stereotypies, poor eye contact, and sensitivities to touch and taste. Some children with *TRPM3*-NDD have also been reported to have frequent aggressive outbursts.

Ophthalmologic involvement. Strabismus is common and has been reported in 15/28 individuals. Nystagmus has been reported in a minority (6/28). Refractive errors are also rarely reported (2/28).

Musculoskeletal manifestations are common. Talipes equinovarus has been reported in 7/28 and hip dysplasia and/or hip subluxation in 7/28. Scoliosis has been reported in 6/28 individuals. Patellar dislocations have also been reported.

Growth. Height, weight, and head circumference are typically in the normal range. One child with height less than the 3rd centile was reported, although this person had a significant scoliosis impacting height [Lines et al 2022].

Neuroimaging (MRI). Cerebellar atrophy has been reported in 6/26 individuals. Nonspecific MRI findings such as mild cortical volume loss (6/26) and periventricular white matter hyperintensities (2/26) have also been reported. Heterotopias have been seen in one individual.

Other

- **Hearing impairment.** Only one individual has been reported to date with a unilateral hearing deficit [Dyment et al 2019].
- **Facial features.** Broad forehead, deep-set eyes, prominent nasal root, bulbous nasal tip, large ear lobes, short philtrum, and micrognathia comprise the facial gestalt of those with *TRPM3*-NDD. However, the features are relatively nonspecific and do not constitute a recognizable syndrome.

Prognosis. Based on current data, life span is not limited by this condition, as several adults have been reported. Data on possible progression of behavior abnormalities or neurologic findings are still limited.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Penetrance is complete though clinical expression is variable.

Prevalence

There is no known prevalence estimate to date; 28 individuals with *TRPM3*-NDD have been reported since 2019.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TRPM3*.

Pathogenic variant c.195A>G (p.Ile65Met) in *TRPM3* alternate transcript trpm3tv9, expressed in the human lens, has been associated with inherited cataracts and glaucoma in a single family [Bennett et al 2014].

Differential Diagnosis

Because the phenotypic features associated with *TRPM3*-related neurodevelopmental disorder are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

No clinical practice guidelines for *TRPM3*-related neurodevelopmental disorder (*TRPM3*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and the needs of an individual diagnosed with *TRPM3*-NDD, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *TRPM3*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Development	Developmental assessment	• Incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	Neurologic eval	• Consider EEG if seizures are a concern. • Consider MRI if ataxia or other movement disorder is present.
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl findings suggestive of ASD
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings that may require subspecialty referral
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	Incl assessment of: • Gross motor & fine motor skills • Talipes equinovarus, hip dysplasia, & scoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Hearing	Audiologic eval	Assess for any hearing loss.
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *TRPM3*-NDD to facilitate medical & personal decision making & to consider variant testing in at-risk relatives
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; *TRPM3*-NDD = *TRPM3*-related neurodevelopmental disorder
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *TRPM3*-NDD. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in pediatric neurology, orthopedics, rehabilitation medicine, physical therapy, occupational therapy, speech-language pathology, ophthalmology, developmental pediatrics, and clinical genetics (see Table 4).

Table 4. Treatment of Manifestations in Individuals with *TRPM3*-Related Neurodevelopmental Disorder

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Ataxia	Physical medicine & rehab / PT & OT to help avoid falls	Consider need for mobility devices, disability parking placard.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. [1] • Education of parents/caregivers [2]
Ophthalmologic involvement	By ophthalmologist	Treatment of refractive errors &/or strabismus
	Low vision services	• Children: through early intervention programs &/or school district • Adults: referral to low vision clinic &/or community vision services
Musculoskeletal manifestations	Standard treatments for talipes equinovarus, hip dysplasia, scoliosis, & patellar dislocations	
Hearing	Hearing aids may be helpful per otolaryngologist	Community hearing services through early intervention or school district
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. A well-known anti-seizure medication, primidone, has been tried in several affected individuals [D Dyment, personal communication]. The use of primidone has not been associated with any formal scientific study and no outcomes in individuals with *TRPM3*-NDD have been reported.
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.

Developmental Delay / Intellectual Disability Management Issues

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

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

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.

- Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
- Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
- Occupational therapy, physical therapy, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
- As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

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

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

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, a nasogastric or gastrostomy tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

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 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.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with *TRPM3*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, ataxia, &/or movement disorders.	
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Neurobehavioral/ Psychiatric	Assessment for autistic features & aggressive or self-injurious behavior	
Eyes	Ophthalmologic eval for evidence of strabismus or refractive errors	Annually or as needed
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit
Hearing	Audiologic eval	Annually
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic

status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

TRPM3-related neurodevelopmental disorder (*TRPM3*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most individuals reported to date with *TRPM3*-NDD whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo TRPM3* pathogenic variant.
- Vertical transmission of a *TRPM3* pathogenic variant from an affected father to an affected son has been reported in one family to date [Burglen et al 2023].
- 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. To date, this has not been reported.

    * A parent with somatic and germline mosaicism for a *TRPM3* pathogenic variant may be mildly/minimally affected.

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

- If a parent of the proband is known to have the *TRPM3* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *TRPM3* pathogenic variant found 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].

Offspring of a proband. Each child of an individual with *TRPM3*-NDD has a 50% chance of inheriting the *TRPM3* 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 *TRPM3* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *TRPM3* 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
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics

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. TRPM3-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
TRPM3	9q21.12-q21.13	Transient receptor potential cation channel subfamily M member 3	TRPM3	TRPM3

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 TRPM3-Related Neurodevelopmental Disorder (View All in OMIM)

608961	TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY M, MEMBER 3; TRPM3
620224	NEURODEVELOPMENTAL DISORDER WITH HYPOTONIA, DYSMORPHIC FACIES, AND SKELETAL ANOMALIES, WITH OR WITHOUT SEIZURES; NEDFSS

Molecular Pathogenesis

TRPM3 encodes a temperature- and neurosteroid-sensitive cation channel. The protein is comprised of six transmembrane domains, and the channel itself has a tetrameric structure with a central pore and four alternative pores. The channel has a voltage-sensing domain as well as the central pore domains. The gene is expressed in neuronal as well as non-neuronal tissues (kidney, eye, pancreas). Missense variants associated with *TRPM3*-related neurodevelopmental disorder (*TRPM3*-NDD) lead to increased basal activity of the cation channel, which results in an increased calcium concentration within the cell. In addition, *TRPM3* pathogenic variants result in an enhanced response to heat and the neurosteroid pregnenolone sulfate [Van Hoeymissen et al 2020, Zhao et al 2020].

Mechanism of disease causation. Gain of function

***TRPM3*-specific laboratory technical considerations.** There are more than 25 isoforms of *TRPM3* due to alternative splicing [Oberwinkler & Philipp 2014].

Table 6. Notable *TRPM3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_020952.6 NP_066003.3	c.2509G>A	p.Val837Met	Most common pathogenic variant reported to date, identified in >50% of affected persons [Dyment et al 2019]

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.

Chapter Notes

Author Notes

Dr David Dyment's research interests are the identification of the molecular causes of rare syndromic and neurogenetic diseases.

Dr Matthew Lines's research focus is on the clinical description and gene identification of rare metabolic diseases.

Dr A Micheil Innes's research is focused on both the clinical delineation and the identification of the molecular basis of rare genetic conditions.

Drs Dyment and Innes are investigators with Care for Rare – SOLVE, a pan Canadian collaboration to investigate the causes of rare genetic diseases and improve the clinical care for patients and families affected by them.

Acknowledgments

Dr David Dyment would like to acknowledge the helpful discussion, expertise, and advice from Drs Joris Vriens and Thomas Voets of the University of Leuven, Leuven, Belgium.

There is an active Facebook family support group for families of children with *TRPM3*-related neurodevelopmental disorder.

Revision History

- 23 February 2023 (sw) Review posted live
- 2 November 2022 (dd) Original submission

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