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UNC80 Deficiency

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Summary

Clinical characteristics

UNC80 deficiency is characterized by developmental delay, neonatal hypotonia, severe intellectual disability, dysmorphic facial features, strabismus, dyskinetic limb movements, and neurobehavioral manifestations. The majority of individuals do not learn to walk. All individuals lack expressive speech; however, many have expressive body language, and a few have used signs to communicate. Seizures may develop during infancy or childhood. Additional common features include clubfeet, joint contractures, scoliosis, postnatal growth deficiency, increased risk of infections, sleeping difficulties, and constipation. Individuals have slow acquisition of developmental skills and do not have features suggestive of neurodegeneration.

Diagnosis/testing

The diagnosis of UNC80 deficiency is established in a proband with suggestive findings and biallelic pathogenic variants in *UNC80* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental services and educational support; melatonin and risperidone have been beneficial for treatment of sleep difficulties; standard treatments for irritability, seizures, spasticity, and dyskinesia; management of nystagmus and/or strabismus per ophthalmologist; feeding therapy or gastrostomy tube feeding as needed; standard management of constipation; braces and/or corrective surgeries as needed for orthopedic abnormalities.

Surveillance: Assess growth, nutritional status, safety of oral intake, and for constipation at each visit. Annual evaluations for developmental and educational needs, behavioral assessment, seizure management, ophthalmology examination, back exam for scoliosis, evaluation of contractures, and assessment of mobility and self-help skills.

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Genetic counseling

UNC80 deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *UNC80* pathogenic variant, each sib of an affected individual has at conception 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. Once the *UNC80* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

UNC80 deficiency **should be suspected** in probands with the following clinical features:

- Developmental delay with severe motor delays and absent speech (less than five words)
- Neonatal hypotonia
- Severe intellectual disability
- Strabismus
- Dyskinesia of the limbs
- Postnatal growth deficiency with postnatal microcephaly in some individuals
- Sleeplessness and irritability
- Constipation
- Seizures in some individuals

Establishing the Diagnosis

The diagnosis of UNC80 deficiency **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *UNC80* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic, and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *UNC80* variants of uncertain significance (or of one known *UNC80* pathogenic variant and one *UNC80* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability (ID) may begin with exome sequencing. Other options include genome sequencing or use of a multigene panel. Note: Single-gene testing (sequence analysis of *UNC80*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **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.

- **An ID multigene panel** that includes *UNC80* and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of ID while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The

genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Table 1. Molecular Genetic Testing Used in UNC80 Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
UNC80	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. Perez et al [2016], Shamseldin et al [2016], Stray-Pedersen et al [2016], Valkanas et al [2016], Bramswig et al [2018], He et al [2018], Obeid et al [2018], Kuptanon et al [2019], Tao et al [2021], 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.

Clinical Characteristics

Clinical Description

UNC80 deficiency is characterized by neonatal hypotonia, developmental delay, severe intellectual disability, and neurobehavioral manifestations. Additional common features include seizures, strabismus, postnatal growth deficiency, constipation, musculoskeletal manifestations, dysmorphic facial features, increased risk of infections, and sleeping difficulties. To date, fewer than 50 individuals have been described with biallelic pathogenic variants in *UNC80* [Perez et al 2016, Shamseldin et al 2016, Stray-Pedersen et al 2016, Valkanas et al 2016, Bramswig et al 2018, He et al 2018, Obeid et al 2018, Kuptanon et al 2019, Tao et al 2021]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. UNC80 Deficiency: Frequency of Select Features

Clinical Feature	% of Persons w/Feature [1]	Comment
Developmental delay	100%	Affects motor, speech, & cognition
Hypotonia	>95%	
Intellectual disability	100%	Severe
Dyskinesia	>90%	
Seizures	>50%	
Strabismus	>90%	

Table 2. continued from previous page.

Clinical Feature	% of Persons w/Feature [1]	Comment
Growth deficiency	>90%	Postnatal short stature & low weight & height (<3rd centile)
Feeding difficulties	>80%	
Constipation	>80%	
Postnatal microcephaly	>50%	
Musculoskeletal manifestations	~50%	Joint contractures, scoliosis, clubfeet

1. Perez et al [2016], Shamseldin et al [2016], Stray-Pedersen et al [2016], Valkanas et al [2016], Bramswig et al [2018], He et al [2018], Obeid et al [2018], Kuptanon et al [2019], Tao et al [2021]

Developmental delay. All individuals have developmental delay. Most individuals have neonatal hypotonia. Oral motor dysfunction leads to difficulty with oral coordination, chewing, and swallowing and therefore feeding difficulties. The majority of individuals do not learn to walk. All individuals lack expressive speech, although many have expressive body language, and a few have used signs to communicate. Individuals have slow acquisition of skills and do not have the loss of skills suggestive of neurodegeneration.

Severe intellectual disability is reported in all individuals.

Neurobehavioral manifestations. Many of the affected individuals have behavioral difficulties including repetitive and self-stimulatory behaviors, irritability, and difficulties with emotional regulation. The majority of individuals with UNC80 deficiency are social (i.e., they prefer people to objects). Some individuals show tactile aversion and hypersensitivity to stimuli. Some individuals seek significant oral stimulation. Self-injurious behaviors have also been reported.

Sleep difficulties are common, with difficulties initiating sleep and sleeping through the night.

Epilepsy. Seizures may develop during infancy or childhood. Focal seizures, generalized tonic-clonic seizures, myotonic seizures, aclonic seizures, and atypical absence seizures have been described. Most affected individuals are well controlled on anti-seizure medications.

Other neurologic manifestations. Dyskinesia was reported in most individuals. Hypertonic extremities and a high-pitched cry have also been reported.

Ophthalmologic features. Strabismus has been reported in most affected individuals, and nystagmus is seen in half of affected individuals. A single individual with structural ocular abnormalities (punctate keratopathy) has been reported. Vision is usually normal.

Growth deficiency. Most individuals have had normal prenatal growth. Postnatally, however, linear growth and weight were below the third centile in most individuals. Poor feeding exacerbates the growth deficiency; however, tube feedings with a calorie-rich diet generally do not result in weight for age above the third centile. Individuals do not have evidence of endocrine anomalies that would account for the growth deficiency. Postnatal microcephaly was also common.

Constipation is very common and has been attributed to hypotonia and severe psychomotor delay.

Musculoskeletal features. Some individuals have congenital clubfeet. Joint contractures (e.g., hip, elbow, knee) can present from an early age. Later-onset scoliosis can be seen. Ongoing physiotherapy, stretching, and bracing improves some of the limitations encountered with contractures and/or scoliosis. In individuals with more severe clubfeet or scoliosis, surgery may be considered.

Small hands and feet are common, with long thin fingers and tapering of the distal phalanges.

Infections. Increased risk of infections has been reported, e.g., recurrent gastroenteritis, upper and lower respiratory tract infections, and less common urinary tract and skin infections.

Nonspecific dysmorphic facial features include triangular and/or long face, frontal bossing, downslanted palpebral fissures, strabismus, broad nasal bridge, anteverted nares, enlarged nares, short and smooth philtrum, thin and/or tented vermilion of the upper lip, micrognathia, and low-set and/or posteriorly rotated and/or large ears.

Nonspecific brain MRI findings. Most affected individuals have normal brain MRI findings. Nonspecific abnormalities such as a thin corpus callosum, mild diffuse brain atrophy, and borderline mild enlargement of the lateral and third ventricles and of the extra-axial space have been reported [Perez et al 2016, Shamseldin et al 2016, Stray-Pedersen et al 2016, Bramswig et al 2018].

Prognosis. Reported individuals span ages from birth to 15 years [Perez et al 2016, Shamseldin et al 2016, Stray-Pedersen et al 2016, Valkanas et al 2016, Bramswig et al 2018]. The oldest known individual is almost age 17 years [M Zaki, personal communication]. One individual has died of complications from infection; postmortem studies of the brain, spinal cord, nerve, muscle, liver, skin, and myocardium did not identify evidence of central nervous malformations or findings attributable to the underlying neurologic disorder [Valkanas et al 2016]. In a cohort of 12 individuals with biallelic *UNC80* pathogenic variants, five individuals died between ages ten months and ten years [Bramswig et al 2018].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

UNC80 deficiency is referred to as "infantile hypotonia with psychomotor retardation and characteristic facies 2" (IHPRF2) in OMIM (616801).

Prevalence

The prevalence is unknown. Fewer than 50 individuals have been reported to date.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *UNC80*.

Differential Diagnosis

Disorders to consider in the differential diagnosis are listed in Table 3.

Table 3. Selected Disorders in the Differential Diagnosis of UNC80 Deficiency

Gene / Genetic Mechanism	Disorder	MOI	Distinguishing Clinical Features
Abnormal parent-specific imprinting w/in PWCR	Prader-Willi syndrome	See footnote 1.	Neonatal hypotonia & poor weight gain followed by obesity, polyphagia, thin vermilion of upper lip w/downturned corners of mouth, genitourinary anomalies, delayed acquisition of speech & mobility

Table 3. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Distinguishing Clinical Features
Deficient expression or function of maternally inherited *UBE3A* allele	Angelman syndrome	See footnote 1.	Bursts of laughter, macrostomia, tongue protrusion, prognathism, widely spaced teeth, mild cortical atrophy
MECP2	Classic Rett syndrome (See MECP2 Disorders.)	XL [1]	Lack of dysmorphic facial features, repetitive movements, loss of developmental skills; primarily in females
NALCN	Hypotonia, infantile, w/ psychomotor retardation & characteristic facies 1 (OMIM 615419)	AR	Distinctive facial features incl prominent forehead, short nose, wide mouth, micrognathia, & large, low-set ears; neuroaxonal dystrophy; optic atrophy; breathing abnormalities
SATB2 (intragenic *SATB2* pathogenic variant, CNV involving *SATB2*, or chromosome translocation disrupting *SATB2*)	*SATB2*-associated syndrome (Glass syndrome)	AD [1]	Cleft palate, arachnodactyly, joint laxity, ectodermal anomalies
SHANK3 (CNV involving *SHANK3* or intragenic *SHANK3* pathogenic variant; may be assoc w/ring chromosome 22)	Phelan-McDermid syndrome	AD [1]	Normal or accelerated growth, dolichocephaly, ptosis, epicanthal folds, large or prominent ears, pointed chin, fleshy hands, dysplastic toenails, tendency to overheat
TBCK	Hypotonia, infantile, w/ psychomotor retardation & characteristic facies 3 (OMIM 616900)	AR	Distinctive facial features incl coarse face, bitemporal narrowing, highly arched eyebrows, deeply set eyes, high nasal bridge w/anteverted nares, macroglossia, gingival hyperplasia, & exaggerated Cupid's bow; abnormal brain imaging; optic atrophy

AD = autosomal dominant; AR = autosomal recessive; CNV = copy number variant; MOI = mode of inheritance; PWCR = Prader-Willi critical region; XL = X-linked

1. Affected individuals typically represent simplex cases (i.e., a single occurrence in the family).

Ring chromosome 22 can also be considered in the differential diagnosis of UNC80 deficiency. Individuals with ring chromosome 22 are distinguished by mild prenatal growth deficiency; mild dysmorphic features including hypertelorism, epicanthal folds, depressed nasal bridge, micrognathia, and cleft palate; coloboma of the iris, choroid, and/or optic nerve; microphthalmia; internal and external ear anomalies; congenital heart malformations; hernias; and genitourinary anomalies.

Management

No clinical practice guidelines for UNC80 deficiency have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with UNC80 deficiency, the evaluations and referrals summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. UNC80 Deficiency: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	If behavioral issues are present
Neurologic	Neurologic eval	Consider EEG if seizures are a concern.
Eyes	Ophthalmologic eval	To assess for abnormal ocular movement, refractive errors, & strabismus
Constitutional	Growth assessment incl height, weight, & head circumference	
Gastrointestinal	Feeding eval & assessment for constipation	
Musculoskeletal	Orthopedic eval	If clubfeet &/or scoliosis is present
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of UNC80 deficiency to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. UNC80 Deficiency: Treatment of Manifestations

Manifestation/ Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	• Developmental services • Educational support	
Neurobehavioral/ Psychiatric	• Treatment per psychologist &/or neuropsychiatrist • Melatonin & risperidone have been shown to be beneficial for treatment of sleep difficulties.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Spasticity/ Dyskinesia	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Eyes	Mgmt per ophthalmologist	For nystagmus &/or strabismus

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Feeding difficulties / Poor weight gain	Feeding therapy &/or gastrostomy tube feeding as needed	
Constipation	Standard mgmt	
Orthopedic manifestations	Braces &/or corrective surgery	As needed for clubfeet, scoliosis, joint contractures

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. 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

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. UNC80 Deficiency: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	Annually
Neurobehavioral/ Psychiatric	Behavioral assessment for hypersensitivity &/or self-injurious behavior	
Neurologic	Assessment to identify & manage seizures	
Ophthalmologic involvement	Ophthalmology exam for ocular manifestations	
Growth/Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Assessment for constipation	
Musculoskeletal	• Orthopedist eval of contractures & back exam for scoliosis • Physical medicine, OT/PT assessment of mobility, self-help skills	Annually

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

UNC80 deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *UNC80* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *UNC80* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one of the proband's 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 [Tao et al 2021].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *UNC80* pathogenic variant, each sib of an affected individual has at conception 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

- The offspring of an individual with UNC80 deficiency are obligate heterozygotes (carriers) for a pathogenic variant in *UNC80*.
- To date, individuals with UNC80 deficiency are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *UNC80* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *UNC80* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.
- Carrier testing for the reproductive partners of known carriers should be considered, particularly if both partners are of the same ethnic background. A founder variant has been identified in the Bedouin population of southern Israel (see Table 7).

Prenatal Testing and Preimplantation Genetic Testing

Once the *UNC80* pathogenic variants have 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 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.

- **MedlinePlus**
  UNC80 deficiency

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. UNC80 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
UNC80	2q34	Protein unc-80 homolog	UNC80	UNC80

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 UNC80 Deficiency (View All in OMIM)

612636	UNC80 HOMOLOG, NALCN CHANNEL COMPLEX SUBUNIT; UNC80
616801	HYPOTONIA, INFANTILE, WITH PSYCHOMOTOR RETARDATION AND CHARACTERISTIC FACIES 2; IHPRF2

Molecular Pathogenesis

The UNC80 protein is part of the NALCN channelosome, a voltage-insensitive and nonselective sodium leak channel [Yu et al 2005, Lu et al 2007, Snutch & Monteil 2007, Lu et al 2010, Cochet-Bissuel et al 2014]. The human NALCN channelosome is predominantly expressed in the brain and requires four proteins for proper function: NALCN, FAM155A, UNC80, and UNC79. It consists of the NALCN-FAM155A pore-forming subcomplex, which is associated intracellularly with the UNC80-UNC79 subcomplex [Kschonsak et al 2022, Zhou at al 2022]. This UNC80-UNC79 subcomplex has a unique and intertwined geometry with large interaction surfaces and connects to NALCN via intracellular linkers [Kschonsak et al 2022]. UNC80 and UNC79 are highly conserved among mammals and are HEAT-repeat proteins composed of a repeating motif of two structural alpha helices [Kschonsak et al 2022]. Targeted deletions of certain UNC80 and UNC79 regions in *Xenopus laevis* oocytes revealed that channelosome function was sensitive to the deletion of some but not all parts of the UNC79-UNC80 interfaces [Kschonsak et al 2022]. Structural mapping of *UNC80* pathogenic variants displayed a sporadic distribution [Zhou et al 2022]. *UNC80* nonsense and frameshift variants may disturb NALCN channelosome function through disruption of the UNC79-UNC80 assembly at certain interfaces [Zhou et al 2022]. *UNC80* missense variants may influence NALCN channelosome function by affecting the local folding and stability of UNC80 [Zhou et al 2022].

Mechanism of disease causation. Loss of function

Table 7. Notable UNC80 Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_032504.2 NP_115893.1	c.151C>T	p.Arg51Ter	Founder variant in persons of Bedouin population of southern Israel [Perez et al 2016]

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

Nuria Bramswig (nuria.braemswig@hhu.de) and Maha Zaki (dr_mahazaki@yahoo.com) are actively involved in clinical research regarding individuals with UNC80 deficiency. They would be happy to communicate with persons who have any questions regarding diagnosis of UNC80 deficiency or other considerations.

Contact Dr Nuria Bramswig (nuria.braemswig@hhu.de) to inquire about review of *UNC80* variants of uncertain significance.

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