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FOXP1 Syndrome

Synonyms: FOXP1 Haploinsufficiency, *FOXP1*-Related Neurodevelopmental Disorder

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Summary

Clinical characteristics

FOXP1 syndrome is characterized by delays in early motor and language milestones, mild-to-severe intellectual deficits, speech and language impairment in all individuals regardless of level of cognitive abilities, and behavior abnormalities (including autism spectrum disorder or autistic features, attention-deficit/hyperactivity disorder, anxiety, repetitive behaviors, sleep disturbances, and sensory symptoms). Other common findings are oromotor dysfunction (contributing to speech and feeding difficulties), refractive errors, strabismus, cardiac abnormalities, renal abnormalities, cryptorchidism, hypertonia, hearing loss, and epilepsy. To date, more than 200 individuals have been identified with FOXP1 syndrome.

Diagnosis/testing

The diagnosis of FOXP1 syndrome is established in a proband with a heterozygous pathogenic variant in *FOXP1* identified by molecular genetic testing and supportive clinical findings.

Management

Treatment of manifestations: Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in pediatrics, developmental medicine or neurodevelopment, neurology, physiatry, occupational and physical therapy, speech-language pathology, psychiatry, psychology, ophthalmology, and medical genetics.

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

Genetic counseling

FOXP1 syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. To date, most probands with FOXP1 syndrome whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo FOXP1* pathogenic variant. Rarely, a parent of an individual with FOXP1 syndrome has somatic and germline mosaicism for the *FOXP1* pathogenic variant or a complex chromosome arrangement involving *FOXP1*. Each child of an individual with FOXP1 syndrome has a 50% chance of inheriting the *FOXP1* pathogenic variant. Risk to future offspring of the parents of the proband is presumed to be low, as the proband most likely has a *de novo FOXP1* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the possibility of parental germline mosaicism; given this risk, prenatal and preimplantation genetic testing may be considered.

Diagnosis

No consensus clinical diagnostic criteria for FOXP1 syndrome have been published.

Suggestive Findings

FOXP1 syndrome should be considered in a proband with the following clinical findings, imaging findings, and family history.

Clinical findings

- Generalized hypotonia of infancy
- Infant feeding issues
- Mild-to-severe intellectual disability
- Speech and language disorder
- Delays in early motor and language milestones
- Behavior abnormalities:
  - Attention-deficit/hyperactivity disorder
  - Anxiety, combined with other clinical signs
  - Autism spectrum disorder or autistic features
  - Repetitive behaviors
- Strabismus, refractive errors
- Cryptorchidism
- Congenital abnormalities of the heart and/or kidneys

Facial features. Nonspecific dysmorphic facial features include a prominent forehead, ocular hypertelorism, down-slanting palpebral fissures, ptosis, short nose with a broad tip or base, thick vermilion, frontal hair upsweep, and irregular dentition, usually with wide spacing between the front teeth [Sollis et al 2016, Meerschaut et al 2017, Siper et al 2017, Lozano et al 2021, Trelles et al 2021].

Brain MRI findings. Structural brain abnormalities, observed on brain MRI in approximately half of affected individuals, include dilated lateral ventricles, white matter abnormalities, arachnoid cysts, large cisterna magna, corpus callosum defects, moderate frontal atrophy, cerebellar defects (including atrophy), and Chiari I malformation [Meerschaut et al 2017, Lozano et al 2021].

Family history. Because FOXP1 syndrome is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may suggest autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of FOXP1 syndrome **is established** in a proband with a heterozygous pathogenic (or likely pathogenic) variant in *FOXP1* identified by molecular genetic testing and suggestive findings (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 section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *FOXP1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular testing approaches. Because the phenotype of FOXP1 syndrome is indistinguishable from many other inherited disorders with intellectual disability, recommended molecular genetic testing approaches include use of a **multigene panel** (see Option 1) or **comprehensive genomic testing** (see Option 2).

Note: Single-gene testing (sequence analysis of *FOXP1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

An intellectual disability multigene panel that includes *FOXP1* and other genes of interest (see Differential Diagnosis) is most likely 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*. (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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in FOXP1 Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method
FOXP1	Sequence analysis [4]	~95% [5]
	Gene-targeted deletion/duplication analysis [6]	~5% [5, 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. Additional individuals with contiguous gene deletions (not included in these calculations) have been reported (see Genetically Related Disorders).
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. S Koene, unpublished data
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. There are three reports of complex rearrangements including inversions and translocations involving the *FOXP1* locus that may be detectable by karyotype [Talkowski et al 2012, Vuillaume et al 2018, Schluth-Bolard et al 2019].

Clinical Characteristics

Clinical Description

FOXP1 syndrome is characterized by mild-to-severe intellectual disability, speech and language impairment in all individuals despite level of cognitive abilities, behavior abnormalities (including autism spectrum disorder or autistic features, attention-deficit/hyperactivity disorder, anxiety, repetitive behaviors, and sensory symptoms), and dysmorphic features.

To date, more than 200 individuals have been identified with a pathogenic variant in *FOXP1* [Carr et al 2010, Hamdan et al 2010, O'Roak et al 2011, Chang et al 2013, Le Fevre et al 2013, Iossifov et al 2014, Srivastava et al 2014, Lozano et al 2015, Sollis et al 2016, Bekheirnia et al 2017, Meerschaut et al 2017, Siper et al 2017, Braden et al 2021, Lozano et al 2021] (see also FOXP1 Foundation). The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. FOXP1 Syndrome: Frequency of Select Features

Feature		% of Persons w/Feature
Developmental delay		>90%
Intellectual disability	Mild to moderate	63%
	Severe	33%
Speech deficits		100%
Language deficits		100%
Oromotor dysfunction		>50%
Drooling		30%
Behavior issues	Repetitive behavior	95%
	Attention-deficit/hyperactivity disorder	75%
	Autism spectrum disorder	24%-50%
	Anxiety disorder	38%

Table 2. continued from previous page.

Feature		% of Persons w/Feature
Motor dysfunction	Infantile hypotonia	29%
	Gait abnormality	15%
	Other musculoskeletal dysfunction	20%
Ophthalmologic issues	Refractive errors	50%
	Strabismus	18%
	Other	5%
Feeding difficulties		21%
Hypertonia / muscle spasms		34%
Hearing loss		17%
Epilepsy		12%
Genital anomalies (males)	Cryptorchidism	22%
	Micropenis	7%
CAKUT		7%
Cardiac abnormality		30%

Adapted from Meerschaut et al [2017], Lozano et al [2021], Trelles et al [2021]
CAKUT = congenital anomalies of the kidney and urinary tract

Developmental delay (DD) and intellectual disability (ID). Common neurologic features include global developmental delay (i.e., language, motor, cognitive) in young children and, with time, mild-to-severe intellectual disability. While intellectual disability is mild to moderate in the majority of individuals, several individuals have borderline to average cognitive functioning. Importantly, even in individuals who do not have intellectual disability, other persistent issues are likely to include learning disabilities, motor problems, and speech and language deficits.

Motor delays. Impairments in both gross and fine motor skills have been identified. Despite motor delays and hypotonia, individuals with FOXP1 syndrome learn to walk (range: age 13-38 months (21.75 ± 5.49); a subset of individuals display gait abnormalities and the majority of individuals display deficits in motor coordination and visual-motor integration [Trelles et al 2021]. Fine motor weakness can affect handwriting and written expression.

Speech deficits. Dysarthria, the most common speech disorder, is a defining feature of FOXP1 syndrome. Apraxic features and phonologic deficits may also co-occur [Braden et al 2021].

The speech difficulties lead listeners to presume expression of language (vocabulary, grammar) is more affected than understanding, but this is not the case.

Language deficits. While all individuals have language deficits to various degrees, language ability ranges from no words to fluent, complex sentences. While language impairment generally persists beyond early childhood, the majority of individuals do develop some expressive language. While language is typically low for most individuals, expressive language (i.e., the ability to express vocabulary and grammar) is a relative strength compared to receptive language (the understanding of vocabulary and grammar) [Braden et al 2021].

Oromotor dysfunction, likely due to poor motor planning and the presence of hypotonia, can contribute to speech and feeding difficulties. Excessive drooling is present until late childhood in around 30% of individuals [Braden et al 2021].

Autism spectrum disorder and other behavioral issues. Although autistic features occur in the majority of individuals, only about 25% meet DSM-5 criteria for autism spectrum disorder (ASD), based on clinical judgement due to strengths in social reciprocity and nonverbal communication (i.e., gestures, eye contact, facial expression).

Development and maintenance of friendships is an area of particular challenge.

Despite certain social communication strengths, repetitive behaviors, restricted interests, and sensory symptoms are highly prevalent even in those who do not meet DSM-5 criteria for ASD. Specifically, long-standing restricted interests are common and can be all encompassing in their intensity (e.g., collecting objects of interest).

Sensory manifestations are characterized by frequent sensory seeking (finger picking is also common), tactile hyporeactivity (i.e., high pain threshold), and auditory hyperreactvity. Repetitive behaviors and sensory manifestations are present in the majority of individuals with FOXP1 syndrome regardless of the diagnosis of ASD.

Behavioral problems include hyperactivity, attention problems, impulsivity, aggression, anxiety, mood lability, obsessions, and compulsions. Attention-deficit/hyperactivity disorder (ADHD) is present in the majority of individuals, often combined with hyperactivity and inattention.

Aggressive behavior is common, often emerging during early childhood and likely due to low frustration tolerance and communication challenges. In most individuals, hyperactivity and aggressive behavior appear to improve with age.

Motor impairments involve both gross and fine motor skills. Despite motor delays and hypotonia, individuals with FOXP1 syndrome learn to walk; some display gait abnormalities, and the majority display deficits in motor coordination and visual-motor integration. Fine motor weakness can affect handwriting and written expression.

Hypotonia, seen in half of affected individuals, can be either generalized or axial. Some individuals have peripheral hypertonia and axial hypertonia. In the latter instance, movement disorder / gait disturbance can include the presence of spastic contractures. Muscle spasms have also been reported.

Ophthalmologic involvement, common in FOXP1 syndrome, includes refractive errors (hypermetropia and myopia) and strabismus (including esotropia). Central vision loss may be present. Although nystagmus has been reported, no specific information is available on the age of onset or cause. Developmental defects of the iris (coloboma, aniridia) and optic nerve hypoplasia have been reported in single individuals.

Cardiac. Congenital heart defects are present in approximately 25% of individuals [Lozano et al 2021], with rates ranging from 14% [Trelles et al 2021] to 47% in older studies [Meerschaut et al 2017]. Atrial septal defects are most common. Patent ductus arteriosus, patent foramen ovale, and pulmonary stenosis are less common. In individual case reports heart defects included hypoplastic left ventricle with atrioventricular septal defect, hypoplastic left ventricle with mitral valve and aortic valve atresia, atrioventricular septal defect, and pulmonary atresia with a single ventricle in the presence of heterotaxy syndrome.

Feeding difficulties. Some feeding problems may be present at birth (e.g., difficulty latching).

Gastrointestinal problems. Constipation and gastroesophageal reflux disease (GERD), the most commonly reported gastrointestinal problems, are frequently overlooked. GERD that emerged during infancy resolved in some individuals.

Swallowing problems may also result from esophageal achalasia, resulting from failure of the lower esophageal sphincter to relax after swallowing [Myers et al 2017].

Hearing impairment. Although reported occasionally, little is known about the specific type of loss (e.g., sensorineural vs conductive). Twelve percent of individuals had frequent ear infections.

Epilepsy. The semiology of seizures in FOXP1 syndrome is highly heterogeneous; to date no pattern specific to FOXP1 syndrome has emerged. Likewise, age of onset of seizures is variable. Anecdotally, most affected individuals respond to standard anti-seizure medications; treatment-refractory seizures appear to be rare.

Other associated features

- **Gastrointestinal.** There are individual reports of gut atresia (no information available on location or length), hepatic and bile duct abnormality (no other details available), esophageal dysmotility, and anal malformation.
- **Genital abnormalities in males** include cryptorchidism and micropenis. It is unknown if genital abnormalities occur in females.
- **CAKUT (congenital anomalies of the kidney and urinary tract)** have been reported in ~7% of individuals. Upper and lower urinary tract defects represent the majority of the detected abnormalities, including unilateral renal agenesis, hydronephrosis, and duplicated renal collecting system.
- **Incontinence** may be present for a longer duration than expected based on cognitive development.

Prognosis. Based on current data, life span is not limited in FOXP1 syndrome [Palumbo et al 2013, Song et al 2015]. Progression of neurologic findings in adulthood has not been described. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with FOXP1 syndrome are underrecognized and underreported.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

FOXP1 syndrome may be referred to as "*FOXP1*-related neurodevelopmental disorder" based on the dyadic naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

Prevalence

FOXP1 syndrome is considered rare. Approximately 200 individuals have been identified in the medical literature and by the FOXP1 Foundation.

According to the SFARI Gene database, *FOXP1* is among the most common genes causing autism spectrum disorder.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with a heterozygous germline pathogenic variant in *FOXP1*.

Contiguous gene deletions encompassing *FOXP1* and adjacent genes have been reported in individuals with intellectual disability (that is generally more severe than in FOXP1 syndrome), neuromotor delay, sensorineural hearing loss, and feeding difficulties. Growth restriction and abnormal facial features have also been reported [Meerschaut et al 2017, Fu et al 2021, Trelles et al 2021].

Hearing impairment occurs more frequently in individuals with extended 3p deletions that include *MITF*, the gene associated with Waardenburg syndrome type IIA (OMIM 193510).

Sporadic tumors occurring as single tumors in the absence of any other findings of FOXP1 syndrome frequently contain a somatic pathogenic variant in *FOXP1* that is **not** present in the germline. In these circumstances predisposition to these tumors is **not** heritable.

Differential Diagnosis

Because the phenotypic features associated with FOXP1 syndrome are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

No clinical practice guidelines for FOXP1 syndrome have been published. Management recommendations below are based on information in the current literature and the authors' clinical experience.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with FOXP1 syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. FOXP1 Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Height, weight	
Developmental delay in general (language, social, motor, &/or cognitive) *	Developmental assessment (by school system, neurology, developmental medicine, speech pathology, &/or psychiatry/ psychology)	Assess developmental skills (incl cognitive, language, social, motor, & adaptive) & need for developmental services.
Neurologic **	Neurologic eval	• Evaluate events suggestive of seizures; consider EEG if seizures are a concern. • Evaluate for abnormalities of tone (i.e., hypotonia & spasticity). • Perform neurologic exam to evaluate for focal &/or other abnormalities that may warrant brain MRI.
Musculoskeletal/ADL **	PT, OT, &/or physical medicine & rehab eval	Assess: • Gross motor & fine motor skills; • Spasticity, joint contractures, scoliosis; • Mobility, ADL, & need for adaptive devices; • Need for ongoing PT therapy (to improve gross motor skills) &/or ongoing OT therapy (to improve fine motor skills, sensory processing).
Speech & language disorder *	Speech-language pathology eval	• Evaluate oral motor function incl drooling. • Evaluate speech production & receptive/expressive language in all persons, regardless of age. • To pinpoint specific diagnoses & make recommendations for targeted therapies
Neurobehavioral/ psychiatric concerns *	Neurologic, psychiatry, &/or developmental medicine eval	• To screen for behavior concerns incl ADHD, impulsivity, anxiety, sleep disturbances, &/or findings suggestive of ASD [1]

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Feeding difficulties**	Nutrition / feeding team eval (OT, SLP)	• To evaluate risk of aspiration & nutritional status • To assess for feeding challenges relative to developmental stage (e.g., breast/bottle feeding in infancy; transition to chewable solids in toddlers)
Ophthalmologic involvement *	Ophthalmologic eval	To assess for refractive errors, strabismus
Cardiac *	Cardiology eval	Electrocardiography & echocardiography is recommended at time of diagnosis.
CAKUT **	Screening abdominal ultrasound if symptomatic (e.g., UTIs)	
Cryptorchidism **	Routine pediatric exam	Referral to pediatric urologist as needed
Genetic counseling *	Genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of FOXP1 syndrome to facilitate medical & personal decision making
Family support & resources *		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral; • Early intervention referral; • Case management support referral.

* = for all individuals; ** = based on concern
ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; CAKUT = congenital anomalies of the kidney and urinary tract; MOI = mode of inheritance; OT = occupational therapy/therapist; PT = physical therapy/therapist; SLP = speech-language pathology/pathologist; UTI = urinary tract infection
1. Gold-standard autism diagnostic assessments such as the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS®-2) and the Autism Diagnostic Interview-Revised (ADI®-R) have high sensitivity but poor specificity in diagnosing autism spectrum disorder in FOXP1 syndrome and should be interpreted with caution.
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for FOXP1 syndrome.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in pediatrics, developmental medicine or neurodevelopment, neurology, physiatry, occupational and physical therapy, speech-language pathology, psychiatry, psychology, ophthalmology, and medical genetics (see Table 4).

Table 4 FOXP1 Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Intellectual disability	Per developmental medicine / neurodevelopmental specialist	See Developmental Delay / Intellectual Disability Management Issues.
Motor delay		
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.

Table 4 continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Speech & language disorder	• Speech & language therapy tailored to child's specific profile & developmental age. • Consider early reading & spelling support as age appropriate.	Augmentative or alternative communication devices in early years may optimize communication development.
Behavioral disorders	Standardized treatment by neurologist, developmental medicine specialist, &/or psychiatrist familiar w/neurodevelopmental behavior problems	May need to develop an educational behavioral intervention plan (BIP)
	Sensory integration therapy w/OT [1]	If sensory processing issues are present
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many different ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [2]
Infant feeding issues	Feeding therapy to help coordination of oral movements for feeding or sensory-related feeding issues. Food & fluid can be modified for safety.	Low threshold for clinical feeding eval by feeding team
Cardiac involvement	Per treating cardiologist	
Refractive error &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	
Excessive drooling		Some persons may be treated w/medication (such as glycopyrrolate). [3]
Cryptorchidism	Per treating 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. • Connect to parent advocacy group.	Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy/therapist; PT = physical therapy/therapist

1. Occupational therapy with the use of sensory-based therapies may be acceptable as one of the components of a comprehensive treatment plan. However, parents should be informed that the amount of research regarding the effectiveness of sensory integration therapy is limited and inconclusive [Zimmer 2012, Zimmer et al 2012].

2. 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.

3. See NICE guidelines on oral glycopyrronium bromide.

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-language, 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 and results from referral to Child Find programs. 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, speech, language, social, or cognitive delay(s). 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.
  - Vocational opportunities and programming including vocational rehabilitation should be considered early with a focus on achievement of meaningful employment
- 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.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as self-feeding, grooming, dressing, and writing.

Oral motor dysfunction. Feeding therapy (typically from a speech-language pathologist or occupational therapist) is recommended to help improve coordination of oral movement skills for feeding or sensory-related feeding issues using relevant approaches including postural modification and altering the consistency of food and fluid [Morgan et al 2012]. Lactating caregivers may need support from a breastfeeding or lactation consultant in the early weeks or months of life.

Gross motor dysfunction. Physical therapy may be recommended for difficulty with crawling, walking, running, and building strength resulting from hypotonia.

Speech and language disorder. Consider evaluation for nonverbal support or alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals with severe speech and 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.

In terms of verbal development, difficulties with motor planning (apraxia) and execution (dysarthria) is severe in the early years of life, and intensive evidence-based motor speech therapies should be applied [Morgan et al 2018]. Early phonologic awareness tasks should be implemented to support speech and later literacy development. Therapies addressing both receptive and expressive semantics and grammar are also recommended. The optimal intervention will be tailored to the child's specific profile as it changes during 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, neurologist, or psychiatrist 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 neurologist, developmental specialist, psychologist, or psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. FOXP1 Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Overall neurodevelopment	Monitor developmental progress & educational needs.	As recommended by neurologist &/or developmental pediatrician overseeing neurodevelopment
Speech & language disorder	• Assessment of ongoing therapy initiated w/early interventional services • Referral to AAC specialist overtime if warranted • Eval for speech disorder subtype over time	As recommended by SLP
Motor delay / ADL	OT/PT assessment of mobility & self-help skills, as well as ongoing therapy	As recommended by OT/PT
Skeletal	Eval for skeletal or neuromuscular problems	As recommended by treating pediatrician, neurologist, or physiatrist
Neurobehavioral/ Psychiatric	Behavioral assessment for signs of ADHD, ASD, anxiety, aggressive behavior, &/or sleeping disturbances	As recommended by treating neurologist, developmental pediatrician, psychologist, or psychiatrist
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	As recommended by feeding team (speech pathologist, dietician, pediatrician)

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Neurologic	Evaluate those w/seizures as clinically indicated.	As recommended by treating neurologist
	Assess for new manifestations such as seizures, changes in tone, & movement disorders.	As recommended by treating neurologist
Ophthalmologic involvement	By treating ophthalmologist	As recommended by treating ophthalmologist
Digestive problems	By treating pediatrician or gastroenterologist	As recommended by treating pediatrician/gastroenterologist
Cardiac involvement	By treating cardiologist	Based on findings & according to standard practice
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, & follow-up genetic counseling if new questions arise (e.g., family planning).	As needed

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy/therapist; PT = physical therapy/therapist; SLP = speech-language pathologist

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.

Icahn School of Medicine at Mount Sinai is currently recruiting for an observational clinical trial on FOXP1 syndrome (NCT03718923).

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

FOXP1 syndrome is an autosomal dominant disorder typically caused by a *de novo FOXP1* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with FOXP1 syndrome whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo FOXP1* pathogenic variant.
- Rarely, a parent of an individual with FOXP1 syndrome has somatic and germline mosaicism for the *FOXP1* pathogenic variant or a complex chromosome arrangement involving *FOXP1*. In one family, an affected parent with a complex inversion disrupting *FOXP1* transmitted the rearrangement to an affected child [Schluth-Bolard et al 2019]. In another family, an unaffected parent carrying a (balanced)

intrachromosomal 3p insertion transmitted a 3p deletion including *FOXP1* to an affected child [Lloveras et al 2014].

- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling. If the proband has a complex chromosomal rearrangement involving *FOXP1*, testing for a chromosome rearrangement in the parents is also recommended.
- If the proband has a genetic alteration involving *FOXP1* that is not identified in either parent, neither parent has a chromosome alteration, 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.

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 *FOXP1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If one of the parents has a chromosome rearrangement, the risk to sibs is increased and depends on the specific chromosome rearrangement and the possibility of other variables.
- If the *FOXP1* genetic alteration found in the proband cannot be detected in the leukocyte DNA of either parent and neither parent has a chromosome alteration, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with FOXP1 syndrome has a 50% chance of inheriting the *FOXP1* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *FOXP1* genetic alteration, 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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Risk to future offspring of the parents of the proband is presumed to be low, as the proband most likely has a *de novo FOXP1* pathogenic variant. There is, however, a recurrence risk (~1%) 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.

- **International FOXP1 Foundation**
  Email: internationalfoxp1foundation@googlegroups.com
  www.foxp1.org
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **Apraxia Kids**
  Phone: 412-785-7072
  Email: info@apraxia-kids.org
  apraxia-kids.org
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net
- **Simons Searchlight Registry**
  Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.
  Phone: 855-329-5638
  Fax: 570-214-7327
  Email: coordinator@simonssearchlight.org
  www.simonssearchlight.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. FOXP1 Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
FOXP1	3p13	Forkhead box protein P1	FOXP1	FOXP1

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 FOXP1 Syndrome (View All in OMIM)

605515	FORKHEAD BOX P1; FOXP1
613670	INTELLECTUAL DEVELOPMENTAL DISORDER WITH LANGUAGE IMPAIRMENT AND WITH OR WITHOUT AUTISTIC FEATURES

Molecular Pathogenesis

FOXP1 syndrome is caused by defects in *FOXP1*, which encodes FOXP1, part of the Forkhead box (FOX) group of proteins, an evolutionarily ancient family of transcription factors characterized by a highly conserved forkhead DNA-binding domain. FOXP1 has been associated with a wide range of functions including development of the brain, heart, esophagus, lung, immune system, and spinal motor neurons. Disruption of FOXP1 function is predicted to impair mitochondrial function and lead to oxidative stress, thereby contributing to cognitive and motor impairment [Fröhlich et al 2019].

The phenotypic spectra of FOXP1 and FOXP2 disruptions suggest that these closely related transcription factors are involved in both shared and distinct neurodevelopmental pathways underlying cognitive diseases through the regulation of common and exclusive targets [Bacon & Rappold 2012].

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

Prof Gudrun Rappold (gudrun.rappold@med.uni-heidelberg) is actively involved in basic and clinical research regarding individuals with FOXP1 syndrome. Dr Alexander Kolevozn (alexander.kolevzon@mssm.edu), Dr Paige Siper (paige.siper@mssm.ed), and Dr Ana Kostic (ana.kostic@mssm.edu) are actively involved in clinical research and drug discovery in FOXP1 syndrome.

Dr Saskia Koene (s.koene@lumc.nl) is actively involved in clinical research regarding individuals with FOXP1 syndrome. She would be happy to communicate with persons who have any questions regarding FOXP1 syndrome.

Dr Ruth Braden (braden.r@unimelb.edu.au) and Professor Angela Morgan (angela.morgan@mcri.edu.au) are actively involved in research investigating speech and language abilities in individuals with FOXP1 syndrome. More information about our work, and how to get involved in studies, is available at www.geneticsofspeech.org.au.

Contact Dr Saskia Koene (s.koene@lumc.nl) to inquire about review of *FOXP1* variants of uncertain significance.

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