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NR2F1-Related Neurodevelopmental Disorder

Synonym: Bosch-Boonstra-Schaaf Optic Atrophy Syndrome (BBSOAS)

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Summary

Clinical characteristics

NR2F1-related neurodevelopmental disorder (*NR2F1*-NDD) is characterized by developmental delay / intellectual disability (ranging from profound to mild) and is commonly associated with hypotonia, visual impairment (due to optic nerve abnormalities and/or cerebral visual impairment), epilepsy, and behavioral manifestations (e.g., autism spectrum disorder, attention-deficit/hyperactivity disorder).

Diagnosis/testing

The diagnosis of *NR2F1*-NDD is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *NR2F1* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no cure for *NR2F1*-NDD. Supportive treatment typically relies on multidisciplinary specialists in the fields of neurology, speech-language pathology, ophthalmology (including low-vision services), gastroenterology, nutrition, occupational therapy, physical therapy, audiology, clinical genetics, and genetic counseling.

Surveillance: Regular monitoring of existing manifestations, the individual's response to supportive care, and the emergence of new manifestations.

Genetic counseling

NR2F1-NDD is an autosomal dominant disorder. Most probands reported to date with an intragenic *NR2F1* pathogenic variant whose parents have undergone molecular genetic testing have the disorder as the result of a

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de novo pathogenic variant. Some recurrences within a family have been reported. Risk to future pregnancies is presumed to be low when the proband has what appears to be a *de novo NR2F1* pathogenic variant; however, there is a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism. Given this risk, prenatal and preimplantation genetic testing may be considered.

Diagnosis

No consensus clinical diagnostic criteria for *NR2F1*-related neurodevelopmental disorder (*NR2F1*-NDD) have been published.

Suggestive Findings

NR2F1-NDD **should be considered** in probands with the following clinical and brain MRI findings.

Clinical findings [Rech et al 2020, Bertacchi et al 2022]

- Developmental delay (i.e., delay in milestone acquisition in at least one domain) and/or intellectual disability
- Hypotonia
- Speech difficulties
- Vision impairment, including:
  - Optic atrophy (OA), optic nerve hypoplasia
  - Cerebral visual impairment (CVI), broadly defined here as bilateral visual impairment due to non-ocular causes (i.e., based in the brain) in the presence of normal pupil reactivity. Clinical assessment was corroborated by a parent report survey of behavioral characteristics of CVI including variable visual functioning, visual latency, difficulty with distance viewing, preference for movement, difficulty with visual complexity, color preference, light-gazing, visual field preference, impaired reflex blink to visual threat, preference for familiar objects, and absence of visually guided reach [Rech et al 2020].
  - Other ophthalmologic findings such as nystagmus, strabismus, amblyopia, and refractive errors
- Behavioral findings including:
  - Autism spectrum disorder or autistic features
  - Attention-deficit/hyperactivity disorder
  - Obsessive-compulsive behavior and/or repetitive behaviors
- Feeding difficulties (oromotor dysfunction, mouth stuffing)
- Seizures including infantile spasms
- Hearing impairment
- Other common findings:
  - Alacrima
  - Love of music
  - Good long-term memory
  - High pain tolerance
  - Sleep disturbances
  - Touch sensitivity

Brain imaging. The following brain MRI findings are strongly suggestive of *NR2F1*-NDD:

- Abnormalities of the corpus callosum (particularly thinning of the corpus callosum)
- Hypoplasia of the optic nerves and optic chiasms
- Other nonspecific findings (See Clinical Description.)

Family history. Because *NR2F1*-NDD is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of *NR2F1*-related NDD **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *NR2F1* 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 variants. (2) Identification of a heterozygous *NR2F1* variant of uncertain significance does not establish or rule out the diagnosis of the disorder.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with **chromosomal microarray analysis** (CMA). Other options may include use of a **multigene panel** or **exome sequencing**.

- **An intellectual disability (ID), optic atrophy (OA), epilepsy, or autism spectrum disorder (ASD) multigene panel** that includes *NR2F1* and other genes of interest (see Differential Diagnosis) is most likely 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*. (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** may be more commonly used and yields results similar to an ID/OA/epilepsy/ASD multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID/OA/epilepsy/ASD, 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 *NR2F1*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
NR2F1	Sequence analysis [3]	80%-85% [4]
	Gene-targeted deletion/duplication analysis [5]	15%-20% [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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Bertacchi et al [2022]
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

NR2F1-related neurodevelopmental disorder (*NR2F1*-NDD) is characterized by developmental delay / intellectual disability (ranging from profound to mild) and is commonly associated with hypotonia, visual impairment (due to optic nerve abnormalities and/or cerebral visual impairment), epilepsy, and behavioral issues (such as autism spectrum disorder and attention-deficit/hyperactivity disorder).

To date, 92 individuals have been described with a pathogenic variant in *NR2F1* [Jurkute et al 2021, Bertacchi et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports. See Table 2.

Table 2. Select Features of *NR2F1*-Related Neurodevelopmental Disorder

Feature		% of Persons w/Feature
Developmental delay		88%
Intellectual disability		87%
Vision impairment	Optic atrophy	67%
	Optic nerve hypoplasia	22%
	Cerebral visual impairment	42%-55% [1]
Hypotonia		62%
Epilepsy		46%
Autism spectrum disorder		38%
Abnormalities of the corpus callosum		33%

Adapted and modified from Bertacchi et al [2022]
1. Jurkute et al [2021], Bertacchi et al [2022]

Developmental delay (DD) and intellectual disability (ID) are very common among individuals with *NR2F1*-NDD. DD can affect both motor and speech milestones. The severity of ID can range from profound (IQ <20) to moderate (IQ = 35-49) to mild (IQ = 50-69) [Bertacchi et al 2022].

Based on published reports to date:

- Children are able to sit independently at an average age of 14 months, crawl at 16 months, and walk at 33 months [Rech et al 2020].
- Children are able to speak their first words at an average age of 32 months and combine words by the age of 47 months [Rech et al 2020].
- Some affected individuals have more significant delays, including severe language/speech delays (e.g., they are nonverbal), and others are not able to walk independently [Rech et al 2020].

Vision impairment and other ophthalmologic findings. Vision impairment in individuals with *NR2F1*-NDD is usually detected in early childhood when they are examined following referrals for evaluation of nystagmus, strabismus, poor fixation, and/or concerns about neurodevelopmental progress. Based on Jurkute et al [2021]:

- Visual acuity is relatively preserved with a mean logMAR of 0.64 (20/90 Snellen equivalent). Fundus examination revealed optic atrophy in 77% of individuals and small and/or tilted hypoplastic optic nerves in 46% of individuals.
- Most individuals have a refractive error (91%) with a predominance of hyperopia (68%).
- Strabismus (77%) and nystagmus (45%) are common features.
- Cerebral visual impairment is present in 55% of children.

Other neurodevelopmental features

- **Hypotonia** can be present at time of birth and may persist throughout childhood [Rech et al 2020].
- **Oromotor dysfunction,** including problems with sucking, chewing, or swallowing, is a common feature in neonates and infants and may occasionally necessitate nasogastric tube feeding [Bertacchi et al 2022].

Seizures, reported in 46% of individuals (42/92) [Bertacchi et al 2022], are more prevalent in individuals with variants in the DNA-binding domain [Rech et al 2020] (see Genotype-Phenotype-Correlation). Generalized tonic-clonic, atonic, myoclonic, absence, and focal seizures as well as infantile epileptic spasms syndrome or febrile seizures have been described [Chen et al 2016, Hino-Fukuyo et al 2017, Mio et al 2020, Rech et al 2020, Bertacchi et al 2022].

Electroencephalography may reveal abnormalities, often predominantly in the occipital brain regions [Bertacchi et al 2022].

Behavioral findings include repetitive behavior, obsessive-compulsive behavior, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) [Rech et al 2020, Bertacchi et al 2022]. While 38% (32/92) of affected individuals met the diagnostic criteria for ASD, autistic traits were reported in an additional 14% (13/92) of individuals [Bertacchi et al 2022]. ADHD was present in 18% (17/92) [Bertacchi et al 2022].

Hearing impairment is less common but has been observed (11%) [Bertacchi et al 2022]. Some individuals may need hearing aids.

Neuroimaging may show several abnormalities including abnormalities of the corpus callosum (particularly a thin corpus callosum), malrotated or dysmorphic hippocampus, white matter loss, and cortical dysgyria that may resemble polymicrogyria [Bertacchi et al 2022]. Hypoplasia of the optic nerves and optic chiasm are also commonly seen on brain MRI [Rech et al 2020].

Other associated features

- **Autonomic dysfunction**, including alacrima (absent or decreased reflex tears) and abnormal temperature regulation, has been described [Rech et al 2020].
- **Growth.** Short stature is present in some individuals [Kaiwar et al 2017, Rech et al 2020].
- No specific dysmorphic features have been observed. If present, dysmorphic features are nonspecific.

Prognosis. In contrast to other inherited optic neuropathies, vision impairment caused by pathogenic variants in *NR2F1* appears to be congenital and non-progressive [Jurkute et al 2021]. Data on possible progression of behavior abnormalities or neurologic findings are currently limited.

Information on life expectancy in individuals with *NR2F1*-NDD is limited. One individual was alive at age 35 years [Bosch et al 2014], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

Preliminary genotype-phenotype correlations based on published reports to date suggest that compared to individuals with pathogenic variants in other domains of *NR2F1*, individuals with pathogenic variants in the DNA-binding domain have a more severe neurodevelopmental phenotype, including greater prevalence of seizures, more severe language/speech delays (e.g., nonverbal), and more severe motor abnormalities (e.g., inability to walk independently) [Chen et al 2016, Rech et al 2020]. The increased clinical severity could result from a dominant-negative effect [Chen et al 2016, Rech et al 2020].

In addition, individuals with heterozygous whole-gene deletions and other variants causing functional haploinsufficiency have a milder phenotype than those with heterozygous missense variants in the DNA-binding domain [Chen et al 2016, Rech et al 2020].

Nomenclature

The title of this *GeneReview*, *NR2F1*-related neurodevelopmental disorder, is based on the dyadic naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

Prevalence

NR2F1-NDD appears to be rare, with an estimated prevalence from 1:100,000 to 1:250,000 people worldwide [Bertacchi et al 2022, Gillentine et al 2022]. To date, 92 individuals with pathogenic variants in *NR2F1* have been described [Bertacchi et al 2022].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *NR2F1*.

Contiguous gene deletions. Deletions of variable size involving *NR2F1* and contiguous genes have been reported in association with intellectual impairment, developmental delay, dysmorphism, ophthalmologic findings, and hypotonia [Al-Kateb et al 2013, Bosch et al 2014, Chen et al 2016]. Large deletions that include contiguous genes may lead to a more complex clinical picture with additional congenital abnormalities, such as periventricular nodular heterotopia and deafness [Bertacchi et al 2022].

Differential Diagnosis

Table 3. Disorders with Ophthalmologic Features in the Differential Diagnosis of *NR2F1*-Related Neurodevelopmental Disorder

Gene	Differential Disorder	MOI	Key Overlapping Feature(s)	Distinguishing Features
ADNP	*ADNP*-related disorder	AD	Hypotonia; severe DD; mild-to-severe ID; seizures; visual impairment (hypermetropia, strabismus, CVI); behavioral findings; autistic features; feeding issues	In *ADNP*-related disorder: characteristic facial features; hand & foot abnormalities; cardiac, urinary tract, & endocrine abnormalities
NGLY1	*NGLY1*-related congenital disorder of deglycosylation (CDDG)	AR	DD/ID; hypolacrima, alacrima; seizures	In *NGLY1*-related CDDG: hyperkinetic mvmts; ↑ liver transaminases
OPA1	Optic atrophy type 1 (OPA1) (OMIM 165500)	AD	Visual impairment; optic atrophy; visual field defects	In OPA1: progressive loss of vision from early childhood w/optic atrophy
WFS1	*WFS1* spectrum disorder	AR	Visual impairment; optic atrophy; visual field defects; sensorineural hearing impairment	In *WFS1* spectrum disorder: progressive loss of vision from early childhood w/optic atrophy; childhood-onset diabetes mellitus; other endocrine abnormalities; diabetes insipidus; progressive neurologic deficits

AD = autosomal dominant; AR = autosomal recessive; CVI = cerebral visual impairment; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance

Management

No clinical practice guidelines for *NR2F1*-related neurodevelopmental disorder (*NR2F1*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *NR2F1*-NDD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *NR2F1*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Ophthalmologic / Vision impairment	Ophthalmologic eval	• To assess for ↓ visual acuity, refractive errors, & abnormal ocular movement (incl strabismus & nystagmus) • Eval for optic nerve abnormalities (optic atrophy & optic nerve hypoplasia) & CVI, which may require subspecialty referral
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• Infants may have problems w/poor latch/suck. • Older children may have trouble chewing & swallowing, incl mouth overstuffing &/or food pocketing. • To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in those w/dysphagia &/or aspiration risk.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Speech delay	By speech-language pathologist	
Psychiatric/ Behavioral	Mental health eval	• Persons age >12 mos: screen for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD. • Use of ADI®-R & ADOS®
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Hearing	Audiologic eval	Assess for hearing loss.
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *NR2F1*-NDD 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.

ADHD = attention-deficit/hyperactivity disorder; ADI®-R = Autism Diagnostic Interview–Revised; ADL = activities of daily living; ADOS® = Autism Diagnostic Observation Schedule; ASD = autism spectrum disorder; CVI = cerebral visual impairment; MOI = mode of inheritance; *NR2F1*-NDD = *NR2F1*-related neurodevelopmental disorder; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *NR2F1*-NDD.

Supportive treatment typically relies on multidisciplinary specialists in the fields of neurology, speech-language pathology, ophthalmology (including low-vision services), gastroenterology, nutrition, occupational therapy, physical therapy, audiology, clinical genetics, and genetic counseling (see Table 5).

Table 5. Treatment of Manifestations in Individuals with *NR2F1*-Related Neurodevelopmental Disorder

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
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]
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Ophthalmologic involvement	Per 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
Cerebral visual impairment	Visual therapy focused on CVI	Early intervention program to stimulate visual development
Hearing	Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district
Bowel dysfunction	Monitor for constipation.	Stool softeners, prokinetics, osmotic agents, or laxatives as needed
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; CVI = cerebral visual impairment; 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.

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:

- 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.

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, 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

See Table 6 for recommendations to monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations.

Table 6. Recommended Surveillance for Individuals with *NR2F1*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At time of diagnosis, then based on recommendation by treating physician
Gastrointestinal	Monitor for constipation.	At regular well-child checks

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Neurologic	Monitor those w/seizures as clinically indicated.	As recommended by treating physician
	Assess for new manifestations incl seizures, changes in tone, mvmt disorders.	Annually
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, ADHD, ASD, & aggressive or self-injurious behavior	At time of diagnosis, then based on recommendation by treating physician
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Ophthalmologic involvement	• Ophthalmologic assessment to evaluate visual function • Low-vision services to assess changes in visual acuity & personal needs	As recommended by treating physician
Hearing	Audiologic eval	Every other year
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).	Annually

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; 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

NR2F1-related neurodevelopmental disorder (*NR2F1*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Note: Vertical transmission of a contiguous gene deletion encompassing *NR2F1* and some recurrences within a family have been reported [Chen et al 2016, Bertacchi et al 2022].

Risk to Family Members

Parents of a proband

- All probands reported to date with an intragenic *NR2F1* pathogenic variant whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo* pathogenic variant.

- 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.

    * A parent with somatic and germline mosaicism for an *NR2F1* 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 *NR2F1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *NR2F1* 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 *NR2F1*-related NDD has a 50% chance of inheriting the *NR2F1* pathogenic variant.

Other family members. Given that most probands with *NR2F1*-related NDD reported to date have the disorder as a result of a *de novo NR2F1* pathogenic variant, the risk to other family members is presumed to be low.

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

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo NR2F1* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal and preimplantation genetic testing may be considered.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most centers 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.

- **NR2F1 Foundation**

Phone: 559-549-5608
Email: info@nr2f1.org
www.nr2f1.org

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **MedlinePlus**
  Intellectual Disability

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. NR2F1-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
NR2F1	5q15	COUP transcription factor 1	NR2F1 database	NR2F1	NR2F1

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 NR2F1-Related Neurodevelopmental Disorder (View All in OMIM)

132890	NUCLEAR RECEPTOR SUBFAMILY 2, GROUP F, MEMBER 1; NR2F1
615722	BOSCH-BOONSTRA-SCHAAF OPTIC ATROPHY SYNDROME; BBSOAS

Molecular Pathogenesis

NR2F1 encodes a highly conserved orphan nuclear receptor that is important for the development of the visual and nervous systems [Bosch et al 2014, Jurkute et al 2021]. Acting as a transcriptional regulator, it binds to the DNA as a homodimer and can activate or repress gene expression [Bertacchi et al 2019]. It contains a DNA-binding domain and a ligand-binding domain. Pathogenic variants in the DNA-binding domain appear to cause a more severe phenotype as a result of a dominant-negative effect [Chen et al 2016].

Mechanism of disease causation. Haploinsufficiency due to either gene deletion or loss-of-function variants. Single-nucleotide variants in the DNA-binding domain may cause a dominant-negative effect.

Chapter Notes

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- 8 December 2022 (bp) Review posted live
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References

Literature Cited

Al-Kateb H, Shimony JS, Vineyard M, Manwaring L, Kulkarni S, Shinawi M. NR2F1 haploinsufficiency is associated with optic atrophy, dysmorphism and global developmental delay. Am J Med Genet A. 2013;161A:377-81. PubMed PMID: 23300014.

Bertacchi M, Parisot J, Studer M. The pleiotropic transcriptional regulator COUP-TFI plays multiple roles in neural development and disease. Brain Res. 2019;1705:75-94. PubMed PMID: 29709504.

Bertacchi M, Tocco C, Schaaf CP, Studer M. Pathophysiological heterogeneity of the BBSOA neurodevelopmental syndrome. Cells. 2022;11:1260. PubMed PMID: 35455940.

Biesecker LG, Adam MP, Alkuraya FS, Amemiya AR, Bamshad MJ, Beck AE, Bennett JT, Bird LM, Carey JC, Chung B, Clark RD, Cox TC, Curry C, Dinulos MBP, Dobyns WB, Giampietro PF, Girisha KM, Glass IA, Graham JM Jr, Gripp KW, Haldeman-Englert CR, Hall BD, Innes AM, Kalish JM, Keppler-Noreuil KM, Kosaki K, Kozel BA, Mirzaa GM, Mulvihill JJ, Nowaczyk MJM, Pagon RA, Retterer K, Rope AF, Sanchez-Lara PA, Seaver LH, Shieh JT, Slavotinek AM, Sobering AK, Stevens CA, Stevenson DA, Tan TY, Tan WH, Tsai AC, Weaver DD, Williams MS, Zackai E, Zarate YA. A dyadic approach to the delineation of diagnostic entities in clinical genomics. Am J Hum Genet. 2021;108:8-15. PubMed PMID: 33417889.

Bosch DG, Boonstra FN, Gonzaga-Jauregui C, Xu M, de Ligt J, Jhangiani S, Wiszniewski W, Muzny DM, Yntema HG, Pfundt R, Vissers LE, Spruijt L, Blokland EA, Chen CA, Lewis RA, Tsai SY, Gibbs RA, Tsai MJ, Lupski JR, Zoghbi HY, Cremers FP, de Vries BB, Schaaf CP, et al. NR2F1 mutations cause optic atrophy with intellectual disability. Am J Hum Genet. 2014;94:303-9. PubMed PMID: 24462372.

Chen CA, Bosch DG, Cho MT, Rosenfeld JA, Shinawi M, Lewis RA, Mann J, Jayakar P, Payne K, Walsh L, Moss T, Schreiber A, Schoonveld C, Monaghan KG, Elmslie F, Douglas G, Boonstra FN, Millan F, Cremers FP, McKnight D, Richard G, Juusola J, Kendall F, Ramsey K, Anyane-Yeboa K, Malkin E, Chung WK, Niyazov D, Pascual JM, Walkiewicz M, Veluchamy V, Li C, Hisama FM, de Vries BB, Schaaf C. The expanding clinical phenotype of Bosch-Boonstra-Schaaf optic atrophy syndrome: 20 new cases and possible genotype-phenotype correlations. Genet Med. 2016;18:1143-1150. PubMed PMID: 26986877.

Gillentine MA, Wang T, Eichler EE. Estimating the prevalence of de novo monogenic neurodevelopmental disorders from large cohort studies. Biomedicines. 2022;10:2865. PubMed PMID: 36359385.

Hino-Fukuyo N, Kikuchi A, Yokoyama H, Iinuma K, Hirose M, Haginoya K, Niihori T, Nakayama K, Aoki Y, Kure S. Long-term outcome of a 26-year-old woman with West syndrome and an nuclear receptor subfamily 2 group F member 1 gene (NR2F1) mutation. Seizure. 2017;50:144-6. PubMed PMID: 28654857.

Jurkute N, Bertacchi M, Arno G, Tocco C, Kim US, Kruszewski AM, Avery RA, Bedoukian EC, Han J, Ahn SJ, Pontikos N, Acheson J, Davagnanam I, Bowman R, Kaliakatsos M, Gardham A, Wakeling E, Oluonye N, Reddy MA, Clark E, Rosser E, Amati-Bonneau P, Charif M, Lenaers G, Meunier I, Defoort S, Vincent-Delorme C, Robson AG, Holder GE, Jeanjean L, Martinez-Monseny A, Vidal-Santacana M, Dominici C, Gaggioli C, Giordano N, Caleo M, Liu GT, Webster AR, Studer M, Yu-Wai-Man P, et al. Pathogenic NR2F1 variants cause a developmental ocular phenotype recapitulated in a mutant mouse model. Brain Commun. 2021;3:fcab162. PubMed PMID: 34466801.

Kaiwar C, Zimmermann MT, Ferber MJ, Niu Z, Urrutia RA, Klee EW, Babovic-Vuksanovic D. Novel NR2F1 variants likely disrupt DNA binding: molecular modeling in two cases, review of published cases, genotype-phenotype correlation, and phenotypic expansion of the Bosch-Boonstra-Schaaf optic atrophy syndrome. Cold Spring Harb Mol Case Stud. 2017;3:a002162. PubMed PMID: 28963436.

Mio C, Fogolari F, Pezzoli L, D'Elia AV, Iascone M, Damante G. Missense NR2F1 variant in monozygotic twins affected with the Bosch-Boonstra-Schaaf Optic Atrophy syndrome. Mol Genet Genomic Med. 2020;8:e1278. PubMed PMID: 32412696.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126-33. PubMed PMID: 26656846.

Rech ME, McCarthy JM, Chen CA, Edmond JC, Shah VS, Bosch DG, Berry GT, Williams L, Madan-Khetarpal S, Niyazov D, Shaw-Smith C, Kovar EM, Lupo PJ, Schaaf CP. Phenotypic expansion of Bosch-Boonstra-Schaaf optic atrophy syndrome and further evidence for genotype-phenotype correlations. Am J Med Genet A. 2020;182:1426-37. PubMed PMID: 32275123.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

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