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NLM Citation: Brockmann K, Staudt M. *FOXG1* Syndrome. 2024 Jun 6. 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/

FOXG1 Syndrome

Synonyms: *FOXG1*-Related Disorder, *FOXG1*-Related Encephalopathy, *FOXG1*-Related Neurodevelopmental Disorder

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Created: June 6, 2024.

Summary

Clinical characteristics

FOXG1 syndrome is characterized by moderate-to-profound developmental delay and intellectual disability, postnatal growth deficiency, congenital or postnatal microcephaly, hyperkinetic/dyskinetic movement disorder, hypotonia, neurobehavioral/psychiatric manifestations (motor stereotypies, impairment of social interaction, abnormal sleep patterns, unexplained episodes of crying, restlessness, and bruxism), feeding difficulties with poor weight gain, strabismus, seizures, spasticity, gastroesophageal reflux, and aspiration. Some individuals have cortical visual impairment, kyphosis, scoliosis, and/or abnormal breathing. Characteristic neuroimaging findings include corpus callosum anomalies (especially a marked, filiform thinning of the rostrum of the corpus callosum), a simplified gyral pattern, and hyperplasia of the fornices.

Diagnosis

The diagnosis of *FOXG1* syndrome is established in a proband with clinical and/or characteristic neuroimaging findings and a heterozygous pathogenic variant in *FOXG1* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental and educational support; consideration of anti-dyskinetic pharmacotherapy; treatment for seizures by an experienced neurologist; treatment of spasticity per orthopedist; physical medicine and rehabilitation, physical therapy, and occupational therapy to help avoid contractures and falls; anti-spasmodic pharmacotherapy; feeding therapy with gastrostomy tube placement as needed; standard treatment of gastroesophageal reflux; treatment for refractive errors and strabismus per ophthalmologist; standard treatments for scoliosis; social work and family support.

Surveillance: At each visit, monitor developmental progress, educational needs, seizures, changes in tone, movement disorders, growth, nutritional status, and safety of oral intake; behavioral assessment for irritability

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and sleep issues; assess for evidence of gastroesophageal reflux, aspiration, and/or respiratory insufficiency; physical medicine, occupational therapy, physical therapy assessment for mobility and self-help skills; monitor for strabismus and need for low vision services per treating ophthalmologist; assess family needs.

Genetic counseling

FOXG1 syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo FOXG1* pathogenic variant. There is, however, a recurrence risk to sibs based on the possibility of parental germline mosaicism. Given this risk, prenatal and preimplantation genetic testing may be considered.

GeneReview Scope

***FOXG1* Syndrome: *GeneReview* Scope**

Genetic Alteration	Comment
Intragenic *FOXG1* pathogenic variants & deletions	Topic of this *GeneReview*
Whole-gene *FOXG1* duplications	Not addressed in this *GeneReview* (See Genetically Related Disorders.)
Contiguous gene duplications/deletions involving *FOXG1*	

Diagnosis

Suggestive Findings

FOXG1 syndrome **should be considered** in probands with the following clinical and brain MRI findings.

Clinical findings

- Severe developmental delay; absent speech development in most individuals
- Severe intellectual disability
- Generalized hypotonia of infancy
- Infant feeding difficulties and poor weight gain
- Hyperkinetic/dyskinetic movement disorder
- Epilepsy with a wide range of seizure types including infantile spasms, focal, complex focal, generalized tonic, atonic, myoclonic, and Lennox-Gastaut syndrome
- Spasticity
- Neurobehavioral/psychiatric manifestations including motor stereotypies, impairment of social interaction, abnormal sleep patterns, unexplained episodes of crying, restlessness, and bruxism
- Gastroesophageal reflux and recurrent aspiration
- Microcephaly (congenital or postnatal onset)
- Short stature in about 50% of individuals
- Strabismus and cortical visual impairment

Brain MRI findings

- Corpus callosum anomalies with filiform thinning of the rostrum
- Thickening of the fornices
- Simplified gyral pattern
- Enlargement of the inner cerebrospinal fluid spaces
- Hypoplasia of the basal ganglia
- Hypoplasia of the frontal lobes

Establishing the Diagnosis

The diagnosis of *FOXG1* syndrome **is established** in a proband with suggestive clinical and/or neuroimaging findings and a heterozygous pathogenic (or likely pathogenic) variant in *FOXG1* 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 *FOXG1* 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** (see Option 1) or a **multigene panel** (see Option 2). Note: Single-gene testing (sequence analysis of *FOXG1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

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 *FOXG1* 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.

Option 2

An intellectual disability multigene panel that includes *FOXG1* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of *FOXG1* syndrome, 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.

Table 1. Molecular Genetic Testing Used in *FOXG1* Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
FOXG1	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	<5% [4, 6, 7]

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. Several additional individuals with contiguous gene deletions (not included in these calculations) have been reported (see Genetically Related Disorders).
7. Individuals with whole-gene *FOXG1* duplications including large contiguous duplications of *FOXG1* and adjacent genes are not included in Table 1; these individuals present with a different phenotype (see Genetically Related Disorders) than individuals with intragenic *FOXG1* loss-of-function pathogenic variants.

Clinical Characteristics

Clinical Description

FOXG1 syndrome is characterized by severe global developmental delay, postnatal growth deficiency, congenital or postnatal microcephaly, moderate-to-profound intellectual disability with absent speech development, epilepsy, hyperkinetic/dyskinetic movement disorder, abnormal sleep patterns, unexplained episodes of crying, and gastroesophageal reflux. To date, more than 150 individuals have been identified with an intragenic *FOXG1* pathogenic variant or deletion of *FOXG1*. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of *FOXG1* Syndrome

Feature		% of Persons w/Feature
Development	Developmental delay	100%
	Intellectual disability	100%
	Hypotonia	95%
	Absence of unassisted walking	85%
	Absence of expressive language	79%
	Absence of functional hand use	60%
	Loss of motor skills	20%

Table 2. continued from previous page.

Feature		% of Persons w/Feature
Additional neurologic features	Hyperkinetic/dyskinetic movement disorder & stereotypic movements	Up to 100%
	Epilepsy	60%-80%
	Spasticity	60%
	Strabismus	85%
	Cortical visual impairment	40%
	Hypersalivation	65%
Neurobehavioral manifestations	Deficient social interactions & poor eye contact	25%-100%
	Abnormal sleep patterns	55%-70%
	Bruxism	75%
	Unexplained crying	70%
	Paroxysmal laughter	50%
Gastrointestinal manifestations	Feeding difficulties	90%
	Gastroesophageal reflux	Up to 90%
Growth	Short stature	50%
	BMI >2 SD below the mean	35%
	Microcephaly (congenital or postnatal onset)	85%

Based on Kortüm et al [2011], Cellini et al [2016], Mitter et al [2018], Brimble et al [2023], Wong et al [2023]
BMI = body mass index; SD = standard deviations

Developmental delay. All individuals with *FOXG1* syndrome have global developmental delay with onset within the first months of life. Severe global developmental delay becomes apparent before age two years. Hypotonia is reported in the majority of individuals [Kortüm et al 2011, Mitter et al 2018]. Only about 50% of individuals achieve unassisted sitting (at a mean age of 28 months), and only about 15% can walk unassisted (at a mean age of 53 months). Limited functional hand use is observable in approximately 40%. Regression of motor skills has been reported [Mitter et al 2018].

In a study of 83 individuals with age at last follow up ranging from 14 months to 32 years, 21% had some verbal expression. Age at first words was reported in nine individuals, with a mean age of 46 months (range: 21 months to 9 years). Mean number of spoken words in those who had some verbal expression was 19 (range: 2-100 words) [Mitter et al 2018].

Intellectual disability. All individuals with *FOXG1* syndrome exhibit intellectual disability too severe to allow for standardized neuropsychological testing.

Hyperkinetic/dyskinetic movement disorder and stereotypic movements are a prominent hallmark of *FOXG1* syndrome and observed in virtually all individuals [Kortüm et al 2011, Cellini et al 2016, Mitter et al 2018, Brimble et al 2023].

Epilepsy is reported in 60% to 80% of individuals [Kortüm et al 2011, Mitter et al 2018, Brimble et al 2023]. Mean age at onset of seizures reported in 40 individuals was 25 months (range: 3 months to 14 years). Onset of seizures after age six years is rare [Mitter et al 2018]. Several reports describe a wide range of seizure types including infantile spasms, focal, complex focal, generalized tonic, atonic, and myoclonic [Kortüm et al 2011, Seltzer et al 2014, Mitter et al 2018, Brimble et al 2023]. Lennox-Gastaut syndrome was observed in three unrelated individuals with a missense variant affecting amino acid 187 [Mitter et al 2018]. EEG findings include

nonspecific focal and multifocal epileptic discharges, but EEG findings may be normal in individuals with epilepsy.

Spasticity is observed in approximately 60% of affected individuals [Kortüm et al 2011, Mitter et al 2018].

Neurobehavioral manifestations. Impairment of social interaction with poor eye contact is present in many individuals [Kortüm et al 2011, Mitter et al 2018]. A recent study reported that 19% of individuals age three years and older were diagnosed with autism spectrum disorder [Brimble et al 2023]. Given the severe intellectual disability of all individuals, the diagnosis of autism should be used cautiously. Additional behavioral features include bruxism, prominent irritability, unexplained crying, and paroxysmal laughter (50%) [Mitter et al 2018]. Abnormal sleep patterns were reported in 55% to 70% of individuals [Mitter et al 2018, Brimble et al 2023].

Gastrointestinal manifestations. Infant feeding difficulties are very common and reported in up to 100% of individuals. In one cohort of 122 individuals, requirement of a feeding tube was reported in 34% [Brimble et al 2023]. Gastroesophageal reflux was observed in 65% to 90% of affected individuals [Kortüm et al 2011, Mitter et al 2018]. While one report stressed that the reflux is often severe and may become a prominent part of the overall phenotype [Kortüm et al 2011], a recent study did not report this feature [Brimble et al 2023].

Growth deficiency is present in most individuals. While 85% had normal length and 93% had normal weight at birth, 48% had short stature (length more than two standard deviations [SD] below the mean) and 34% were underweight (BMI more than two SD below the mean) at follow up [Mitter et al 2018]. In a cohort of 83 individuals, microcephaly (head circumference more than two SD below the mean) was present in 24% at birth and in 84% at last follow up.

Ophthalmologic involvement. Strabismus is a common feature, reported in 65% to 85% of affected individuals [Mitter et al 2018, Brimble et al 2023]. Cortical visual impairment was reported to occur in 40% in one study [Brimble et al 2023].

Musculoskeletal features. Kyphosis and/or scoliosis were reported in 40% of affected individuals [Mitter et al 2018].

Respiratory abnormalities. Abnormal breathing was observed in 30% of affected individuals; however, additional details regarding abnormal breathing were not reported [Mitter et al 2018].

Hearing impairment. Only one study of 122 registry participants with *FOXG1* syndrome mentioned hearing loss, with a frequency of 4% [Brimble et al 2023].

Facial features. In individuals with intragenic pathogenic variants of *FOXG1*, no specific dysmorphic features have been observed. If present, dysmorphic features are nonspecific.

Neuroimaging. Corpus callosum anomalies and simplified gyral pattern are characteristic of *FOXG1* syndrome [Kortüm et al 2011, Vegas et al 2018], especially a marked, filiform thinning of the rostrum of the corpus callosum. The combination of corpus callosum anomaly with simplified gyral pattern and hyperplasia of the fornices was observed in about 50% of individuals and is highly characteristic of, possibly pathognomonic for, *FOXG1* syndrome [Pringsheim et al 2019]. Neuroimaging also showed enlargement of inner cerebrospinal fluid spaces, hypoplasia of basal ganglia, and hypoplasia of the frontal lobes [Kortüm et al 2011, Pringsheim et al 2019]. While these MRI findings are characteristic, they may be unrecognized, especially thickening of the fornices. This feature was first described in 2019 [Pringsheim et al 2019]. More severe neuroimaging anomalies are associated with more severe clinical phenotypes [Pringsheim et al 2019]. Rarely, the brain MRI may be normal [Pringsheim et al 2019].

Prognosis. Data on the long-term course of individuals with *FOXG1* syndrome is scarce. However, *FOXG1* syndrome appears to be a stable encephalopathy; loss of motor or language skills is rare and there is no evidence for a progressive, neurodegenerative course. It is unknown whether life span in individuals with *FOXG1*

syndrome is abnormal. One reported individual is alive at age 32 years [Mitter et al 2018], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

Several reports have indicated a genotype-phenotype association.

Individuals with truncating pathogenic variants or intragenic deletions show more severe clinical phenotypes than those with missense pathogenic variants [Kortüm et al 2011, Mitter et al 2018, Brimble et al 2023]. The most severe clinical phenotypes were observed in individuals with a frameshift or nonsense pathogenic variant in the N-terminal domain and the forkhead domain, except conserved site 1. In contrast, milder phenotypes were associated with missense pathogenic variants in the forkhead conserved site 1 [Mitter et al 2018]. Simplified gyral pattern occurred significantly more frequently in individuals with pathogenic frameshift and nonsense variants in the N-terminal domain [Pringsheim et al 2019]. For most of the neuroimaging anomalies, no genotype-phenotype correlations were discernible [Pringsheim et al 2019].

Of note, three unrelated individuals who developed Lennox-Gastaut syndrome all had a missense pathogenic variant affecting amino acid 187 [Mitter et al 2018].

Penetrance

To date, no individuals (e.g., parent) with a pathogenic variant have been reported to be non-penetrant. Thus, penetrance is expected to be complete.

Nomenclature

FOXG1 syndrome was designated "congenital variant of Rett syndrome" in early descriptions. Kortüm et al [2011] observed that this designation was misleading because "while many features do overlap with Rett syndrome, several features beyond the congenital onset differ as well." Features of *FOXG1* syndrome that distinguish the disorder from Rett syndrome include distinctive neuroimaging abnormalities, the presence of a hyperkinetic/dyskinetic movement disorder, and the lack of regression.

Prevalence

To date, no data on the prevalence of *FOXG1* syndrome is available. The two largest cohorts described included 83 and 122 individuals [Mitter et al 2018, Brimble et al 2023], but it is likely that individuals included in Mitter et al [2018] participated in the patient registry and were reported in Brimble et al [2023]. According to the International FOXG1 Foundation, a US-based parental support group, approximately 1,000 people have been diagnosed worldwide.

Genetically Related (Allelic) Disorders

***FOXG1* whole-gene duplication**. The clinical characteristics of *FOXG1* duplication overlap with those associated with *FOXG1* deletions / intragenic pathogenic variants, but there are also clear differences. In general, individuals with *FOXG1* duplications have milder developmental delay than those with *FOXG1* deletions / intragenic pathogenic variants. Onset of seizures is usually earlier; many individuals have infantile spasms that respond well to hormonal treatment. Head circumference and neuroimaging in individuals with *FOXG1* duplication is usually normal [Brunetti-Pierri et al 2011, Seltzer et al 2014, Wong et al 2019]. A study comparing key characteristics of epilepsy and development after age three years in individuals with *FOXG1*-related disorders found that individuals with deletions / intragenic pathogenic variants showed older mean age of epilepsy diagnosis, higher current number of anti-seizure medication, worse ambulation, and worse functional

hand use compared to those with *FOXG1* duplications [Seltzer et al 2014]. Verbal language and social skills were impaired equally in both groups.

Contiguous gene duplications. Several individuals with *FOXG1* duplications have larger contiguous duplications of 14q12. Some of these individuals have dysmorphic facial features.

Contiguous gene deletions. Deletions encompassing *FOXG1* and adjacent genes (e.g., *PRKD1* and *NOVA1*) have been reported in individuals with facial dysmorphisms (including prominent metopic suture, epicanthal folds, bulbous nasal tip, tented upper lip, everted lower lip, and large ears) in addition to features consistent with *FOXG1* syndrome [Papa et al 2008, Mencarelli et al 2009]. These observations indicate that the deletion of *PRKD1* contributes to the contiguous gene deletion phenotype.

Differential Diagnosis

Table 3. Selected Disorders of Interest in the Differential Diagnosis of *FOXG1* Syndrome

Gene / Genetic Mechanism	Disorder	MOI	Features of Disorder	
			Overlapping w/*FOXG1* syndrome	Distinguishing from *FOXG1* syndrome
CDKL5	*CDKL5*-related early infantile epileptic encephalopathy (See CDLK5 Deficiency Disorder.)	XL	• Severe DD/ID • Hypotonia • Central visual impairment • Deceleration of growth (weight, height, head circumference) after birth	• Predominant severe refractory infantile-onset epilepsy • Neuroimaging may show progressive cerebral atrophy (but not malformations, as characteristically observed in *FOXG1* syndrome).
MECP2	*MECP2*-related Rett syndrome (See *MECP2* Disorders.)	XL	• Global DD • Sleep disturbances • Seizures • Hand stereotypies & loss of purposeful hand skills • Breathing irregularities • Agitation	• In females, apparently normal psychomotor development during 1st 6-18 mos of life • Psychomotor regression is characteristically observed. • Gait abnormalities • Absence of hyperkinetic/ dyskinetic movement disorder • Neuroimaging is normal.
Deficient expression or function of maternally inherited *UBE3A* allele	Angelman syndrome	See footnote 1.	• Severe DD/ID • Severe speech impairment • Acquired microcephaly • Seizures	• Unique behavior w/apparent happy demeanor, frequent laughing, smiling, & excitability • Gait ataxia (not hypotonia &/or spasticity as in *FOXG1* syndrome) • Highly characteristic EEG features are noted early in disease course. • Neuroimaging is typically normal.

DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Individuals with Angelman syndrome typically represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* genetic alteration associated with a very low recurrence risk.

Management

No clinical practice guidelines for *FOXG1* syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *FOXG1* syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. *FOXG1* Syndrome: 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
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern. • To incl eval for hyperkinetic/dyskinetic movement disorder
Neurobehavioral	Neuropsychiatric eval	• For infants: screening for irritability, episodes of crying, abnormal sleep patterns • For persons age >12 mos: screening for concerns incl sleep disturbances, impairment of social interaction
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl assessment for feeding difficulties • To incl eval for gastroesophageal reflux • To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement &/or fundoplication in persons w/dysphagia &/or aspiration risk.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, &/or need for low vision services
Hearing	Audiologic eval	Assess for hearing loss.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *FOXG1* syndrome 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

ADL = activities of daily living; 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 *FOXG1* syndrome. 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. *FOXG1* Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Hyperkinetic/dyskinetic movement disorder	Consider anti-dyskinetic pharmacotherapy (e.g., pimozide, biperiden, tetrabenazine, trihexyphenidyl hydrochloride, clonidine, cannabinoids).	No single drug has been found to be convincingly effective.
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]
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
	Anti-spasmodic pharmacotherapy: • Local: botulinum toxin • Systemic: baclofen, tolperisone, nitrazepam	
Feeding issues / Poor weight gain / Gastrointestinal	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues. • Standard therapies for gastroesophageal reflux	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Eyes/Vision	Treatment per ophthalmologist for refractive errors, strabismus	
	No specific treatment for cerebral visual impairment	Early intervention program to stimulate visual development
Scoliosis	Standard treatment per orthopedist	
Bowel dysfunction	Monitor for constipation. [2]	Stool softeners, prokinetics, osmotic agents, or laxatives as needed
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; 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. Incidence of constipation has not been reported in individuals with *FOXG1* syndrome; however, constipation is a common issue in most neurodevelopmental disorders.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the US; 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., 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, when necessary.

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. *FOXG1* Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
Neurobehavioral	Assess for irritability &/or sleep issues.	
Feeding/ Gastrointestinal	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake • Assessment for gastroesophageal reflux	
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Ophthalmologic involvement	Monitor for strabismus.	Per treating ophthalmologist(s)
	Assess need for low vision services.	At each visit
Gastrointestinal	Monitor for constipation. [1]	
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).	

OT = occupational therapy; PT = physical therapy

1. Incidence of constipation has not been reported in individuals with *FOXG1* syndrome; however, constipation is a common issue in most neurodevelopmental disorders.

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

FOXG1 syndrome 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 *FOXG1* syndrome whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo FOXG1* pathogenic variant.
- Rarely, a proband with *FOXG1* syndrome has the disorder as the result of a *FOXG1* pathogenic variant inherited from an unaffected, mosaic parent [Diebold et al 2014, Papandreou et al 2016].
- 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 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 (gonadal) cells only.

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

- If a parent of the proband is known to have the *FOXG1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *FOXG1* 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 [Diebold et al 2014, Papandreou et al 2016]. Seltzer et al [2014] described sib recurrence due to presumed parental mosaicism in two families.

Offspring of a proband

- Individuals with *FOXG1* syndrome are not known to reproduce; however, many are not yet of reproductive age.

- Each child of an individual with *FOXG1* syndrome has a 50% chance of inheriting the *FOXG1* pathogenic variant.

Other family members. Given that most probands with *FOXG1* syndrome reported to date have the disorder as a result of a *de novo FOXG1* pathogenic variant, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Risk to future pregnancies is presumed to be low, as the proband most likely has a *de novo FOXG1* pathogenic variant. There is, however, a recurrence risk to sibs based on the possibility of parental germline mosaicism. Given this risk, prenatal and preimplantation genetic testing may be considered.

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

- **FOXG1 Research Foundation**

  foxg1research.org

- **International FOXG1 Foundation**

  Email: info@foxg1.org

  foxg1.org

- **Global FOXG1 Patient Registry**

  The FOXG1 syndrome patient registry is an online international platform available in English, French, German, Spanish, and Mandarin.

  FOXG1 Patient Data Center

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. FOXG1 Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

FOXG1	14q12	Forkhead box protein G1	RettBASE	FOXG1	FOXG1

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 FOXG1 Syndrome (View All in OMIM)

164874	FORKHEAD BOX G1; FOXG1
613454	RETT SYNDROME, CONGENITAL VARIANT

Molecular Pathogenesis

FOXG1 is composed of one coding exon and belongs to the forkhead family of genes. *FOXG1* encodes forkhead box protein G1 (FOXG1), a transcription repressor expressed in fetal and adult brain. It is essential for the development of the forebrain (telencephalon) and for structures deriving from the telencephalon, including the cerebral cortex, hippocampus, and basal ganglia in mice. FOXG1 affects the early phase of cortical development by regulating progenitor cell proliferation and differentiation in the neocortex and is considered a key promoter of neocortical lamination. FOXG1 has a critical role in the formation of the postnatal and adult hippocampal dentate gyrus and in interneuron development. These functional characteristics of FOXG1 do not explain the full clinical phenotype, but may relate to single though nonspecific features such as intellectual disability, hyperkinetic/dyskinetic movement disorder, and dysplasia of predominantly the frontal part of the corpus callosum [Mitter et al 2018, Wong et al 2019].

Mechanism of disease causation. Intragenic deletions and truncating variants result in loss of function of the protein. This likely holds true to a lesser extent for pathogenic missense variants.

Note: The pathomechanism of *FOXG1* duplication (see Genetically Related Disorders) is not understood. In vitro and animal studies have shown that overexpression of *FOXG1* leads to dendrite elongation, whereas knockdown or knockout of *FOXG1* leads to reduced axon and dendrite length, as well as dendrite branching and spine densities [Wong et al 2019].

Chapter Notes

Acknowledgments

KB and MS thank all our colleagues who worked with us in our *FOXG1* syndrome projects. These studies would not have been possible without the invaluable cooperation of the patients and their families.

This work was supported by funding from the Niedersächsisches Ministerium für Wissenschaft und Kultur, grant no. 74ZN1284 (to KB).

Revision History

- 6 June 2024 (sw) Review posted live
- 13 November 2023 (kb) Original submission

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