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Deafness-Dystonia-Optic Neuronopathy Syndrome

Synonyms: DDON, Mohr-Tranebjaerg Syndrome

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Summary

Clinical characteristics

Males with deafness-dystonia-optic neuronopathy (DDON) syndrome have prelingual or postlingual sensorineural hearing impairment in early childhood, slowly progressive dystonia or ataxia in the teens, slowly progressive decreased visual acuity from optic atrophy beginning at approximately age 20 years, and dementia beginning at approximately age 40 years. Psychiatric symptoms such as personality change and paranoia may appear in childhood and progress. The hearing impairment appears to be consistent in age of onset and progression, whereas the neurologic, visual, and neuropsychiatric signs vary in degree of severity and rate of progression. Females may have mild hearing impairment and focal dystonia.

Diagnosis/testing

The diagnosis of DDON syndrome is established in either a male proband who has a hemizygous *TIMM8A* pathogenic variant (~50% of affected males) or a female proband who has a heterozygous *TIMM8A* pathogenic variant (~50% of affected females) or a contiguous gene deletion of Xq22.1 involving *TIMM8A* (~50% of affected males and females).

Management

Treatment of manifestations: Educational programs for developmental and sensory deficits, including training in tactile sign language. Because auditory neuronopathy is the cause of the hearing loss, hearing aids have only variable success. Physical medicine and rehabilitation, physical and occupational therapy to improve fine and gross motor skills and mobility, to prevent contractures, and to provide adaptive devices to improve activities of daily living. Standard treatment of behavioral issues / psychiatric disorders. Ensure appropriate social work involvement to connect families with local resources, respite, and support, especially care coordination with multiple subspecialty appointments, equipment, medications, and supplies.

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Surveillance: Regular neurologic evaluation and assessment for dementia and/or psychiatric manifestations; annual developmental, speech-language, and vision assessments in childhood; regular physical therapy and occupational therapy for review of activities of daily living, gross motor and fine motor needs; routine follow up of the social support and social services needs of the family/caregivers.

Genetic counseling

DDON syndrome is inherited in an X-linked manner. If the mother of a proband with DDON syndrome has the causative genetic alteration (i.e., a *TIMM8A* pathogenic variant or a contiguous gene deletion of Xq22.1 involving *TIMM8A*), the chance of transmitting the genetic alteration in each pregnancy is 50%. Males who inherit the genetic alteration will be affected; females who inherit the genetic alteration will be heterozygotes and may have mild hearing impairment and focal dystonia. Males who reproduce pass the genetic alteration to all of their daughters and none of their sons.

Prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic testing are possible if the DDON-causing genetic alteration in the family is known.

Diagnosis

Formal diagnostic criteria for deafness-dystonia-optic neuronopathy (DDON) syndrome have not been established.

Scope of this chapter. Deafness-dystonia-optic neuronopathy (DDON) syndrome occurs as either a single-gene disorder resulting from a pathogenic variant in *TIMM8A* or a contiguous gene deletion at Xq22.1 that includes *BTK* and additionally causes X-linked agammaglobulinemia (XLA). XLA will not be discussed further in this chapter.

Suggestive Findings

Deafness-dystonia-optic neuronopathy (DDON) syndrome is suspected in males with the following:

- Progressive sensorineural hearing impairment with prelingual or postlingual onset:
  - Absent stapedius reflex
  - Abnormal findings on auditory brain stem response testing
  - Normal evoked otoacoustic emissions, indicating normal outer hair cells [Richter et al 2001]
  - Normal findings on CT scan of the inner ear [Mohr & Mageroy 1960, Tranebjaerg et al 1995]
- Movement disorder (dystonia/ataxia)
- Gradual onset and slow progression of personality changes, paranoia, dementia
- Gradual decrease in visual acuity associated with optic atrophy
- Gradual onset and slow progression of dysphagia
- A family history consistent with X-linked inheritance

Establishing the Diagnosis

The diagnosis of deafness-dystonia-optic neuronopathy (DDON) syndrome **is established** in a proband who has **one of the following** on molecular genetic testing (see Table 1) [Tranebjaerg 2012]:

- A hemizygous *TIMM8A* pathogenic (or likely pathogenic) variant in a male proband (~50% of affected males) or a heterozygous *TIMM8A* pathogenic (or likely pathogenic) variant in a female proband (~50% of affected females)
- A contiguous gene deletion of Xq22.1 involving *TIMM8A* (~50% of affected males and females)

Note: (1) The clinical features of DDON in individuals with a contiguous gene deletion and in individuals with smaller pathogenic variants are indistinguishable, apart from the additional presence of X-linked agammaglobulinemia in the former. (2) 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. (3) Identification of a hemizygous or heterozygous *TIMM8A* variant of uncertain significance does not establish or rule out the diagnosis.

Options for molecular genetic testing can include a chromosomal microarray analysis (CMA) or use of a multigene panel depending on the phenotype and family history.

Option 1

In a child with hearing loss and evidence of a family history suggestive of XLA, **CMA** should be performed first. CMA uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TIMM8A*) that cannot be detected by sequence analysis.

Option 2

In a young child with hearing impairment and no other phenotypic findings, there should be a strong suspicion of DDON if the auditory phenotype is auditory neuropathy. **A deafness / hearing impairment** or an **auditory neuropathy multigene panel** that includes *TIMM8A* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., *BTK* as described by Sedivá et al [2007]) may not be detected by these methods and would require CMA for detection (see Table 1).

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 DDON Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TIMM8A	Sequence analysis [3]	22/42 [4]
	Gene-targeted deletion/duplication analysis [5]	20/42 [6]
	CMA [7]	18/42 [8]

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. Tranebjaerg [2012], Montaut et al [2018], Wang et al [2019]
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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Sedivá et al [2007]) may not be detected by these methods.
6. Most deletions not detectable by sequence analysis are large deletions that include *BTK*. A single intragenic exon 2 deletion has been reported [Ha et al 2012].
7. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TIMM8A*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the Xq22.1 region. CMA designs in current clinical use target the Xq22.1 region.
8. Tranebjaerg [2012], Szaflarska et al [2018], Wang et al [2019]

Clinical Characteristics

Clinical Description

Deafness-dystonia-optic neuronopathy (DDON) syndrome is a progressive disorder with prelingual or postlingual sensorineural hearing impairment in early childhood. The hearing impairment is always the presenting manifestation. Typically, DDON is associated with slowly progressive dystonia or ataxia in the teens, slowly progressive decreased visual acuity from approximately age 20 years, and dementia from approximately age 40 years. Psychiatric manifestations such as personality change and paranoia may appear in childhood and progress. The deafness and pronounced visual impairment severely compromise communication in late adulthood.

Note: The term "neuronopathy" refers to the destruction of the cell bodies of neurons and is different from "neuropathy," which is defined as a functional disturbance in the peripheral nervous system.

The hearing impairment appears to be more consistent in age of onset and progression than the neurologic, visual, and neuropsychiatric features, which vary in degree of severity and rate of progression. Life span may show extreme variation, even within a family. For example, in one large family, one member had rapidly progressive dystonia ("dystonia musculorum deformans") and died at age 16 years; other affected family members died in their sixties [Tranebjaerg et al 1995].

Audiologic features. The average age of onset of sensorineural hearing impairment is approximately 18 months, although some affected individuals have apparent congenital prelingual hearing impairment [Swerdlow & Wooten 2001, Ujike et al 2001]. The hearing impairment progresses rapidly and is typically profound before age ten years. Vestibular function is normal.

The hearing impairment results from an auditory neuropathy as shown by intact otoacoustic emissions associated with absent auditory brain stem responses in some individuals and convincing histopathologic evidence in five males with molecularly proven DDON syndrome with near-total loss of cochlear neurons and severe loss of vestibular neurons [Bahmad et al 2007, Wang et al 2019]. As expected from auditory neuropathy many individuals with DDON syndrome, at least in early stages of the disease, have intact otoacoustic emissions [Richter et al 2001, Brookes et al 2008, Wang et al 2019].

Of note, isolated hearing impairment without other manifestations of DDON syndrome has not been reported with *TIMM8A* pathogenic variants.

Neurologic features. The finding of *gegenhalten* (defined as diffuse resistance to movement of a limb) may be the first neurologic manifestation. The movement disorder may appear either as dystonia or ataxia. The onset may be as early as childhood, or much later. The movement disorder is progressive and the gait gradually becomes unstable. Affected individuals have brisk tendon reflexes, ankle clonus, and extensor plantar responses. Eventually they need a cane for walking and finally become wheelchair bound. Dystonic contractures may develop [Scribanu & Kennedy 1976, Jensen 1981, Jensen et al 1987, Tranebjaerg et al 1995, Hayes et al 1998].

Although many affected individuals develop dystonia by their thirties, some, ascertained through severely affected male relatives with a typical phenotype, have no detectable neurologic dysfunction in their thirties [Ujike et al 2001, Ha et al 2012].

Dysphagia develops late in the course and often causes aspiration pneumonia and its complications.

A mild peripheral sensory neuropathy may be present.

Spinal cord dysfunction was present in an individual with DDON syndrome with prolonged somatosensory evoked potentials and disturbed central motor conduction to lower extremities in motor evoked potentials [Binder et al 2003].

Seizures are not characteristic.

Neuropsychologic features. Behavioral abnormalities may be present from childhood, with mild intellectual disability, personality changes, restlessness, anxiety, reduced impulse control, aggressive outbursts, and compromised ability to concentrate. Later, paranoid psychiatric features may be present with fear of poisoned food, imaginary sensory impulses from skin, and imaginary foreign bodies in the eyes leading to self-mutilating behavior. Gradually, dementia develops.

Ophthalmologic features. Optic neuronopathy may be subclinical for many years [Ujike et al 2001] and may be apparent only when prolongation of the P100 wave latency is detected on visual evoked potential testing [Ponjavic et al 1996,Tranebjaerg et al 2001].

In childhood, color vision and visual fields are normal [Tranebjaerg et al 1995, Ponjavic et al 1996]. Visual impairment may first be evident in the late teens as photophobia, reduced visual acuity, acquired color vision defect, and central scotomas. Ophthalmologic examination in children reveals normal-appearing optic nerves; in adults, the optic nerves become pale. The appearance of the retina is usually normal, as are night vision and the electroretinogram [Ponjavic et al 1996].

Slowly progressive decline in visual acuity leads to legal blindness around age 30 to 40 years [Tranebjaerg et al 1995, Ponjavic et al 1996, Tranebjaerg et al 2000a, Tranebjaerg et al 2000b, Tranebjaerg et al 2001].

Other characteristics

- Males with DDON syndrome have normal fertility.

- Frequent occurrence of hip fractures in affected males appears to be associated with poor neuromuscular coordination and increased risk for stumbling rather than an abnormality in calcium metabolism or intrinsic bone abnormalities [Tranebjaerg et al 1995].
- Cardiomyopathy does not occur.
- Decrease in respiratory capacity does not occur, except for that related to aspiration pneumonia.

Heterozygotes

Older females from the original family described by Tranebjaerg et al [1995] possibly had mild involvement. Recently, females ascertained through families with classically affected males have been shown to have mild hearing impairment and focal dystonia (e.g., "writer's cramp") [Swerdlow & Wooten 2001, Swerdlow et al 2004]. While skewed X-chromosome inactivation may contribute to this phenomenon [Orstavik et al 1996, Plenge et al 1999], X-chromosome inactivation studies were not reported in the families with the most severely involved heterozygous females [Swerdlow & Wooten 2001, Swerdlow et al 2004].

Female probands have been reported [Swerdlow & Wooten 2001, Klempir et al 2010, Ha et al 2012].

Other Studies in Affected Males

Neuroimaging (CT, MRI, or PET scan) shows general brain atrophy in the majority of males from age 40 years or, in some cases, earlier [Tranebjaerg et al 2001].

More sophisticated neuroimaging studies such as PET/MRI reveal hypometabolic areas, predominantly over the right striatum and parietal cortex, and marked atrophy of the occipital lobes [Hayes et al 1998, Swerdlow & Wooten 2001, Ujike et al 2001, Binder et al 2003].

Neurophysiologic investigations show cochlear dysfunction.

Neuropathologic abnormalities include general brain atrophy and gliosis, microcalcifications, and neuronal cell death in spiral ganglion cells of the cochlea, Scarpa's ganglion, the retinal ganglion cell layer, the optic nerves, and the calcarine fissures (visual cortex) [Scribanu & Kennedy 1976, Reske-Nielsen et al 1988, Hayes et al 1998, Merchant et al 2001, Tranebjaerg et al 2001].

Otopathologic findings clearly support that DDON syndrome is an auditory neuropathy. Temporal bones from five individuals with molecularly verified DDON syndrome showed near-total loss of cochlear neurons and severe loss of vestibular neurons [Merchant et al 2001, Bahmad et al 2007].

The spinal cord is atrophic with loss of fibers in the dorsal roots and posterior columns, as seen in Friedreich ataxia [Tranebjaerg et al 2001].

Muscle biopsy shows normal enzyme activity of energy-generating systems, no structural abnormalities, and no aggregations of mitochondria. Electron microscopy reveals mild neurogenic atrophy [Tranebjaerg et al 1995, Tranebjaerg et al 2001, Binder et al 2003]. Activities of complexes I through IV of the mitochondrial respiratory chain in muscle biopsy revealed a mild deficiency for complex IV in a male with a *de novo* p.Gln38Ter stop variant, but no abnormalities could be demonstrated in cultivated fibroblasts [Blesa et al 2007]. No pathogenic variants were identified in the mtDNA genes encoding the complex IV subunits COI, COII, and COIII or in five tRNA mtDNA genes [Blesa et al 2007].

Genotype-Phenotype Correlations

The limited number of affected individuals, the extremely variable clinical course, and the family-specific nature of each pathogenic variant identified limits detection of genotype-phenotype correlations.

It is noteworthy that the clinical features of DDON in individuals with a contiguous gene deletion and in individuals with smaller pathogenic variants are indistinguishable, apart from presence or absence of X-linked agammaglobulinemia in those with a contiguous gene deletion [Tranebjaerg 2012] (see Genetically Related Disorders).

Nomenclature

In 1960, Mohr and Mageroy described an X-linked recessive childhood-onset sensorineural hearing impairment, which was believed to be nonsyndromic and thus was designated DFN-1, indicating that it was the first described X-linked nonsyndromic form of hearing impairment [Mohr & Mageroy 1960]. Tranebjaerg et al [1995] reinvestigated the family, updated the pedigree, and identified associated neurologic, visual, and behavioral findings. The syndrome was renamed Mohr-Tranebjaerg syndrome and later deafness-dystonia-optic neuronopathy (DDON) syndrome.

Opticoacoustic nerve atrophy (Jensen syndrome), reported by Jensen [1981], Jensen et al [1987], and Reske-Nielsen et al [1988], and deafness-dystonia syndrome, reported clinically in two families by Scribanu & Kennedy [1976] and Hayes et al [1998], are the same as DDON syndrome. *TIMM8A* pathogenic variants have been identified in individuals with these two disorders [Tranebjaerg et al 1997, Tranebjaerg et al 2000b, Tranebjaerg et al 2001].

Prevalence

The prevalence of DDON syndrome is unknown. It has been identified in several populations worldwide.

A recent comprehensive review chapter identified 91 affected individuals from 37 families [Tranebjaerg 2012].

Dystonia of all types occurs with a prevalence between 70 and 329 per million [ESDE Collaborative Group 2000]. No large-scale molecular genetic testing of cohorts of males with dystonia has been published.

Hearing impairment has a prevalence of 1:800, approximately 1% of which is attributed to X-linked inheritance.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *TIMM8A*.

Differential Diagnosis

Specific disorders that share features with deafness-dystonia-optic neuronopathy (DDON) syndrome. See Table 2.

Note: *De novo* pathogenic variants in *TIMM8A* in some families may mimic autosomal recessive inheritance and thus complicate the ability to distinguish between X-linked and autosomal causes of dystonia.

Table 2. Other Genes of Interest in the Differential Diagnosis of DDON Syndrome

Gene(s) [1]	Differential Disorder	MOI	Features of Differential Disorder	
			Overlapping w/DDON syndrome	Distinguishing from DDON syndrome
MT-TL1 [2]	MELAS	Mat	• The combination of optic atrophy, hearing loss, & neurologic signs suggests mt disorders such as MELAS. • See also Mitochondrial Disorders Overview.	• Dystonia uncommon in MELAS • Short stature, generalized tonic-clonic seizures, recurrent headaches/vomiting, & anorexia common in MELAS
SERAC1	MEGDEL syndrome	AR	Dystonia & deafness	Leigh-like features, impaired oxidative phosphorylation, & 3-methylglutaconic aciduria
SUCLA2	*SUCLA2*-related mtDNA depletion syndrome, encephalomyopathic form w/methylmalonic aciduria [3]	AR	• Progressive disorder • Dystonia & severe hearing impairment	• Hypotonia, abnormal muscle histopathology, & ↑ methylmalonic acid concentration • Ophthalmologic findings normal • Several cases reported from Faroe Islands
PRPS1	Arts syndrome (See Phosphoribosylpyrophosphate Synthetase Deficiency.) [4]	XL	Intellectual impairment, ataxia, & hearing impairment	Arts syndrome findings range from isolated hearing impairment to hearing impairment assoc w/optic atrophy, hypotonia, ataxia, ID, & signs of peripheral neuropathy, but not dystonia.
XK	McLeod neuroacanthocytosis syndrome	XL	Movement disorder, cognitive impairment, & psychiatric symptoms in males	• Neurodegenerative basal ganglia disease • Neuromuscular manifestations incl (mostly subclinical) sensorimotor axonopathy & clinically relevant muscle weakness or atrophy • Hematologic manifestations: RBC acanthocytosis, compensated hemolysis, & McLeod blood group phenotype • Dilated cardiomyopathy & arrhythmias
CDH23 *CIB2* *MYO7A* *PCDH15* *USH1C* *USH1G* *USH1H* [5]	Usher syndrome type I	AR	• Visual & hearing impairment • In persons w/DDON, Usher may first be suspected because hearing impairment in DDON may be congenital & in Usher type II may be progressive.	• Impaired vision results from retinal dystrophy, which first manifests as impaired dark adaptation [6] (vs DDON, where appearance of retina is usually normal, as are night vision & ERG). • No neurologic abnormalities
ADGRV1 *USH2A* *WHRN* [5]	Usher syndrome type II	AR		

Table 2. continued from previous page.

Gene(s) [1]	Differential Disorder	MOI	Features of Differential Disorder	
			Overlapping w/DDON syndrome	Distinguishing from DDON syndrome
WFS1	Wolfram syndrome	AR	• Optic atrophy, movement disorder, dementia, & psychiatric abnormalities may occur. • Hearing impairment in ~60% of persons by age 20 yrs • Consider Wolfram in simplex males (i.e., single case in a family) who appear to have DDON.	• Juvenile onset of diabetes mellitus • Involvement of most organs • No dystonia
FXN	Friedreich ataxia	AR	• Slowly progressive ataxia w/onset age usually <25 yrs • May be assoc w/ sensorineural hearing impairment (10% of persons) & often subclinical optic atrophy (25%)	• Rarely presents w/hearing impairment or optic atrophy (hearing loss is always a presenting finding in DDON) • Dystonia & other movement disorders uncommon • Tendon reflexes usually (not always) depressed in Friedreich ataxia • Cardiomyopathy common

AR = autosomal recessive; CNS = central nervous system; ERG = electroretinogram; ID = intellectual disability; Mat = maternal; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MOI = mode of inheritance; mt = mitochondrial; RBC = red blood cell; XL = X-linked

1. Genes are in alphabetic order.

2. The m.3243A>G pathogenic variant in the mitochondrial gene *MT-TL1* is present in approximately 80% of individuals with MELAS. Pathogenic variants in *MT-TL1*nor other mtDNA genes, particularly *MT-ND5*, can also cause this disorder.

3. The disorder was identified in a Muslim family and ten remotely related individuals from the Faroe Islands, where a high carrier frequency (1 in 33) is caused by a founder variant [Ostergaard et al 2007].

4. See also other heredodegenerative X-linked disorders characterized by intellectual impairment, movement disorder, and hearing impairment, including Farlow syndrome (OMIM 301840), Schimke syndrome (OMIM 312840), Wells syndrome (OMIM 312910), and Schmidley syndrome (OMIM 301790).

5. See Phenotypic Series: Usher syndrome for additional genes associated with this phenotype in OMIM.

6. Ophthalmoscopy and electroretinography can be used to determine the cause of visual impairment.

Hearing impairment. Hearing impairment shows genetic heterogeneity (see Hereditary Hearing Loss and Deafness Overview). The diagnosis of DDON syndrome needs to be considered in males with prelingual hearing impairment in the absence of family history of hearing loss if more common genetic causes (e.g., DFNB1, Pendred syndrome) have been excluded. X-linked hearing impairment without additional manifestations may be linked to other DFN loci (see Phosphoribosylpyrophosphate Synthetase Deficiency).

The presence of immunodeficiency and hearing impairment in a male should raise the possibility of a contiguous gene deletion at Xq22 involving *TIMM8A* and *BTK*.

Dystonia. Dystonias are a heterogeneous group of disorders (see Hereditary Dystonia Overview). Hearing impairment does not appear to be commonly associated with other dystonias.

Management

Evaluations Following Initial Diagnosis

Affected males. To establish the extent of disease and needs in a male diagnosed with deafness-dystonia-optic neuronopathy (DDON) syndrome, 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 Males with DDON Syndrome

System/Concern	Evaluation	Comment
Hearing impairment	Formal audiologic assessment w/focus on possibility of auditory neuropathy	To determine extent of hearing impairment
	Speech-language assessment	To determine speech therapy needs
Dystonia/ Ataxia	Neurologic assessment	To provide baseline information
	Orthopedics / physical medicine & rehab / PT & OT eval	Incl assessment of: • Gross motor & fine motor skills • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Vision impairment	Ophthalmologic eval incl VEP	Incl visual acuity, color vision testing, visual field testing for evidence of central scotomas
Development	Developmental assessment; consider specialized testing for deaf &/or visually impaired persons.	Incl motor, adaptive, cognitive evaluation for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons w/dementia &/or psychiatric disturbance
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	Incl genetic counseling
	Family support & resources	Assess need for: • Community or online resources (e.g., Parent to Parent); • Social work involvement for parental support.

OT = occupational therapy; PT = physical therapy; VEP = visual evoked potential

Heterozygous females. The evaluation of a heterozygous female depends on whether she is a symptomatic proband (see Table 3) or primarily a healthy female relative of a male proband.

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with DDON Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Poor visual acuity / Blindness	Corrective lenses / standard treatment	Community vision services through early intervention or school district

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Hearing impairment / Deafness	Treatment of SNHL, w/focus on auditory neuropathy, depends on degree of hearing impairment. [1]	• Start hearing habituation (auditory & speech training, sign language) as soon as possible. • Community hearing services through early intervention or school district
	Cochlear implant	• CT of bony landmarks & MRI of vestibular & facial nerves as part of pre-cochlear implant assessment [2, 3] • Cochlear implants may provide sound awareness & even speech recognition in presence of cochlear abnormalities. [4] • Outcome is expected to be variable in auditory neuropathy.
Communication	Depends on degree of hearing & vision impairment	Refer to community deaf-blind services & state Deafblind Project as soon as possible after birth. [8]
Dystonia	Physical medicine & rehab / PT & OT	• To improve gross motor skills & mobility & prevent contractures • To improve fine motor skills • Provide adaptive devices to improve activities of daily living.
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Behavioral concerns	Standard medications for obsessive-compulsive disorder	Behavioral therapy combined w/stress reduction is sometimes helpful.
	Behavior therapy, stress reduction, & standard medications for pervasive developmental disorder	Behaviors may mimic autism but are different; [9] may be exacerbated by sensory processing issues.
	Establish an appropriate method of communication & provide adequate stimulation for exploration in a safe environment for ADHD.	May be more helpful than medication
Family needs	Ensure appropriate social work involvement to connect families w/local resources, respite, & support.	Ongoing assessment for need of home nursing
	Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies	Consider involvement in adaptive sports or Special Olympics.

ADHD = attention-deficit/hyperactivity disorder; DD/ID = developmental delay / intellectual disability; OT = occupational therapy; PT = physical therapy; SNHL = sensorineural hearing loss

1. See Hereditary Hearing Loss and Deafness Overview for details about treatment options.

Developmental Delay / Intellectual Disability Management Issues

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

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, 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:

- Individualized education plan (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.
  - PT, OT, 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 by 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, an NG-tube or G-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 is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

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

Surveillance

Table 5. Recommended Surveillance for Individuals with DDON Syndrome

System/Concern	Evaluation	Frequency
Hearing impairment	Audiologic eval	Annually
Speech & language development	By speech & language therapist	
Dystonia	Neurologic exam to monitor progression of dystonia & review medications	Regular follow up depending on rate of progression
	PT/OT: review activities of daily living, gross motor & fine motor needs	
Vision impairment	Visual acuity	
Psychiatric/ Behavioral	When clinically relevant	Individual follow up based on clinical findings
Developmental progress & educational needs	• Effect of hearing impairment, vision impairment, mvmt disorder, changes in behavior &/or cognitive abilities when clinically relevant • Be aware of signs of dementia in adults.	Individual program for follow up
Family/caregiver needs	Assess need for social work support (e.g., respite care, home nursing, other local resources) & care coordination.	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

Deafness-dystonia-optic neuronopathy (DDON) syndrome is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the DDON syndrome-causing genetic alteration (i.e., a pathogenic variant in *TIMM8A* or a contiguous gene deletion at Xq22.1); therefore, he does not require further evaluation/testing.
- If a male proband has a sib with the same DDON syndrome-causing genetic alteration, the mother of the proband is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the DDON syndrome-causing genetic alteration cannot be detected in her leukocyte DNA, she most likely has germline mosaicism (maternal germline mosaicism has been suspected but not molecularly proven in any published cases).
- If a male is the only affected family member (i.e., a simplex case), the mother may be heterozygous for the DDON syndrome-causing genetic alteration or the affected male may have a *de novo* DDON syndrome-causing genetic alteration, in which case the mother is not a heterozygote. *De novo* deletions have been documented in multiple cases [Tranebjaerg et al 2000a, Blesa et al 2007, Brookes et al 2008, Tranebjaerg 2012].

Parents of a female proband

- A female proband may have inherited the DDON syndrome-causing genetic alteration from either her mother or her father, or the DDON syndrome-causing genetic alteration may be *de novo*.
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* DDON syndrome-causing genetic alteration from those with an inherited genetic alteration. Molecular genetic testing of the mother (and possibly the father, or subsequently the father) can help to determine if the genetic alteration was inherited. (Note: Parental germline mosaicism would not be detected by molecular genetic testing of leukocyte DNA.)

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a DDON syndrome-causing genetic alteration, the chance of transmitting it in each pregnancy is 50%. Males who inherit the genetic alteration will be affected; females who inherit the genetic alteration will be heterozygotes and may present with mild hearing loss or focal dystonia at an older age (see Clinical Description, Heterozygotes).

- If the proband represents a simplex case and if the DDON syndrome-causing genetic alteration cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism.

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

- If the mother of the proband has the DDON syndrome-causing genetic alteration, the chance of transmitting it in each pregnancy is 50%. Males who inherit the genetic alteration will be affected; females who inherit the genetic alteration will be heterozygotes and may present with mild hearing impairment or focal dystonia at an older age (see Clinical Description, Heterozygotes).
- If the father of the proband has a DDON syndrome-causing genetic alteration, he will transmit it to all of his daughters and none of his sons.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the DDON syndrome-causing genetic alteration cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism.

Offspring of a male proband. Males who reproduce pass the DDON syndrome-causing genetic alteration to all of their daughters and none of their sons.

Offspring of a female proband. Women with a DDON syndrome-causing genetic alteration have a 50% chance of transmitting the genetic alteration to each child.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the genetic alteration, the parent's family members may be at risk.

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is possible if the DDON syndrome-causing genetic alteration in the family has been identified.

Specific risk issues. The absence of manifestations in most young heterozygous females may present families with additional challenges in clarifying risk status if the DDON syndrome-causing genetic alteration in the family has not been identified. It is unknown whether X-chromosome inactivation studies could be used to detect skewed X-chromosome inactivation in heterozygotes.

Related Genetic Counseling Issues

The progression of individual symptoms shows considerable inter- and intrafamilial variability, making a reliable prediction of the degree of severity difficult. Some families have shown skewed X-chromosome inactivation in heterozygous females, which may explain the occurrence of mild manifestations in some heterozygous females [Orstavik et al 1996, Plenge et al 1999].

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the DDON syndrome-causing genetic alteration has been identified in the family, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. 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.

- **Dystonia UK**
  United Kingdom
  Email: info@dystonia.org.uk
  dystonia.org.uk
- **National Library of Medicine Genetics Home Reference**
  Deafness-dystonia-optic neuronopathy syndrome
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **BabyHearing.org**
  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.
  babyhearing.org
- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Email: dystonia@dystonia-foundation.org
  dystonia-foundation.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org

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. Deafness-Dystonia-Optic Neuronopathy Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar

Table A. continued from previous page.

TIMM8A	Xq22.1	Mitochondrial import inner membrane translocase subunit Tim8 A	TIMM8A	TIMM8A

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 Deafness-Dystonia-Optic Neuronopathy Syndrome (View All in OMIM)

300356	TRANSLOCASE OF INNER MITOCHONDRIAL MEMBRANE 8A; TIMM8A
304700	MOHR-TRANEBJAERG SYNDROME; MTS

Molecular Pathogenesis

TIMM8A encodes the 97-amino acid mitochondrial import inner membrane translocase subunit TIMM8A involved in the mitochondrial transport processes. The yeast ortholog, Tim8p, is similar to five small yeast mitochondrial intermembrane space proteins – Tim8p, Tim9p, Tim10p, Tim12p, and Tim13p – but is most similar to Tim8p, which exists as a soluble 70-kd complex with Tim13p and Tim9p [Koehler et al 1999a, Koehler et al 1999b].

TIMM8A contains putative Zn-binding domains with four conserved cysteine residues. The product is involved in mitochondrial protein import [Koehler et al 1999a, Koehler et al 1999b], and like the yeast Tim8p, it assembles in a 70-kd complex in the mitochondrial intermembrane space with mitochondrial import inner membrane translocase subunit TIMM13, the protein encoded by *TIMM13*. Evidence from yeast indicates that this complex is critical for the import of TIMM23, which therefore may be insufficiently present in the inner membrane, resulting in the human disorder [Roesch et al 2002].

Protein expression and immunocytochemical studies indicate that TIMM8A and TIMM13 are coexpressed at high levels in Purkinje cells in the cerebellum, but not in glial cells [Roesch et al 2004]. Expression and import studies show that the calcium-binding aspartate/glutamate carriers, citrin and aralar1, are new substrates for the TIMM8A/TIMM13 protein complex [Roesch et al 2004]. The morphology of muscle mitochondria and biochemical characterization are only borderline abnormal [Koehler et al 1999a, Koehler et al 1999b, Paschen et al 2000, Tranebjaerg et al 2000a, Rothbauer et al 2001, Tranebjaerg et al 2001].

Mechanism of disease causation. DDON occurs through a loss-of-function mechanism.

Deletion of *TIMM8A* as part of a contiguous gene deletion that includes *BTK* occurs frequently, resulting in the presence of both DDON and X-linked agammaglobulinemia (XLA) [Tranebjaerg 2012]. Of note, deletion breakpoints preferentially involve Alu elements in smaller deletions (<10 kb) in individuals with both DDON and XLA [Arai et al 2011, Tranebjaerg 2012].

Although some variants are inherited, *de novo* variants are often observed [Tranebjaerg 2012].

***TIMM8A*-specific laboratory technical considerations**

- *TIMM8A* comprises only two exons.
- *TIMM8A* has a pseudogene, *TIMM8AP1*. Since *TIMM8AP1* is a processed pseudogene, and since there are a sufficient number of sequence differences between the gene and pseudogene, it appears unlikely that *TIMM8AP1* will interfere with the analysis of *TIMM8A*.

Chapter Notes

Revision History

- 21 November 2019 (bp) Comprehensive update posted live
- 31 January 2013 (me) Comprehensive update posted live
- 24 March 2009 (cd) Revision: deletion/duplication analysis available clinically
- 3 April 2008 (me) Comprehensive update posted live
- 8 April 2005 (me) Comprehensive update posted live
- 5 February 2004 (cd) Revision: change in testing
- 6 February 2003 (me) Review posted live
- 23 August 2002 (lt) Original submission

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