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EBF3 Neurodevelopmental Disorder

Synonym: Hypotonia, Ataxia, and Delayed Development Syndrome (HADDS)

Dhanya Lakshmi Narayanan, MD, DM,[1] Kerstin Kutsche, PhD,[2] and Katta M Girisha, MD, DM[1]

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Summary

Clinical characteristics

EBF3 neurodevelopmental disorder (*EBF3*-NDD) is associated with developmental delay (DD) / intellectual disability (ID), speech delay, gait or truncal ataxia, hypotonia, behavioral problems, and facial dysmorphism. Variability between individuals with *EBF3*-NDD is significant. Although all affected children have DD noted in early infancy, intellect generally ranges from mild to severe ID, with two individuals functioning in the low normal range. Less common issues can include genitourinary abnormalities and gastrointestinal and/or musculoskeletal involvement. To date, 42 symptomatic individuals from 39 families have been reported.

Diagnosis/testing

The diagnosis of *EBF3*-NDD is established in a proband with suggestive findings and a heterozygous pathogenic variant in *EBF3* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental delay / intellectual disability, speech delay, hypotonia and ataxia, behavioral issues, genitourinary abnormalities, gastrointestinal involvement, and musculoskeletal involvement are managed as per standard care.

Surveillance: Follow up of manifestations at each clinic visit.

Genetic counseling

EBF3-NDD is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. If a parent is known to have the *EBF3* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. If the *EBF3* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population

Author Affiliations: 1 Department of Medical Genetics Kasturba Medical College Manipal, India; Email: dhanya.lakshmi@manipal.edu; Email: girish.katta@manipal.edu. 2 Institute of Human Genetics University Medical Center Hamburg-Eppendorf Hamburg, Germany; Email: kkutsche@uke.de.

because of the possibility of parental germline mosaicism. Once the *EBF3* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *EBF3* neurodevelopmental disorder have been published.

Suggestive Findings

EBF3 neurodevelopmental disorder (*EBF3*-NDD) **should be considered** in individuals with the following clinical and brain MRI findings and family history.

Clinical findings include developmental delay (DD) or intellectual disability (ID) AND any of the following features presenting in infancy or childhood:

- Microcephaly
- Generalized hypotonia
- Feeding difficulties
- Genitourinary abnormalities such as micropenis, cryptorchidism, vesicoureteral reflux, renal anomalies
- Strabismus
- Speech delay, mainly expressive speech delay, dysarthria
- Ataxia
- High pain threshold or decreased pain sensitivity
- Behavioral anomalies including stereotypic movements (e.g., rotating movements, chewing on clothes, head retropulsion), perseverative social behavior, short attention span
- Facial dysmorphism. See Chao et al [2017] (full text; see Figure 1), Harms et al [2017] (full text; see Figure 1), Lopes et al [2017] (full text; see Figure 1), Sleven et al [2017] (full text; see Supplementary figure S3), Tanaka et al [2017] (full text; see Figure 2).

Brain MRI findings. The following MRI findings were observed in a smaller number of affected individuals:

- Cerebellar vermis hypoplasia (5 individuals) [Chao et al 2017, Harms et al 2017, Sleven et al 2017, Tanaka et al 2017]
- Cerebellar atrophy or hypoplasia (1 individual) [Ignatius et al 2020]
- Small inferior posterior cerebellar lobes and hypoplasia of the posterior vermis with mild prominence of the ventricles and sulci (1) [Chao et al 2017]
- Abnormal configuration of cerebellar folia arranged in radial shape (1) [D'Arrigo et al 2020]

Family history. Because *EBF3*-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 *EBF3* neurodevelopmental disorder (*EBF3*-NDD) **is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *EBF3* identified by molecular genetic testing (see Table 1).

Note: Identification of a heterozygous *EBF3* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular Genetic Testing

Testing in a child with developmental delay or an older individual with intellectual disability typically begins with **chromosomal microarray analysis** (CMA). If CMA is not diagnostic, the next step is typically either a

multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *EBF3*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

An intellectual disability (ID) multigene panel that includes *EBF3* 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 *EBF3*-NDD, some panels for intellectual disability may not include this gene. In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID whereas some multigene panels may not. **Genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in *EBF3* Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Families with a Pathogenic Variant [2, 3] Detectable by Method
EBF3	Sequence analysis [4]	39/39 [5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. See Genetically Related Disorders for information (not included in these calculations) on additional individuals with either a contiguous gene deletion [Lopes et al 2017, Ignatius et al 2020, Turro et al 2020] or a balanced 10;22 translocation disrupting *EBF3* [Murcia Pienkowski et al 2019].
4. 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.
5. Iossifov et al [2014], Blackburn et al [2017], Chao et al [2017], Eldomery et al [2017], Harms et al [2017], Sleven et al [2017], Tanaka et al [2017], Monies et al [2019], Beecroft et al [2020], D'Arrigo et al [2020], Harkness et al [2020], Hildebrand et al [2020], Husson et al [2020], Ignatius et al [2020] (Patients 8, 9, and 10)
6. 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.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

EBF3 neurodevelopmental disorder (*EBF3*-NDD) is associated with developmental delay, intellectual disability, speech delay, gait or truncal ataxia, hypotonia, behavioral problems, and facial dysmorphism. Less common

issues can include genitourinary abnormalities, gastrointestinal involvement, and/or musculoskeletal involvement.

To date, 42 symptomatic individuals from 39 families have been reported [Iossifov et al 2014, Blackburn et al 2017, Chao et al 2017, Eldomery et al 2017, Harms et al 2017, Sleven et al 2017, Tanaka et al 2017, Monies et al 2019, Beecroft et al 2020, D'Arrigo et al 2020, Harkness et al 2020, Hildebrand et al 2020, Husson et al 2020, Ignatius et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports (when information is available on these features).

Developmental delay (DD) and intellectual disability (ID). All affected individuals have developmental delay noted in early infancy. The severity of intellectual disability is highly variable (mild to severe). IQ is in low normal range for two individuals [Author, unpublished data]. Marked delay in speech (mostly in expressive speech) is common, though the severity of speech delay is also highly variable. Some individuals have articulation defects and dysarthria.

Other neurodevelopmental features. Hypotonia is generalized and present from early infancy. Gait ataxia or truncal ataxia is commonly observed. Frequent falls may be noted. Most affected individuals did not have seizures. Two individuals had febrile seizures [Harms et al 2017]. A single febrile seizure was reported in an additional individual [Sleven et al 2017].

Behavioral abnormalities. Short attention span and features of ADHD were seen in six individuals. Five individuals had decreased pain sensitivity or high tolerance to pain. Stereotypic behaviors were observed in two individuals. Affected individuals may have autistic features or pervasive behavioral abnormalities.

Genitourinary abnormalities include the following:

- Vesicoureteric reflux (4 individuals)
- Undescended testes (3)
- Bicornuate uterus (1 of 24 females)
- Neurogenic/atonic bladder (2 individuals)
- Renal dysplasia (1)
- Recurrent urinary tract infections

Gastrointestinal

- Gastroesophageal reflux disease (3 individuals)
- Dysphagia (3)
- Constipation (3)
- Cyclical vomiting with failure to thrive (1)

Musculoskeletal

- Syndactyly of second and third toe (2)
- Pectus excavatum (2)
- Bilateral talipes (2)
- Severe scoliosis in a mother and son that required corrective surgery (2)
- Scoliosis and severe hip and knee contractures (1)

Growth

- Short stature (3)
- Microcephaly (3)

Prognosis. It is unknown whether life span in *EBF3*-NDD is abnormal. One individual is alive at age 31 years, demonstrating that survival into adulthood is possible [Beecroft et al 2020].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

To date 42 individuals from 39 families with this disorder have been described (additionally, 2 mothers who are mosaic are asymptomatic). As it is a recently identified condition, exact prevalence is not known.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with a germline heterozygous pathogenic variant in *EBF3*.

Lopes et al [2017] described a female age 11 years with a *de novo* 600-kb deletion in 10q26.3 that included three genes: *MGMT*, *EBF3*, and *GLRX11*. She had intellectual disability, hypotonia, motor and speech delay, stereotypic movements, and aggressive behavior. She did not have ataxia. She had a triangular face, arched eyebrows, anteverted nares, bulbous nasal tip, small mouth with downturned corners, small low-set ears with prominent anti-helix, pointed chin, short neck, and prominent fetal pads in her fingers. Her EEG and brain MRI were normal [Lopes et al 2017].

Ignatius et al [2020] described an individual with a *de novo* 570-kb deletion in 10q26.3 (chr10: 131538728-132108832) and cerebellar ataxia. No additional phenotypic information was provided.

Turro et al [2020] described an individual with a 2.9-Mb deletion in 10q26.2-q26.3 (chr10: 129942146-132848717) that included *EBF3* and 15 additional genes. Neurodevelopmental delay was reported, but no additional phenotypic information was provided.

Partial deletion of the terminal portion of the q arm of chromosome 10 (chromosome 10q26 deletion syndrome; OMIM 609625) is characterized by developmental delay, intellectual disability, distinct facial features, urogenital abnormalities, and cardiac abnormalities. Depending on the breakpoints involved the phenotypic features of this condition may vary significantly. Four individuals have been previously described with ataxia, intellectual disability, and hyperemia of the hands and a distal 10q26.3 deletion which included *EBF3* [Lacaria et al 2017].

Differential Diagnosis

Because the phenotypic features associated with *EBF3* neurodevelopmental disorder are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Note: Hereditary ataxia syndromes can also be considered in children presenting with developmental delay or intellectual disability in combination with ataxia (see Hereditary Ataxia Overview). In a cohort of 50 children with ataxia, genetic alterations involving *EBF3* (including 1 multigene deletion) were identified in three children [Ignatius et al 2020].

Management

No clinical practice guidelines for *EBF3* neurodevelopmental disorder (*EBF3*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *EBF3*-NDD, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with *EBF3* Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Constitutional	Measure height, weight, head circumference.	Attention to possible feeding issues &/or poor weight gain
Neurologic	Neurologic eval	To incl brain MRI (if not performed at time of diagnosis) when there are specific neurologic findings of concern
Dysarthria	Speech & language eval	To determine need for speech & language therapy &/or alternate means of communication
Developmental delay	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	Persons age >12 mos: screen for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Musculoskeletal / Activities of daily living	Orthopedics / physical medicine & rehab / PT/OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Ataxia • Mobility, activities of daily living, & need for adaptive devices
Gastrointestinal	Gastroenterology	If indicated, assessment for GERD, dysphagia, constipation
Genitourinary	Kidney & urinary tract eval	• To assess for vesicoureteral reflux, cryptorchidism, neurogenic bladder, renal dysplasia • Ultrasound eval of kidney & urinary bladder
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *EBF3*-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; ASD = autism spectrum disorder; MOI = mode of inheritance; GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 3. Treatment of Manifestations in Individuals with *EBF3* Neurodevelopmental Disorder

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
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
Bowel dysfunction	Monitor for constipation.	Stool softeners, prokinetics, osmotic agents, or laxatives as needed

Table 3. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage subspecialty appointments, equipment, medications, & supplies.	Consider involvement in adaptive sports or Special Olympics.

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 be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - 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

Table 4. Recommended Surveillance for Individuals with *EBF3* Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for constipation.	
Neurologic	Assess for new manifestations such as ataxia.	
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for new manifestations incl anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Genitourinary	Follow up of vesicoureteral reflux, renal dysplasia, cryptorchidism	Per treating urologist
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Ataxia and intellectual disability could result in frequent falls in childhood; supervision of patient activity at home is recommended to limit the risk.

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

EBF3 neurodevelopmental disorder (*EBF3*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with *EBF3*-NDD whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo EBF3* pathogenic variant.
- Some individuals with *EBF3*-NDD have the disorder as the result of a pathogenic variant inherited from an affected parent [Beecroft et al 2020] or from an unaffected parent with somatic/germline mosaicism [Harms et al 2017, Sleven et al 2017, Ignatius et al 2020].
- 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, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
    - 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 only in the germ cells.)

      Maternal somatic/germline mosaicism has been reported [Harms et al 2017, Ignatius et al 2020]. In one family two affected sibs had a heterozygous pathogenic variant in *EBF3* but the pathogenic variant was not identified in parental leukocyte DNA [Sleven et al 2017]

      * A parent with somatic and germline mosaicism for an *EBF3* pathogenic variant may be mildly/minimally affected.

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

- If a parent is known to have the *EBF3* pathogenic variant identified in the proband, the risk to sibs of inheriting the pathogenic variant is 50%.
- If the *EBF3* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Harms et al 2017, Sleven et al 2017].

Offspring of a proband. Each child of an individual with *EBF3*-NDD has a 50% chance of inheriting the *EBF3* pathogenic variant.

Other family members. Given that most probands with *EBF3*-NDD reported to date have the disorder as a result of a *de novo EBF3* 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 young adults who are affected and parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *EBF3* 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 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.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net

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. EBF3 Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
EBF3	10q26.3	Transcription factor COE3	EBF3	EBF3

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 EBF3 Neurodevelopmental Disorder (View All in OMIM)

607407	EARLY B-CELL FACTOR 3; EBF3
617330	HYPOTONIA, ATAXIA, AND DELAYED DEVELOPMENT SYNDROME; HADDS

Molecular Pathogenesis

EBF3 encodes early B cell factor 3 (EBF3), one of four members of the EBF transcription factor family, involved in neuronal differentiation and maturation [Dubois & Vincent 2001, Pozzoli et al 2001].

Mechanism of disease causation. Missense variants affect the DNA binding domain of EBF3. Additional *EBF3* pathogenic variants include nonsense, splice, frameshift, and in-frame duplication. Both dominant negative and loss-of-function mechanisms are discussed [Chao et al 2017, Harms et al 2017, Sleven et al 2017].

Table 5. Notable *EBF3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001005463.3 NP_001005463.1	c.487C>T	p.Arg163Trp	Recurrent variants affecting codon 163 are located in a CpG island, a mutational hotspot [Blackburn et al 2017]
	c.488G>A	p.Arg163Gln	Chao et al [2017]
	c.488G>T	p.Arg163Leu	
	c.488G>C	p.Arg163Pro	
	c.512G>A	p.Gly171Asp	Reported in 2 unrelated persons [Harms et al 2017, D'Arrigo et al 2020]
	c.616C>T	p.Arg206Ter	Reported in 2 unrelated persons [Sleven et al 2017, Beecroft et al 2020]
	c.625C>T	p.Arg209Trp	Reported in 2 unrelated persons [Harms et al 2017, Ignatius et al 2020]
	c.626G>A	p.Arg209Gln	Reported in 2 unrelated persons [Tanaka et al 2017, Harkness et al 2020]

Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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