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IRF2BPL-Related Disorder

Synonyms: NEDAMSS (Neurodevelopmental Disorder With Regression, Abnormal Movements, Loss of Speech, and Seizures); *IRF2BPL* Mutation Syndrome

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Summary

Clinical characteristics

IRF2BPL-related disorder is characterized by mild-to-profound developmental delay (with regression in many individuals), intellectual disability, seizures (generalized tonic-clonic, myoclonic, absence, focal tonic-clonic, complex partial, infantile spasms, and/or atonic seizures), movement disorder (ataxia, dystonia, tremor, and parkinsonism), spasticity, and neurobehavioral/psychiatric manifestations (autism spectrum disorder, autistic features, anxiety, depression, and psychosis). Feeding issues, gastrointestinal dysmotility, and ophthalmologic manifestations are also reported. Brain MRI can show focal or diffuse cortical and/or subcortical atrophy, cerebellar atrophy (particularly of the vermis), brainstem atrophy, and corpus callosum abnormalities including thinning/atrophy or thickening. Onset is highly variable and can be in the first year of life through the sixth decade. In some individuals the course of the disorder is progressive or debilitating.

Diagnosis/testing

The diagnosis of *IRF2BPL*-related disorder is established in a proband with characteristic clinical findings and a heterozygous pathogenic variant in *IRF2BPL* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental and educational support; standard treatment of epilepsy and movement disorder by an experienced neurologist; standard treatment of spasticity per orthopedist, neurologist, physical medicine and rehabilitation specialist, physical therapist, and occupational therapist; feeding support for poor weight gain; standard treatment for gastric dysmotility; treatment of vision deficits per ophthalmologist

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with treatment of more complex findings per ophthalmic subspecialist; treatment of pubertal delay per endocrinologist; family and social work support.

Surveillance: At each visit, assess developmental progress, educational needs, cognitive function, seizures, movement disorder, spasticity, contractures, behavioral issues, growth, nutritional status, gastrointestinal dysmotility, and family needs; physical medicine and/or occupational and physical therapy assessment for mobility and self-help skills at each visit; dilated eye exam per treating ophthalmologist; assessment of pubertal development at each visit through adolescence.

Genetic counseling

IRF2BPL-related disorder is inherited in an autosomal dominant manner. The majority of individuals diagnosed with *IRF2BPL*-related disorder have the disorder as the result of a *de novo* pathogenic variant; approximately 9% of individuals reported to date have an affected parent. Each child of an individual with *IRF2BPL*-related disorder has a 50% chance of inheriting the *IRF2BPL* pathogenic variant. Once the *IRF2BPL* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

IRF2BPL-related disorder **should be considered** in probands with the following clinical and imaging findings and family history.

Clinical findings in individuals presenting at age <18 years

- Mild-to-profound developmental delay (Developmental regression has been described in 50% of individuals.)
- Intellectual disability
- Epilepsy (generalized tonic-clonic, myoclonic [with photoparoxsymal response], absence, focal tonic-clonic, complex partial, infantile spasms, and/or atonic seizures)
- Movement disorders (ataxia, dystonia, tremor, and parkinsonism; less commonly, athetosis, chorea, and myoclonus)
- Neurobehavioral/psychiatric manifestations (autism spectrum disorder, autistic features, anxiety, depression, and psychosis)
- Ophthalmologic manifestations (dysconjugate gaze, ophthalmoplegia, gaze palsy, slow saccades; less commonly, keratoconus, cataracts, and retinal pigmentary anomalies)

Clinical findings in individuals presenting in adolescence and adulthood

- Epilepsy (generalized tonic-clonic, myoclonic, absence, and focal tonic-clonic seizures)
- Movement disorders (dystonia with or without dysarthria, ataxia, choreoathetosis)
- Cognitive decline
- Anarthria, aphonia
- Psychiatric manifestations (recurrent psychosis)
- Ophthalmologic manifestations (macular degeneration, gaze palsy, and abnormal saccades)

Note: Presentation can be as late as the sixth decade.

Imaging findings on brain MRI

- Focal or diffuse cortical and/or subcortical atrophy
- Cerebellar atrophy (particularly of the vermis)

- Brainstem atrophy
- Corpus callosum abnormalities (thinning/atrophy, thickening)

Note: Brain MRI can be normal, particularly in early childhood.

Family history. Because *IRF2BPL*-related disorder is often 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 *IRF2BPL*-related disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *IRF2BPL* 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 *IRF2BPL* 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 may begin with exome sequencing / genome sequencing [Manickam et al 2021, van der Sanden et al 2023]. Other options include the use of chromosomal microarray analysis (CMA) or a multigene panel. Note: In the absence of a family history of *IRF2BPL*-related disorder, single-gene testing (sequence analysis of *IRF2BPL*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability / epilepsy / movement disorders multigene panel** that includes *IRF2BPL* 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*. Of note, given the rarity of *IRF2BPL*-related disorder, some panels for intellectual disability may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an intellectual disability multigene panel, with the additional advantage that exome sequencing includes genes recently identified as causing intellectual disability, whereas some multigene panels may not. To date, the majority of *IRF2BPL* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing. **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 *IRF2BPL*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
IRF2BPL	Sequence analysis [3]	<100% [4]
	Gene-targeted deletion/duplication analysis [5]	Rare [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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. 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. To date, a large deletion including *IRF2BPL* has been reported in two individuals with features consistent with *IRF2BPL*-related disorder including autistic behavior, cognitive impairment, and seizures or abnormal EEG. However, these deletions included additional genes beyond *IRF2BPL*, so the specific contribution of the loss of *IRF2BPL* to these phenotypes is uncertain [Vaisfeld et al 2021].

Clinical Characteristics

Clinical Description

IRF2BPL-related disorder is characterized by mild-to-profound developmental delay with or without regression, intellectual disability, seizures, movement disorder (ataxia, dystonia, tremor, parkinsonism), spasticity, and autism spectrum disorder. Feeding issues, gastrointestinal dysmotility, and ophthalmologic manifestations are also reported. Onset is highly variable and can be in the first year of life through the sixth decade. To date, more than 60 individuals have been identified with a pathogenic variant in *IRF2BPL*. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of *IRF2BPL*-Related Disorder

Feature	% of Persons w/Feature [1]	Comment
Developmental delay	87%	Mild to profound, w/developmental regression in 50%
Intellectual disability	53%	
Seizures	43%	Generalized tonic-clonic (50%), myoclonic (42%), absence (33%), focal tonic-clonic (16%), & infantile spasms
Movement disorder	40%	Ataxia (30%), dystonia (27%), tremor (13%), parkinsonism (13%); athetosis, chorea, & myoclonus are rare.
Autism spectrum disorder (ASD)	33%	Autistic features w/o diagnosis of ASD are also reported.
Feeding / gastrointestinal issues	33%	Swallowing difficulties, gastrointestinal dysmotility, & feeding intolerance
Abnormal brain MRI	23%	Focal or diffuse cortical &/or subcortical atrophy, cerebellar & brainstem atrophy, & thinning/atrophy of corpus callosum

Table 2. continued from previous page.

Feature	% of Persons w/Feature [1]	Comment
Joint contractures	10%	

1. Percentages are from a completed but unpublished clinical study that collected self-reported features in 32 individuals with *IRF2BPL*-related disorder [LDM Pena, unpublished data; see NCT03892798]. Percentages reported in Table 2 may differ from those reported in the literature and included in Clinical Description.

Developmental delay occurs in most individuals and is mild to profound. There is no information regarding specific developmental domains that could be more severely affected. Hypotonia is common and contributes to gross motor delays.

Some individuals have progressive loss of gross motor, fine motor, and self-help skills. Early signs of developmental regression can include dysarthria, dysphagia, and dysconjugate gaze. Lack of balance and coordination with frequent falls is also described. Increased difficulty with walking and/or sitting is reported in 38% of individuals, increased falls in 25%, progressive articulation difficulties in 19%, and loss of speech in 6%. Regression has been described as early as age eight months and can occur throughout early adulthood.

Intellectual disability. Cognitive assessment may be hindered by the lack of communication skills. Cognitive decline has been inferred in several individuals but is difficult to ascertain due to lack of systematic evaluations [Heide et al 2023, Horovitz et al 2023].

Epilepsy. Seizures are common and are reported by 43% of affected individuals and/or families [LDM Pena, personal communication]. The types of seizures reported include generalized tonic-clonic, myoclonic, absence, focal tonic-clonic, complex partial, infantile spasms, and atonic seizures. Approximately 40%-50% of those with epilepsy have multiple seizure types. Progressive myoclonic epilepsy phenotypes have been described [Costa et al 2023]. Seizures can arise throughout the life span, including in adulthood [Costa et al 2023, Gardella et al 2023].

Movement disorders can include ataxia, dystonia, tremor, and parkinsonism. Onset can occur as late as young adulthood [Ganos et al 2014]. Other less frequently described movement disorders include athetosis, chorea, and myoclonus [Shelkowitz et al 2019].

Additional cerebellar signs include eye movement abnormalities and dysdiadochokinesia.

Spasticity. Some individuals develop increased muscle tone, particularly of the lower extremities. Hyperreflexia and joint contractures have also been described.

Neurobehavioral/psychiatric manifestations. Some individuals are diagnosed with autism spectrum disorder or have autistic features without a diagnosis of autism. Attention-deficit/hyperactivity disorder, anxiety, depression, and psychosis have also been reported [Spagnoli et al 2020, Sainio et al 2022].

Feeding and gastrointestinal manifestations include swallowing difficulties, gastrointestinal dysmotility, and feeding intolerance.

Ophthalmologic involvement. Dysconjugate gaze, ophthalmoplegia, gaze palsy, and slow saccades have been reported. Keratoconus has rarely been described [Ganos et al 2019, Prilop et al 2020], as have cataracts [Prilop et al 2020], retinal pigmentary anomalies [Shelkowitz et al 2019], and macular degeneration in one individual [Marcogliese et al 2018].

Neuroimaging. Commonly reported brain imaging findings include focal or diffuse cortical and/or subcortical atrophy, cerebellar atrophy (particularly of the vermis), brainstem atrophy, and thinning/atrophy of the corpus callosum [Pisano et al 2022]. Less commonly, thickening of the corpus callosum has been observed. Other nonspecific findings include supratentorial T_2 hyperintensities. Some individuals with normal initial brain imaging demonstrate progressive atrophy with cerebral and/or cerebellar volume loss on subsequent imaging.

Brain imaging is reportedly normal in 30%-50% of individuals in published reports [Shelkowitz et al 2019, Pisano et al 2022, Chen et al 2024].

Growth. No consistent abnormality of growth is reported.

Other. *IRF2BPL* pathogenic variants (a missense variant and an in-frame deletion of one amino acid) have been reported in individuals with delayed puberty from two families [Mancini et al 2019]. Further studies are needed to assess the potential involvement of *IRF2BPL* in delayed puberty.

Adult onset. Although *IRF2BPL*-related disorder does not show clearly defined early- vs late-onset presentations, several individuals with adult onset have been described. The phenotype in those with later onset includes ataxia, dystonia, and dysarthria [Ganos et al 2014, Ganos et al 2019, Prilop et al 2020, Antonelli et al 2022, Sainio et al 2022, Horovitz et al 2023]. In general, the adults who have epilepsy developed seizures earlier in life.

Prognosis. Several adults with *IRF2BPL*-related disorder have been reported. Data on progression of behavior abnormalities or neurologic findings are limited. In some individuals, the course of the disorder is progressive or debilitating, and care may require mechanical ventilation due to respiratory insufficiency, gastrostomy tube feeding, supportive equipment to maintain independence, and therapies to maintain mobility and/or prevent disuse sequelae.

Genotype-Phenotype Correlations

Pathogenic variants (including missense and nonsense) located downstream of the nuclear localization signal may be associated with a less severe phenotype without a progressive loss of milestones or movement disorder. However, the precise genomic location for this genotype-phenotype correlation is currently unknown.

To date, three variants have been associated with a concordant phenotype of NEDAMSS (neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures) reported in at least three different families (NM_024496.4): c.496G>T (p.Glu166Ter), c.519C>G (p.Tyr173Ter), and c.562C>T (p.Arg188Ter) [Marcogliese et al 2018, Tran Mau-Them et al 2019, Hong et al 2020, Qian et al 2021, Costa et al 2023, Yang et al 2023].

Penetrance

Penetrance for *IRF2BPL*-related disorder appears to be high; however, substantial intrafamilial and interfamilial variability in age of onset and clinical features has been observed. Developmental delay and intellectual disability were reported in a female with an *IRF2BPL* pathogenic variant inherited from her apparently unaffected mother who died at age 45 years of an unrelated cause [Heide et al 2023]. Possible reduced penetrance has been observed in several additional families [LDM Pena & P Marcogliese, personal observations].

Prevalence

Prevalence is unknown. To date, more than 60 affected individuals have been described.

Genetically Related (Allelic) Disorders

IRF2BPL variants (a missense variant and an in-frame deletion of one amino acid) have been reported in individuals with delayed puberty from two families [Mancini et al 2019]. Further studies are needed to assess the potential involvement of *IRF2BPL* in delayed puberty.

Differential Diagnosis

Because *IRF2BPL*-related disorder is clinically indistinguishable from many other inherited disorders with similar neurologic findings, diagnosing this condition on clinical grounds only without molecular genetic testing is not feasible. All disorders with neurodevelopmental features and/or ataxia without other distinctive findings should be considered in the differential diagnosis. See:

- OMIM Phenotypic Series:
  - Autosomal dominant intellectual developmental disorder
  - Autosomal recessive intellectual developmental disorder
  - Nonsyndromic X-linked intellectual developmental disorder
  - Syndromic X-linked intellectual developmental disorder
  - Developmental and epileptic encephalopathy
- Hereditary Ataxia Overview

Selected disorders with a high degree of clinical overlap are listed in Table 3.

Table 3. Selected Disorders in the Differential Diagnosis of *IRF2BPL*-Related Disorder

Gene / Genetic Mechanism	Disorder	MOI	Key Features of Disorder	
			Overlapping w/*IRF2BPL*-related disorder	Distinguishing from *IRF2BPL*-related disorder
GRIK2	*GRIK2*-related NDD w/ impaired language & ataxia ± seizures (OMIM 619580)	AD	• Global DD • Speech impairment • Ataxia • Seizures	Hypomyelination in brain
MECP2	*MECP2* classic Rett syndrome (See *MECP2* Disorders.)	XL	• Regression • Ataxia • Seizures	• Short stature • Acquired microcephaly • Hand stereotypies
SARS1	*SARS1*-related NDD w/ microcephaly, ataxia, & seizures (OMIM 617709)	AR	• Global DD • Seizures • Ataxia	• Microcephaly • Hearing loss • Cardiomyopathy
ZNF142	*ZNF142*-related NDD w/ impaired speech & hyperkinetic movements (OMIM 618425)	AR	• Global DD • Movement disorder • Seizure • Speech impairment	Facial dysmorphism
Disruption of maternally imprinted *UBE3A*	Angelman syndrome	See footnote 1.	• Seizures • Ataxia • DD/ID	• Characteristic craniofacial features • Microcephaly • Unique behavior w/ apparent happy demeanor

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; NDD = neurodevelopmental disorder

1. The risk to sibs of a proband with Angelman syndrome depends on the genetic mechanism leading to the loss of *UBE3A* function (see Angelman Syndrome).

Management

No clinical practice guidelines for *IRF2BPL*-related disorder have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *IRF2BPL*-related disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. *IRF2BPL*-Related Disorder: 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 • For persons age >5 yrs: consider baseline neurocognitive eval
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern. Note: Abnormal EEG may precede clinical seizures. • Consider dedicated movement disorder eval.
Movement disorder / Spasticity / Contractures	Physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Dysarthria	Speech eval	Consider communication device or alternative mode of communication.
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl findings suggestive of ASD, ADHD, anxiety, depression, &/or psychosis
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/ dysphagia &/or aspiration risk.
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings (e.g., cataract, retinal dystrophy) that may require referral for subspecialty care &/or low vision services
Respiratory	Consider PFTs & spirometry.	To assess respiratory complications in those w/progressive neuromuscular compromise
Endocrine	Assess growth velocity & pubertal development.	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *IRF2BPL*-related disorder to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine 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; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PFT = pulmonary function test; PT = physical therapy

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. *IRF2BPL*-Related Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	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]
Movement disorder	Standardized treatment by experienced neurologist	
Spasticity	Treatment per orthopedist / neurologist / physical medicine & rehab specialist / PT & OT, incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Poor weight gain	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Gastric dysmotility	Standard treatment per gastroenterologist	
Eyes	• Treatment per ophthalmologist for vision deficits • Treatment per ophthalmic subspecialists for more complex findings (e.g., cataract, retinal changes)	
Pubertal delay	Treatment per endocrinologist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapist; PT = physical therapist
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 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 from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, 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.

Neurobehavioral/Psychiatric 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

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. *IRF2BPL*-Related Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Neurologic	• Assess cognitive function. • Assess for new or increasing seizures. • Assess for new manifestations such as movement disorders &/or spasticity.	
Musculoskeletal	• Physical medicine, OT/PT assessment of mobility, self-help skills • Assess for contractures.	
Neurobehavioral/ Psychiatric	Behavioral assessment for ASD, ADHD, anxiety, depression, &/or psychosis	
Feeding/ Gastrointestinal	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake • Assessment for gastrointestinal dysmotility	
Ophthalmologic involvement	Dilated eye exam	Per treating ophthalmologist(s)
Respiratory	Consider PFTs & spirometry to assess respiratory complications in those w/progressive neuromuscular compromise.	As needed
Endocrine	Assess pubertal development	At each visit throughout adolescence
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PFT = pulmonary function test; 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

IRF2BPL-related disorder is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The majority of individuals diagnosed with *IRF2BPL*-related disorder have the disorder as the result of a *de novo IRF2BPL* pathogenic variant.
- Approximately 9% of individuals with *IRF2BPL*-related disorder reported to date have an affected parent.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- 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 gonadal (or somatic and gonadal) 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 (gonadal) cells only.

      * A parent with somatic and gonadal mosaicism for an *IRF2BPL* pathogenic variant may be mildly/minimally affected.
- The family history of some individuals diagnosed with *IRF2BPL*-related disorder may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- While penetrance for *IRF2BPL*-related disorder appears to be high, substantial variability in age of onset and clinical features has been reported among affected individuals within the same family (see Penetrance).
- If the *IRF2BPL* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental gonadal mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown, sibs are still presumed to be at increased risk for *IRF2BPL*-related disorder because of the possibility of reduced penetrance or late onset in a heterozygous parent and the possibility of parental gonadal mosaicism.

Offspring of a proband. Each child of an individual with *IRF2BPL*-related disorder has a 50% chance of inheriting the *IRF2BPL* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *IRF2BPL* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *IRF2BPL* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

No specific resources for *IRF2BPL*-Related Disorder have been identified by *GeneReviews* staff.

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. IRF2BPL-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar

Table A. continued from previous page.

IRF2BPL	14q24.3	Probable E3 ubiquitin-protein ligase IRF2BPL	IRF2BPL	IRF2BPL

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 IRF2BPL-Related Disorder (View All in OMIM)

611720	INTERFERON REGULATORY FACTOR 2-BINDING PROTEIN LIKE; IRF2BPL
618088	NEURODEVELOPMENTAL DISORDER WITH REGRESSION, ABNORMAL MOVEMENTS, LOSS OF SPEECH, AND SEIZURES; NEDAMSS

Molecular Pathogenesis

IRF2BPL is an intronless gene that encodes probable E3 ubiquitin-protein ligase IRF2BPL (IRF2BPL), a transcriptional regulator that may also have E3 ubiquitin ligase activity [Higashimori et al 2018]. It has been shown to bind the promoter of the gonadotropin-releasing hormone [Mancini et al 2019]. IRF2BPL binds to casein kinase I isoform alpha, a Wnt/beta-catenin antagonist. Loss of IRF2BPL in *Drosophila*, zebra fish, and cells of individuals with *IRF2BPL*-related disorder leads to increased proto-oncogene Wnt-1 (encoded by *WNT1*) transcription and Wnt/beta-catenin signaling. Some neurobehavioral phenotypes in *Drosophila* and zebra fish can be ameliorated by pharmacologic or genetic Wnt/beta-catenin inhibition [Marcogliese et al 2022]. In cancer cell lines, IRF2BPL may ubiquitinate beta-catenin directly, leading to its degradation, but to date there has yet to be a link between IRF2BPL activity and oncogenesis [Higashimori et al 2018]. Cells from affected individuals display abnormal mitochondrial respiration and morphology that can be rescued by clearing damaged mitochondria pharmacologically [Sinha Ray et al 2022].

To date, all seven pathogenic frameshift or nonsense variants (six lead to truncation prior to the nuclear localization signal [NLS], and one leads to truncation after the NLS) in *IRF2BPL* that have been assessed biochemically escape nonsense-mediated decay and lead to the production of a truncated protein [Marcogliese et al 2018, Tran Mau-Them et al 2019, Sinha Ray et al 2022]. These truncated alleles result in loss of IRF2BPL function [Marcogliese et al 2018, Marcogliese et al 2022]. However, truncated IRF2BPL has also been shown to have dominant-negative activity, sequestering full-length IRF2BPL from the nucleus to the cytoplasm [Sinha Ray et al 2022].

Although no clear genotype-phenotype correlation has been confirmed, pathogenic variants causing truncation proximal to the polyglutamine tract (amino acids 103-127) may be associated with increased severity, and pathogenic variants causing truncation downstream of the NLS (amino acids 542-545) display more variability with milder presentation and/or later onset.

Mechanism of disease causation. Haploinsufficiency and/or dominant-negative effect

***IRF2BPL*-specific laboratory technical considerations.** *IRF2BPL* has a glutamine-rich domain, a polyalanine repeat, and is guanine/cytosine rich in general, which may cause technical difficulties with sequence analysis. The authors recommend consideration of pathogenic variant confirmation, particularly variants in these domains, by an orthogonal method.

Chapter Notes

Author Notes

Contact Dr Paul Marcogliese (paul.marcogliese@umanitoba.ca) to inquire about review of *IRF2BPL* variants of uncertain significance.

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