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NLM Citation: Fahrner JA. *TET3*-Related Beck-Fahrner Syndrome. 2023 May 18. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

TET3-Related Beck-Fahrner Syndrome

Synonyms: *TET3*-BEFAHRS, TET3 Deficiency

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Created: May 18, 2023.

Summary

Clinical characteristics

TET3-related Beck-Fahrner syndrome (*TET3*-BEFAHRS) is a condition within the spectrum of mendelian disorders of the epigenetic machinery (MDEMs) or chromatinopathies. Clinical features typically include intellectual disability / developmental delay ranging from mild to severe affecting both motor and language skills. Most affected individuals are verbal and ambulatory, with most walking by age 15-36 months. Hypotonia in infancy and childhood can exacerbate motor and expressive speech delay and, in some cases, cause feeding difficulties that require nasogastric or gastrostomy tube feeding. Some affected individuals display movement disorders. About one third of affected individuals have epilepsy. Other neurobehavioral features can include autism, anxiety, and attention-deficit/hyperactivity disorder. Strabismus and refractive errors are found in about half of affected individuals. Both conductive and sensorineural hearing loss have been observed. Approximately half of individuals exhibit typical growth and half exhibit growth abnormalities, with overgrowth being more common than undergrowth and macrocephaly being the most common manifestation of altered growth. While many affected individuals have dysmorphic features, these are typically nonspecific. Congenital heart defects, brain malformations, and genitourinary anomalies are less common findings.

Diagnosis/testing

The diagnosis of *TET3*-BEFAHRS is established in a proband with suggestive findings and a heterozygous pathogenic variant in *TET3* identified by molecular genetic testing. DNA methylation profiling can help confirm variant pathogenicity.

Management

Treatment of manifestations: Standardized treatment with anti-seizure medication (ASM) by an experienced neurologist; feeding therapy; gastrostomy tube placement may be required for persistent feeding issues; pressure-equalizing tubes for conductive hearing loss; hearing aids for sensorineural hearing loss; standard treatment for

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constipation, musculoskeletal issues, refractive error, strabismus, nystagmus, behavioral issues, developmental delay / intellectual disability, congenital heart defects, and genitourinary anomalies.

Surveillance: At each visit: measurement of growth parameters; evaluation of nutritional status and safety of oral intake; assessment for new manifestations, such as seizures and changes in tone; monitoring of developmental progress and educational needs; behavioral assessment; assessment for signs and symptoms of constipation; assessment of mobility and self-help skills; clinical evaluation for kyphosis and/or scoliosis. At least annually: complete ophthalmology evaluation and audiology evaluation.

Pregnancy management: Exposure to ASMs may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from ASM exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of ASMs to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given ASM during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible.

Genetic counseling

TET3-BEFAHRS is an autosomal dominant disorder. Most probands have a *de novo* pathogenic variant, though inherited variants have been reported. Rarely, affected individuals can have biallelic pathogenic variants inherited in *trans* from heterozygous parents who have milder features of *TET3*-BEFAHRS. This is now thought to represent autosomal dominant inheritance with variable expressivity as opposed to autosomal recessive inheritance. The risk to the sibs of the proband depends on the genetic status of the proband's parents. If one parent of the proband has a *TET3* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant and being affected is 50%. If both parents of a proband have a *TET3* pathogenic variant, sibs have a 75% chance of inheriting one or two pathogenic variants and being affected and a 25% chance of inheriting neither pathogenic variant and not being affected. Once the *TET3* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *TET3*-related Beck-Fahrner syndrome (*TET3*-BEFAHRS) have been published.

Suggestive Findings

TET3-BEFAHRS **should be considered** in individuals with the following clinical findings.

Clinical findings

- Mild-to-severe developmental delay or intellectual disability

AND

- Any of the following features presenting in infancy or childhood:
  - Generalized hypotonia of infancy
  - Infant feeding difficulties
  - Movement disorders, including motor tics, myoclonic jerks, dysmetria, posturing, and/or dystonia
  - Epilepsy, including generalized tonic-clonic, focal, and/or absence seizures
  - Neuropsychiatric issues, such as anxiety, attention-deficit/hyperactivity disorder, autism spectrum disorder, social interaction disorder, and occasionally depression or psychosis

- Abnormalities in growth, most typically overgrowth, including macrocephaly and/or tall stature, although microcephaly and/or short stature have also been observed
- Ophthalmologic involvement, such as strabismus, refractive errors, and nystagmus
- Musculoskeletal findings, such as joint hypermobility, hip dysplasia, scoliosis, and kyphosis
- Nonspecific dysmorphic features (See Clinical Description.)

Establishing the Diagnosis

The diagnosis of *TET3*-BEFAHRS **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *TET3* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *TET3* variant of uncertain significance without finding a second, pathogenic variant does not establish or rule out the diagnosis. (3) A characteristic epigenetic signature for *TET3*-BEFAHRS has been established and may aid in the determination of the clinical significance of uncertain variants [Levy et al 2021a].

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 include use of a multigene panel, exome sequencing, and DNA methylation profiling. Note: Single-gene testing (sequence analysis of *TET3*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

An intellectual disability and/or overgrowth multigene panel that includes *TET3* and other genes of interest (see Differential Diagnosis) may be considered. 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 *TET3*-BEFAHRS, some panels for intellectual disability and/or overgrowth 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 that includes *TET3* with the additional advantage that exome sequencing includes genes recently identified as causing intellectual disability, whereas some multigene panels may not. Due to the recent delineation of this disorder, its rarity, and the *TET3* gene not being on all panels for intellectual disability, comprehensive genomic testing like exome sequencing may be considered the diagnostic test of choice for *TET3*-BEFAHRS.

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.

DNA methylation profiling, sometimes referred to as an epigenetic signature, in whole blood can be performed as a clinical (non-research-based) test [Levy et al 2021b, Sadikovic et al 2021]. *TET3*-BEFAHRS has a unique DNA methylation profile that can differentiate affected individuals from controls and affected individuals from individuals with other disorders with distinct DNA methylation profiles [Levy et al 2021a]. DNA methylation profiling (or epigenetic signature) can be used either as an initial diagnostic tool to identify *TET3*-BEFAHRS or

to confirm pathogenicity of a DNA sequence variant of uncertain significance identified in *TET3* [Levy et al 2021a]. If used as an initial diagnostic tool, subsequent targeted gene sequencing of *TET3* may be beneficial to identify the specific pathogenic variant(s) in an affected person.

Table 1. Molecular Genetic Testing Used in *TET3*-Related Beck-Fahrner Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
TET3	Sequence analysis [3]	28/28 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from Beck et al [2020], Levy et al [2021a], Seyama et al [2022], and Sager et al [2023].
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
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

TET3-related Beck-Fahrner syndrome (*TET3*-BEFAHRS) is a condition within the spectrum of mendelian disorders of the epigenetic machinery (MDEMs) [Fahrner & Bjornsson 2014], also called chromatin-modifying disorders or chromatinopathies. The most common phenotypic manifestations of *TET3*-BEFAHRS and other MDEMs are intellectual disability / developmental delay typically affecting both motor and language skills. Similar to other MDEMs [Fahrner & Bjornsson 2019], individuals with *TET3*-BEFAHRS have neurologic, behavioral, and psychiatric features, with some individuals exhibiting growth abnormalities as well [Beck et al 2020, Levy et al 2021a, Seyama et al 2022, Sager et al 2023]. Additional tissue-diverse manifestations affecting the eyes, hearing, and musculoskeletal and gastrointestinal systems have also been observed [Beck et al 2020, Levy et al 2021a, Seyama et al 2022]. See Nomenclature for a mnemonic for the most common features of *TET3*-BEFAHRS.

To date, 28 individuals from 16 families have been identified with pathogenic variants in *TET3* [Santos-Cortez et al 2018, Beck et al 2020, Levy et al 2021a, Seyama et al 2022, Sager et al 2023]. Four affected individuals had copy number variants in addition to pathogenic *TET3* variants, and one affected individual had biallelic variants in a gene that causes an autosomal recessive disorder that does not fully explain her phenotype [Beck et al 2020, Levy et al 2021a]. It remains unclear if these additional genetic variants are contributing to the phenotypes in these reported individuals.

Table 2. *TET3*-Related Beck-Fahrner Syndrome: Frequency of Select Features

Feature	Proportion of Persons w/ Feature	Comment
Developmental delay &/or intellectual disability	25/26	One or more of the following: speech / gross motor / fine motor delay
Common facial characteristics	21/23	See **Facial features** following this table.
Social communication disorder	11/13	

Table 2. continued from previous page.

Feature	Proportion of Persons w/ Feature	Comment
Autistic features / autism spectrum disorder	9/14	Some affected persons may not have had a formal eval for autism.
Anxiety	8/11	
Hypotonia	13/23	Information about hypotonia is often lacking in affected adults.
Hearing loss	7/10	Predominantly conductive
Musculoskeletal findings	9/19	Joint hypermobility, hip dysplasia, scoliosis/kyphosis
Attention-deficit/ hyperactivity disorder	6/13	
Growth abnormalities [1]	9/19	6/19 had overgrowth & 3/19 had undergrowth.
Gastrointestinal manifestations	8/18	Feeding difficulties &/or constipation
Ophthalmologic findings	9/22	Refractive errors, strabismus, nystagmus
Seizure disorder	9/24	A variety of different types have been reported.
Other abnormal movements	7/23	Incl tics, myoclonic jerks, dysmetria, posturing, & dystonia
Congenital heart defects	5/19	Incl valve abnormalities or complex congenital heart disease

1. Defined as height and/or head circumference two standard deviations or more above or below the mean for age and sex

Developmental delay (DD) / intellectual disability (ID). The most common finding in individuals with *TET3*-BEFAHRS is DD and/or ID, ranging from mild to severe. DD is often global, meaning that two or more areas are affected, including gross motor, fine motor, and/or speech. However, in some individuals isolated DD (e.g., gross motor delay) has occurred [Levy et al 2021a; J Fahrner, personal observation]. Most individuals with *TET3*-BEFAHRS are verbal and ambulatory, with most walking by age 15-36 months.

Other neurodevelopmental features

- Hypotonia is present in a subset of affected individuals and is most notable in infancy and childhood. Hypotonia can affect the acquisition of motor skills and expressive speech.
- Infant feeding difficulties occur in some affected individuals, which in some cases have required nasogastric or gastrostomy tube feeding (see Management).
- Spasticity has been described in one individual.
- Movement disorders, including motor tics, myoclonic jerks, dysmetria, posturing, and dystonia have been observed.

Epilepsy. Slightly more than one third of affected individuals have epilepsy.

- Generalized tonic-clonic seizures with occasional sharp- and slow-wave discharges in the right central area on EEG were observed in two brothers from a single family [Levy et al 2021a].
- In another unrelated male, clinical presentation and EEG findings were consistent with electrical status epilepticus during slow-wave sleep, and the affected male experienced regression [Sager et al 2023]. Pulse steroid therapy, intravenous immunoglobulin, and oral valproic acid were administered initially and led to clinical improvement. Subsequently, steroid therapy and intravenous immunoglobulin were discontinued and clobazam was added to valproic acid therapy, leading to improvement on the EEG.
- Absence seizures were observed in an affected female (whose EEG showed an abnormal focus on the right) and in an affected male. The male individual began having seizures around age 33 months, initially

febrile partial seizures and then non-febrile absence seizures and myoclonic jerks of the limbs with preserved consciousness. Initial EEG showed bioccipital biphasic spikes, which progressed first to abundant bicentral spikes and waves with increased frequency during sleep and then to continuous spikes and waves of slow-wave sleep, similar to the male with electrical status epilepticus during slow-wave sleep. Seizures were refractory to therapy with sodium valproate, levetiracetam, lamotrigine, and clobazam; only a combination of sultiame and steroids was effective for this individual [Beck et al 2020].

- A female presented with complex partial seizures; her EEG showed an abnormal focus over the left temporal and occipital regions [Seyama et al 2022].
- One affected individual presented with infantile spasms with an abnormal EEG at age six months [Beck et al 2020].

Neuropsychiatric findings. Autistic features or formal diagnoses of autism spectrum disorder were present in roughly two thirds of individuals evaluated for this feature, and an even larger percentage had difficult and/or delayed social interactions suggestive of social communication disorder. Anxiety was present in a large proportion of affected individuals, as was attention-deficit/hyperactivity disorder. A few affected individuals had depression or psychosis in adolescence or adulthood.

Facial features. Twenty-one of twenty-three affected individuals exhibited common craniofacial features. Most affected individuals exhibited a long face with a tall and/or broad forehead. Approximately one half of affected individuals exhibited a myopathic face with an open-mouth appearance, protruding ears, and a highly arched palate. Approximately one third of affected individuals exhibited a short nose with a long philtrum, and a slightly larger proportion had brachycephaly. A few individuals exhibited thick or arched eyebrows, epicanthal folds, or downslanted palpebral fissures. One individual exhibited cleft lip and palate and an asymmetric jaw.

Ophthalmologic involvement. Nine of 22 affected individuals exhibited ophthalmologic findings. The most common manifestation was strabismus, with one individual having ophthalmoplegia. Vision abnormalities were also observed and included myopia and hyperopia. A few individuals had nystagmus or ptosis. A single individual had lacrimal duct stenosis, and another had microphthalmia.

Hearing/ear abnormalities. Seven of ten affected individuals exhibited hearing loss [Levy et al 2021a, Seyama et al 2022].

- Four affected individuals had conductive hearing loss and two experienced accompanying recurrent otitis media requiring tympanostomy tubes.
- Two affected sibs exhibited sensorineural hearing loss.
- Another affected individual had microtia and atresia of the left external ear canal.

Musculoskeletal features. Nine of 19 individuals exhibited musculoskeletal findings, including the following:

- Joint hypermobility (4 affected individuals)
- Hip dysplasia in infancy (3 affected individuals)
- Kyphosis and/or scoliosis (2 affected individuals)
- Inguinal hernia (1 affected individual)

Growth. Nine of 19 individuals had growth abnormalities, six of whom had overgrowth and three of whom had undergrowth. Ten of 19 individuals did not have reported growth abnormalities.

- Of those with overgrowth, four had macrocephaly, one had tall stature, and one had both macrocephaly and tall stature. The latter individual also had nephromegaly and cardiomegaly, suggestive of generalized somatic overgrowth.
- Of those with undergrowth, three had microcephaly, with two of these individuals also exhibiting short stature.

All growth abnormalities were postnatal, except in one individual whose birth length was greater than two standard deviations above the mean for gestational age. Three individuals (including two sibs) had birth weights greater than two standard deviations below the mean for age.

Neuroimaging. Of the 13 individuals who have undergone brain magnetic resonance imaging (MRI), eight had identified abnormalities [Beck et al 2020, Levy et al 2021a, Seyama et al 2022, Sager et al 2023], which in many cases were nonspecific. Findings included the following:

- Increased extra-axial spaces in four unrelated affected individuals
  - Two of these individuals exhibited mild ventriculomegaly and another had accompanying periventricular leukomalacia.
  - The fourth individual exhibited agenesis of the corpus callosum in addition to having an enlarged trigone and temporal horn. That individual's affected sib also had isolated agenesis of the corpus callosum.
- Two related affected individuals – a mother and son – exhibited white matter changes, with the son's abnormality involving the periventricular white matter and the mother's not otherwise specified.
- Two individuals exhibited hypoplasia of the cerebellum and enlarged/mega cisterna magna; one individual exhibited hypoplasia of the tectum mesencephali.

Other associated features

- **Gastrointestinal issues.** Eight of 18 affected individuals exhibited gastrointestinal manifestations, with seven having infantile feeding difficulties and two having constipation. One had pyloric stenosis.
- **Cardiovascular anomalies.** Five of 19 individuals exhibited cardiovascular anomalies, including the following:
  - Valve abnormalities (3 affected individuals): pulmonic stenosis in one individual, aortic insufficiency with a ventricular septal defect in another, and an unspecified type of valve abnormality with an unspecified abnormality on EKG in the third individual
  - Tetralogy of Fallot (1 affected individual)
  - A small, hemodynamically-insignificant arterial collateral from the descending aorta (1 affected individual)
- **Genitourinary anomalies.** Three individuals had genitourinary anomalies, with one individual having cryptorchidism, another having hypospadias, and a third having nephromegaly in the setting of generalized somatic overgrowth.

Prognosis. It is unclear whether individuals with *TET3*-BEFAHRS have a decreased life span. One reported individual is alive at age 56 years [Beck et al 2020], demonstrating that survival into adulthood is possible. This condition is not thought to be progressive; however, in the setting of poorly controlled seizures, it is possible that neurologic function could regress. 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

No genotype-phenotype correlations have been confirmed.

Nomenclature

The BEFAHRS abbreviation can be used as a mnemonic for the most common features as follows: *B*ehavioral differences, *E*pilepsy, common *F*acial features, *A*utistic features, *H*ypotonia, *R*etardation of psychomotor development, and *S*ize differences [Levy et al 2021a].

Prevalence

The prevalence of *TET3*-BEFAHRS is unknown. To date, 28 individuals from 16 families have been reported with pathogenic variants in *TET3* [Santos-Cortez et al 2018, Beck et al 2020, Levy et al 2021a, Seyama et al 2022, Sager et al 2023]. The author is aware of additional affected individuals and welcomes contact and queries from clinicians who care for affected individuals (see Author Notes).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TET3*.

Differential Diagnosis

Although there is significant phenotypic overlap with other mendelian disorders of the epigenetic machinery (also called chromatin-modifying disorders or chromatinopathies; see Table 3), the clinical presentation of *TET3*-related Beck-Fahrner syndrome (*TET3*-BEFAHRS) is typically nonspecific global developmental delay and, consequently, all disorders associated 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.

Table 3. Selected Chromatin-Modifying Disorders of Interest in the Differential Diagnosis of *TET3*-Related Beck-Fahrner Syndrome

Gene	Disorder	MOI	Clinical Characteristics
ASXL3	Bainbridge-Ropers syndrome	AD	DD/ID w/speech & language delay &/or absent speech. Autistic features & issues w/feeding in some persons. Typically nonspecific dysmorphic facial features. Affected persons may have hypotonia that can transition to spasticity resulting in unusual posture w/flexion contractions of elbows, wrists, & fingers.
DNMT3A [1]	Tatton-Brown-Rahman syndrome	AD	Overgrowth/ID syndrome. Obesity / ↑ weight, joint hypermobility, hypotonia, behavioral/psychiatric issues, kyphoscoliosis, & seizures. Subtle dysmorphic features, incl round face w/coarse features, thick horizontal low-set eyebrows, narrow (as measured vertically) palpebral fissures, & prominent upper central incisors. (Facial gestalt is most easily recognizable in teenage yrs.)
	Heyn-Sproule-Jackson syndrome (OMIM 618724)	AD	DD/ID; microcephaly; short stature; strabismus
FMR1	Fragile X syndrome (See *FMR1* Disorders.)	XL	Characterized in males by DD & ID w/variety of behavioral issues. ASD in 50%-70%. Characteristic craniofacial features, hypotonia, gastroesophageal reflux, strabismus, seizures, sleep disorders, joint laxity, pes planus, scoliosis, & recurrent otitis media.
KMT2D *KDM6A*	Kabuki syndrome	AD XL	Typical facial features (long palpebral fissures w/eversion of lateral 3rd of lower eyelid; arched, notched, & broad eyebrows; short columella w/ depressed nasal tip; large, prominent, or cupped ears), minor skeletal anomalies, infantile hypotonia, persistence of fetal fingertip pads, ID, & postnatal growth deficiency.
NFIX	Malan syndrome (OMIM 614753)	AD	DD/ID; macrocephaly; tall stature; tall/broad forehead; long face; strabismus; nystagmus; hypotonia; anxiety

Table 3. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics
NSD1	Sotos syndrome	AD	Cardinal features (present in ≥90% of persons w/Sotos syndrome) are distinctive facial appearance (broad & prominent forehead w/ dolichocephalic head shape; sparse frontotemporal hair; downslanting palpebral fissures; malar hypoplasia & flushing; long & narrow face; long chin), learning disability, & overgrowth.
SETD2	*SETD2* neurodevelopmental disorder ± macrocephaly/ overgrowth (Luscan-Lumish syndrome) (See *SETD2* Neurodevelopmental Disorders.)	AD	Macrocephaly/overgrowth. Can also include DD/ID, obesity, advanced bone age, & behavioral findings (most typically ASD). This spectrum also includes individuals who have normal growth.

AD = autosomal dominant; ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. In contrast to Tatton-Brown-Rahman syndrome, which is caused by loss-of-function pathogenic variants in *DNMT3A*, Heyn-Sproul-Jackson syndrome is caused by gain-of-function pathogenic variants (see Tatton-Brown-Rahman Syndrome, Genetically Related Disorders).

Management

No clinical practice guidelines for *TET3*-related Beck-Fahrner syndrome (*TET3*-BEFAHRS) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *TET3*-BEFAHRS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *TET3*-Related Beck-Fahrner Syndrome: Recommended Evaluations

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters, incl head circumference	To assess for tall or short stature, macrocephaly, &/or microcephaly
Neurologic	Neurologic eval	• To assess for tone & any movement disorders • To incl brain MRI, as clinically indicated • Consider EEG if seizures are a concern.
Hypotonia	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, social communication disorder, &/or findings suggestive of ASD
Musculoskeletal	Assessment for joint hypermobility, scoliosis, pes planus, & hip dysplasia	Consider referral to orthopedist.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	Consider eval for nasogastric or gastrostomy tube in those w/ persistent feeding issues.
Eyes	Ophthalmologic eval	To assess for strabismus, nystagmus, refractive errors
Ears/Hearing	Audiology eval	To assess for hearing loss
	Assess for chronic otitis media & ear anomalies.	Consider referral to otolaryngologist.
Cardiovascular	Echocardiogram	To assess for congenital heart defects, incl valve anomalies
	Consider EKG.	To assess for rhythm disturbance
Genitourinary	Physical exam to assess for genitourinary anomalies in males	Consider referral to urologist.
	Consider abdominal or kidney ultrasound.	To assess for structural anomalies &/or organomegaly
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *TET3*-BEFAHRS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as the Beck-Fahrner Syndrome Foundation and Parent to Parent; • Social work involvement for parental support.	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *TET3*-BEFAHRS.

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. *TET3*-Related Beck-Fahrner Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
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]
Abnormalities in tone / Movement disorders	Orthopedics / physical medicine & rehab / PT & OT	Consider need for positioning & mobility devices, disability parking placard.
Feeding difficulties	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Behavioral issues (ADHD, anxiety, ASD)	Referral to developmental pediatrician, neuropsychologist, or psychiatrist	• Standard ADHD or anxiety medications may be effective; none has been demonstrated effective specifically for this disorder. • Standard autism therapies (e.g., ABA therapy) may be effective.
Kyphosis/scoliosis, hip dysplasia, pes planus	Standard treatment by orthopedist	May incl bracing &/or surgery
Ophthalmologic involvement	Standard treatment of refractive errors, strabismus, &/or nystagmus by ophthalmologist	
Hearing loss	Consider: • Pressure equalizing tubes for those w/ conductive hearing loss; • Hearing aids for those w/sensorineural hearing loss. [2]	Refer to ENT specialist & audiologist.
Congenital heart defects / Rhythm disturbances	Standard treatment per cardiologist	
Genitourinary anomalies	Standard treatment per urologist	
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.

ABA = applied behavior analysis; ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
2. Cochlear implants can also be considered, per ENT and audiologist recommendations.

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.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., orthotics, adaptive strollers).

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.

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

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. *TET3*-Related Beck-Fahrner Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Growth/Feeding	• Measurement of growth parameters, incl weight, length/height, & head circumference • Eval of nutritional status & safety of oral intake	At each visit
Neurologic	Monitor those w/seizures as clinically indicated.	
	Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
Development	Monitor developmental progress & educational needs.	
Psychiatric/Behavioral	Behavioral assessment for anxiety, attention, autistic, & aggressive or self-injurious behavior	
Gastrointestinal	Assess for signs & symptoms of constipation.	
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).	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills; clinical eval for joint hypermobility	
	Clinical eval for kyphosis &/or scoliosis	
Eyes	Complete ophthalmology eval	At least annually
Hearing	Audiology eval	

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.

Pregnancy Management

In general, women with epilepsy or a seizure disorder of any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication (ASM) during pregnancy reduces this risk. However, exposure to ASMs may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from ASM exposure is often less than that associated with exposure to

an untreated maternal seizure disorder. Therefore, use of ASMs to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given ASM during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

See MotherToBaby for further information on medication use during pregnancy.

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

TET3-related Beck-Fahrner syndrome (*TET3*-BEFAHRS) is an autosomal dominant disorder; individuals with a *TET3* pathogenic variant are affected.

In some families reported to date, however, individuals with *TET3*-BEFAHRS have biallelic pathogenic variants, raising the possibility of an autosomal recessive mode of inheritance. However, the family histories of these individuals are consistent with autosomal dominant inheritance; in most cases the heterozygous parents of these probands also had features consistent with *TET3*-BEFAHRS, although milder than those in their affected children [Beck et al 2020]. In a more recently reported family in which two affected children had biallelic variants inherited in *trans*, neither parent was reported to be affected; however, it is unclear whether the parents were fully evaluated [Seyama et al 2022].

Risk to Family Members (Autosomal Dominant Inheritance)

Parents of a proband

- Of the 12 probands reported to date with a heterozygous *TET3* pathogenic variant, nine probands had *TET3*-BEFAHRS as the result of a *de novo* pathogenic variant, and three probands had the disorder as the result of a pathogenic variant inherited from an affected parent [Beck et al 2020, Levy et al 2021a, Seyama et al 2022, Sager et al 2023].
- Six probands from three families reported to date with biallelic *TET3* pathogenic variants inherited pathogenic variants from their heterozygous parents [Beck et al 2020, Seyama et al 2022]. In these families, heterozygous parents often had relatively mild features consistent with *TET3*-BEFAHRS [Beck et al 2020].
- One proband was initially reported to have biallelic variants inherited in *trans* in *TET3*, suggestive of autosomal recessive inheritance. However, only one (the maternally inherited variant) exhibited reduced catalytic activity in vitro [Beck et al 2020]. Subsequent DNA methylation profiling confirmed pathogenicity of the maternally inherited variant but not of the paternally inherited variant. This, and the mother's relatively mild phenotype, suggest a monoallelic pathogenic variant and autosomal dominant

inheritance with variable expressivity in this family, though we cannot completely rule out some contribution from the paternal variant in the proband [Levy et al 2021a].

- The above observations suggest that *TET3*-BEFAHRS is an autosomal dominant condition with variable expressivity and hypomorphic alleles that sometimes mimic autosomal recessive inheritance as opposed to true autosomal recessive inheritance. The methylation signature supports this as well.
- If the proband appears to be the only affected family member (i.e., a simplex case), targeted molecular genetic testing for the pathogenic variant(s) identified in the proband is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the proband has a heterozygous pathogenic variant that 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.
- If the proband has biallelic pathogenic variants and a pathogenic variant is detected in only one parent (and parental identity testing has confirmed biological maternity and paternity), it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].

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

- If one parent of the proband has a *TET3* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant and being affected is 50%.
- If both parents of a proband have a *TET3* pathogenic variant, sibs have a 75% chance of inheriting one or two pathogenic variants and being affected and a 25% chance of inheriting neither pathogenic variant.
- If the *TET3* 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 theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *TET3* pathogenic variant(s) but are clinically unaffected, sibs are still presumed to be at increased risk for *TET3*-BEFAHRS because of the theoretic possibilities of reduced penetrance in a heterozygous parent or parental germline mosaicism.

Offspring of a proband

- Unless a proband with a heterozygous *TET3* pathogenic variant has children with an individual who also has a *TET3* pathogenic variant, the proband's offspring will have a 50% chance of inheriting a *TET3* pathogenic variant. Consanguinity increases the likelihood that an affected individual may have a reproductive partner who is heterozygous for a *TET3* pathogenic variant.
- Severely affected individuals with biallelic *TET3* pathogenic variants are not known to reproduce.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a *TET3* 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 have a *TET3* pathogenic variant.

Prenatal Testing and Preimplantation Genetic Testing

Once the *TET3* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **Beck-Fahrner Syndrome Foundation**
  Email: jaime@beckfahrner.org
  www.beckfahrner.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. TET3-Related Beck-Fahrner Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
TET3	2p13.1	Methylcytosine dioxygenase TET3	TET3	TET3

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 TET3-Related Beck-Fahrner Syndrome (View All in OMIM)

613555	TET METHYLCYTOSINE DIOXYGENASE 3; TET3
618798	BECK-FAHRNER SYNDROME; BEFAHRS

Molecular Pathogenesis

TET3-related Beck-Fahrner syndrome (*TET3*-BEFAHRS) is a mendelian disorder of the epigenetic machinery (MDEM) [Fahrner & Bjornsson 2014], also termed chromatinopathy. MDEMs result from germline pathogenic variants in genes encoding components of the epigenetic or chromatin-modifying machinery [Fahrner & Bjornsson 2014]. Chromatin consists of DNA and associated histone proteins, and epigenetics refers to marks on chromatin (DNA or histones) that alter gene expression without changing the DNA sequence. The MDEM genes are divided into groups based on whether they place ("write"), remove ("erase"), or interpret ("read") epigenetic marks or remodel chromatin [Bjornsson 2015, Fahrner & Bjornsson 2019]. *TET3*-BEFAHRS is a neurodevelopmental disorder of the DNA methylation eraser system. It results from pathogenic variants in *TET3*, which is a dioxygenase that oxidizes 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and on to additional intermediates (5-formylcytosine and 5-carboxycytosine), which are eventually removed and replaced with unmethylated cytosine, completing the process of active DNA demethylation [Wu & Zhang 2017].

Hypomorphic or loss-of-function pathogenic variants in *TET3* reduce the ability of the enzyme to oxidize 5mC to 5hmC in vitro [Beck et al 2020]. Genome-wide DNA methylation profiling of whole blood revealed a distinct

and hypermethylated DNA methylation profile (or episignature) in affected individuals compared to controls [Levy et al 2021a]. This supports a hypomorphic/loss-of-function disease mechanism that leads to broad, epigenomic changes with the potential to disrupt gene expression. It is hypothesized that altered expression of key target genes ultimately leads to disease manifestations of *TET3*-BEFAHRS. Because epigenetic and chromatin marks differ among tissues, however, it remains unclear whether the DNA methylation changes in blood reflect what is happening in disease-relevant tissues like the brain.

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

Jill A Fahrner, MD, PhD, is an Assistant Professor in the Departments of Genetic Medicine and Pediatrics at the Johns Hopkins University School of Medicine. She is a physician-scientist with a long-standing interest in epigenetics, chromatin, and genetic and epigenetic mechanisms of disease. She is Director of the multidisciplinary Epigenetics and Chromatin Clinic at Johns Hopkins University, where she and her team care for patients with mendelian disorders of the epigenetic machinery / chromatinopathies (including *TET3*-BEFAHRS), as well as imprinting disorders. The goal of her ongoing laboratory research is to understand disease mechanisms of and develop therapies for mendelian disorders of the epigenetic machinery.

A main focus of Dr Fahrner's research is *TET3*-BEFAHRS, which she recently delineated as the first neurodevelopmental disorder of the DNA demethylation machinery. She and her team continue to recruit research participants with *TET3*-BEFAHRS to collect additional information about the phenotype of affected individuals; this will improve understanding of disease manifestations. In particular, Dr Fahrner's team is interested in collecting detailed neuropsychological information; this type of information could serve as an outcome measure in potential future clinical trials. In addition, the Fahrner laboratory has ongoing studies to refine the DNA methylation profile for *TET3*-BEFAHRS in whole blood, and they are using human cellular models to better understand the molecular aspects of the disease. These studies may help to identify targeted therapies for *TET3*-BEFAHRS in the future.

Dr Fahrner's web page: www.hopkinsmedicine.org/profiles/details/jill-fahrner

Email Dr Fahrner (jfahrne1@jhmi.edu) if you are interested in learning more about research opportunities for *TET3*-BEFAHRS or in scheduling an appointment with her in the multidisciplinary Epigenetics and Chromatin Clinic at Johns Hopkins University.

TET3-BEFAHRS family-specific resources may include the Beck-Fahrner Syndrome Foundation (see Resources) or the *TET3*-BEFAHRS Facebook group.

Acknowledgments

Thank you to the patients and families and to the clinicians and researchers who have contributed to ongoing *TET3*-BEFAHRS research. Thank you to the Beck-Fahrner Syndrome Foundation for ongoing support. Dr Fahrner acknowledges research support from the National Institutes of Health (NIH) / National Institute for Child Health and Human Development (NICHD; K08HD086250). She has support from the Maryland Stem Cell Research Fund (2022-MSCRFL-5846) and a Johns Hopkins Catalyst Award for her ongoing *TET3*-BEFAHRS research.

Revision History

- 18 May 2023 (ma) Review posted live

- 12 September 2022 (jf) Original submission

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