FOXP1 syndrome

https://www.ncbi.nlm.nih.gov/books/NBK594825/

SummaryClinical 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.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.

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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.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.

DiagnosisNo consensus clinical diagnostic criteria for FOXP1 syndrome have been published.Suggestive FindingsFOXP1 syndrome should be considered in a proband with the following clinical findings, imaging findings, and family history.

Clinical findings

Generalized hypotonia of infancyInfant feeding issuesMild-to-severe intellectual disabilitySpeech and language disorderDelays in early motor and language milestonesBehavior abnormalities:Attention-deficit/hyperactivity disorderAnxiety, combined with other clinical signsAutism spectrum disorder or autistic featuresRepetitive behaviorsStrabismus, refractive errorsCryptorchidismCongenital abnormalities of the heart and/or kidneysFacial 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 DiagnosisThe 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 1An 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 2Comprehensive 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 SyndromeView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2, 3 Detectable by Method

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Strabismus, refractive errors

Cryptorchidism

Congenital abnormalities of the heart and/or kidneys

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Clinical CharacteristicsClinical DescriptionFOXP1 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 FeaturesView in own windowFeature% of Persons w/FeatureDevelopmental delay>90%Intellectual disabilityMild to moderate63%Severe33%Speech deficits100%Language deficits100%Oromotor dysfunction>50%Drooling30%Behavior issuesRepetitive behavior95%Attention-deficit/hyperactivity disorder75%Autism spectrum disorder24%-50%Anxiety disorder38%Motor dysfunctionInfantile hypotonia29%Gait abnormality15%Other musculoskeletal dysfunction20%Ophthalmologic issuesRefractive errors50%Strabismus18%Other5%Feeding difficulties21%Hypertonia / muscle spasms34%Hearing loss17%Epilepsy12%Genital anomalies (males)Cryptorchidism22%Micropenis7%CAKUT7%Cardiac abnormality30%Adapted from Meerschaut et al [2017], Lozano et al [2021], Trelles et al [2021]CAKUT = congenital anomalies of the kidney and urinary tractDevelopmental 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 CorrelationsNo genotype-phenotype correlations have been identified.NomenclatureFOXP1 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.PrevalenceFOXP1 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.

Clinical DescriptionFOXP1 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. 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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.

Table 2. FOXP1 Syndrome: Frequency of Select FeaturesView in own windowFeature% of Persons w/FeatureDevelopmental delay>90%Intellectual disabilityMild to moderate63%Severe33%Speech deficits100%Language deficits100%Oromotor dysfunction>50%Drooling30%Behavior issuesRepetitive behavior95%Attention-deficit/hyperactivity disorder75%Autism spectrum disorder24%-50%Anxiety disorder38%Motor dysfunctionInfantile hypotonia29%Gait abnormality15%Other musculoskeletal dysfunction20%Ophthalmologic issuesRefractive errors50%Strabismus18%Other5%Feeding difficulties21%Hypertonia / muscle spasms34%Hearing loss17%Epilepsy12%Genital anomalies (males)Cryptorchidism22%Micropenis7%CAKUT7%Cardiac abnormality30%Adapted from Meerschaut et al [2017], Lozano et al [2021], Trelles et al [2021]CAKUT = congenital anomalies of the kidney and urinary tract

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Incontinence may be present for a longer duration than expected based on cognitive development.

Genotype-Phenotype CorrelationsNo genotype-phenotype correlations have been identified.

NomenclatureFOXP1 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.

PrevalenceFOXP1 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) DisordersNo 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 DiagnosisBecause 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.

ManagementNo 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 DiagnosisTo 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 DiagnosisView in own windowSystem/ConcernEvaluationComment

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Neurologic **

Neurologic evalEvaluate 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 evalAssess:

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 evalEvaluate 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 evalTo screen for behavior concerns incl ADHD, impulsivity, anxiety, sleep disturbances, &/or findings suggestive of ASD 1

Feeding difficulties**

Nutrition / feeding team eval (OT, SLP)To evaluate risk of aspiration & nutritional statusTo assess for feeding challenges relative to developmental stage (e.g., breast/bottle feeding in infancy; transition to chewable solids in toddlers)

Ophthalmologic involvement *

Ophthalmologic evalTo assess for refractive errors, strabismus

Cardiac *

Cardiology evalElectrocardiography & echocardiography is recommended at time of diagnosis.

CAKUT **

Screening abdominal ultrasound if symptomatic (e.g., UTIs)

Cryptorchidism **

Routine pediatric examReferral to pediatric urologist as needed

Genetic counseling *

Genetics professionals 2To 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 concernADHD = 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 infection1. 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 nurseTreatment of ManifestationsThere 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 ManifestationsView in own windowManifestation/ConcernTreatmentConsiderations/Other

Intellectual disability

Per developmental medicine / neurodevelopmental specialistSee Developmental Delay / Intellectual Disability Management Issues.

Motor delay

Spasticity

Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & fallsConsider need for positioning & mobility devices, disability parking placard.

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 problemsMay need to develop an educational behavioral intervention plan (BIP)Sensory integration therapy w/OT 1If sensory processing issues are present

Epilepsy

Standardized treatment w/ASM by experienced neurologistMany 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/therapist1. 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 IssuesThe 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 employmentA 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 ConcernsChildren 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.SurveillanceTo 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 SurveillanceView in own windowSystem/ConcernEvaluationFrequency

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 servicesReferral to AAC specialist overtime if warrantedEval 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 therapyAs recommended by OT/PT

Skeletal

Eval for skeletal or neuromuscular problemsAs recommended by treating pediatrician, neurologist, or physiatrist

Neurobehavioral/

Psychiatric

Behavioral assessment for signs of ADHD, ASD, anxiety, aggressive behavior, &/or sleeping disturbancesAs recommended by treating neurologist, developmental pediatrician, psychologist, or psychiatrist

Feeding

Measurement of growth parametersEval of nutritional status & safety of oral intake

As recommended by feeding team (speech pathologist, dietician, pediatrician)

Neurologic

Evaluate those w/seizures as clinically indicated.As recommended by treating neurologistAssess for new manifestations such as seizures, changes in tone, & movement disorders.As recommended by treating neurologist

Ophthalmologic involvement

By treating ophthalmologistAs recommended by treating ophthalmologist

Digestive problems

By treating pediatrician or gastroenterologistAs recommended by treating pediatrician/gastroenterologist

Cardiac involvement

By treating cardiologistBased 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 neededADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy/therapist; PT = physical therapy/therapist; SLP = speech-language pathologistEvaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.Therapies Under InvestigationSearch 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).

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Neurologic evalEvaluate 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 evalAssess:

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).

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psychiatric concerns *

Neurologic, psychiatry, &/or developmental medicine evalTo screen for behavior concerns incl ADHD, impulsivity, anxiety, sleep disturbances, &/or findings suggestive of ASD 1

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Ophthalmologic involvement *

Ophthalmologic evalTo assess for refractive errors, strabismus

Cardiac *

Cardiology evalElectrocardiography & echocardiography is recommended at time of diagnosis.

CAKUT **

Screening abdominal ultrasound if symptomatic (e.g., UTIs)

Cryptorchidism **

Routine pediatric examReferral to pediatric urologist as needed

Genetic counseling *

Genetics professionals 2To 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 concernADHD = 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 infection1. 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

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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).

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

To screen for behavior concerns incl ADHD, impulsivity, anxiety, sleep disturbances, &/or findings suggestive of ASD 1

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)

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 concernADHD = 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 infection1. 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

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Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of ManifestationsThere 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 ManifestationsView in own windowManifestation/ConcernTreatmentConsiderations/Other

Intellectual disability

Per developmental medicine / neurodevelopmental specialistSee Developmental Delay / Intellectual Disability Management Issues.

Motor delay

Spasticity

Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & fallsConsider need for positioning & mobility devices, disability parking placard.

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 problemsMay need to develop an educational behavioral intervention plan (BIP)Sensory integration therapy w/OT 1If sensory processing issues are present

Epilepsy

Standardized treatment w/ASM by experienced neurologistMany 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/therapist1. 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 IssuesThe 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 employmentA

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 ConcernsChildren 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.

Table 4 FOXP1 Syndrome: Treatment of ManifestationsView in own windowManifestation/ConcernTreatmentConsiderations/Other

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Excessive drooling

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Family/Community

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Manifestation/ConcernTreatmentConsiderations/Other

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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

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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.

Social/Behavioral ConcernsChildren 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.

SurveillanceTo 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 SurveillanceView in own windowSystem/ConcernEvaluationFrequency

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 servicesReferral to AAC specialist overtime if warrantedEval 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 therapyAs recommended by OT/PT

Skeletal

Eval for skeletal or neuromuscular problemsAs recommended by treating pediatrician, neurologist, or physiatrist

Neurobehavioral/

Psychiatric

Behavioral assessment for signs of ADHD, ASD, anxiety, aggressive behavior, &/or sleeping disturbancesAs recommended by treating neurologist, developmental pediatrician, psychologist, or psychiatrist

Feeding

Measurement of growth parametersEval of nutritional status & safety of oral intake

As recommended by feeding team (speech pathologist, dietician, pediatrician)

Neurologic

Evaluate those w/seizures as clinically indicated.As recommended by treating neurologistAssess for new manifestations such as seizures, changes in tone, & movement disorders.As recommended by treating neurologist

Ophthalmologic involvement

By treating ophthalmologistAs recommended by treating ophthalmologist

Digestive problems

By treating pediatrician or gastroenterologistAs recommended by treating pediatrician/gastroenterologist

Cardiac involvement

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

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Evaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under InvestigationSearch 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 InheritanceFOXP1 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 TestingRisk 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.

Mode of InheritanceFOXP1 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.

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.

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].

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.

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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 TestingRisk 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: 202-387-1968Fax: 202-387-2193

www.aaidd.org

Apraxia Kids

Phone: 412-785-7072Email: info@apraxia-kids.org

apraxia-kids.org

MedlinePlus

Intellectual Disability

VOR: Speaking out for people with intellectual and developmental disabilities

Phone: 877-399-4867Email: info@vor.net

www.vor.net

Simons Searchlight Registry

Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.

Phone: 855-329-5638Fax: 570-214-7327Email: coordinator@simonssearchlight.org

www.simonssearchlight.org

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

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Email: info@apraxia-kids.org

apraxia-kids.org

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Molecular GeneticsInformation 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 DatabasesView in own windowGeneChromosome LocusProteinHGMDClinVar

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) View in own window

605515FORKHEAD BOX P1; FOXP1

613670INTELLECTUAL DEVELOPMENTAL DISORDER WITH LANGUAGE IMPAIRMENT AND WITH OR WITHOUT AUTISTIC FEATURESMolecular PathogenesisFOXP1 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

Table A.FOXP1 Syndrome: Genes and DatabasesView in own windowGeneChromosome

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Table B.OMIM Entries for FOXP1 Syndrome (View All in OMIM) View in own window

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Chapter NotesAuthor NotesProf Gudrun Rappold (grebledieh-inu.dem@dloppar.nurdug) is actively involved in basic and clinical research regarding individuals with FOXP1 syndrome. Dr Alexander Kolevozn (ude.mssm@nozvelok.rednaxela), Dr Paige Siper (de.mssm@repis.egiap), and Dr Ana Kostic (ude.mssm@citsok.ana) are actively involved in clinical research and drug discovery in FOXP1 syndrome.Dr Saskia Koene (ln.cmul@eneok.s) 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 (ua.ude.bleminu@r.nedarb) and Professor Angela Morgan (ua.ude.ircm@nagrom.alegna) 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 (ln.cmul@eneok.s) to inquire about review of FOXP1 variants of uncertain significance.AcknowledgmentsWe acknowledge the involvement of Dr Henning Fröhlich and Prof Maja Hempel in this project. Research support is from the Deutsche Forschungsgemeinschaft and the Medical Faculty of the University of Heidelberg.We acknowledge individuals with FOXP1 syndrome and their families for their generous contributions to our research, and the FOXP1 Foundation for their ongoing support.Revision History21 September 2023 (bp) Review posted live26 August 2022 (gr) Original submission

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ReferencesLiterature CitedBacon

C, Rappold

GA. The distinct and overlapping phenotypic spectra of FOXP1 and FOXP2 in cognitive disorders.

Hum Genet.

2012;131:1687-98.

[PMC free article: PMC3470686] [PubMed: 22736078]Bekheirnia

MR, Bekheirnia

N, Bainbridge

MN, Gu

S, Coban Akdemir

ZH, Gambin

T, Janzen

NK, Jhangiani

SN, Muzny

DM, Michael

M, Brewer

ED, Elenberg

E, Kale

AS, Riley

AA, Swartz

SJ, Scott

DA, Yang

Y, Srivaths

PR, Wenderfer

SE, Bodurtha

J, Applegate

CD, Velinov

M, Myers

A, Borovik

L, Craigen

WJ, Hanchard

NA, Rosenfeld

JA, Lewis

RA, Gonzales

ET, Gibbs

RA, Belmont

JW, Roth

DR, Eng

C, Braun

MC, Lupski

JR, Lamb

DJ. Whole-exome sequencing in the molecular diagnosis of individuals with congenital anomalies of the kidney and urinary tract and identification of a new causative gene.

Genet Med.

2017;19:412-20.

[PMC free article: PMC5362362] [PubMed: 27657687]Biesecker

LG, Adam

MP, Alkuraya

FS, Amemiya

AR, Bamshad

MJ, Beck

AE, Bennett

JT, Bird

LM, Carey

JC, Chung

B, Clark

RD, Cox

TC, Curry

C, Dinulos

MBP, Dobyns

WB, Giampietro

PF, Girisha

KM, Glass

IA, Graham

JM

Jr, Gripp

KW, Haldeman-Englert

CR, Hall

BD, Innes

AM, Kalish

JM, Keppler-Noreuil

KM, Kosaki

K, Kozel

BA, Mirzaa

GM, Mulvihill

JJ, Nowaczyk

MJM, Pagon

RA, Retterer

K, Rope

AF, Sanchez-Lara

PA, Seaver

LH, Shieh

JT, Slavotinek

AM, Sobering

AK, Stevens

CA, Stevenson

DA, Tan

TY, Tan

WH, Tsai

AC, Weaver

DD, Williams

MS, Zackai

E, Zarate

YA. A dyadic approach to the delineation of diagnostic entities in clinical genomics.

Am J Hum Genet.

2021;108:8-15.

[PMC free article: PMC7820621] [PubMed: 33417889]Braden

RO, Amor

DJ, Fisher

SE, Mei

C, Myers

CT, Mefford

H, Gill

D, Srivastava

S, Swanson

LC, Goel

H, Scheffer

IE, Morgan

AT. Severe speech impairment is a distinguishing feature of FOXP1-related disorder.

Dev Med Child Neurol.

2021;63:1417-26.

[PubMed: 34109629]Carr

CW, Moreno-De-Luca

D, Parker

C, Zimmerman

HH, Ledbetter

N, Martin

CL, Dobyns

WB, Abdul-Rahman

OA. Chiari I malformation, delayed gross motor skills, severe speech delay, and epileptiform

discharges in a child with FOXP1 haploinsufficiency.

Eur J Hum Genet.

2010;18:1216-20.

[PMC free article: PMC2987472] [PubMed: 20571508]Chang

SW, Mislankar

M, Misra

C, Huang

N, Dajusta

DG, Harrison

SM, McBride

KL, Baker

LA, Garg

V. Genetic abnormalities in FOXP1 are associated with congenital heart defects.

Hum Mutat.

2013;34:1226-30.

[PMC free article: PMC5717756] [PubMed: 23766104]Fröhlich

H, Kollmeyer

ML, Linz

VC, Stuhlinger

M, Groneberg

D, Reigl

A, Zizer

E, Friebe

A, Niesler

B, Rappold

G. Gastrointestinal dysfunction in autism displayed by altered motility and achalasia in Foxp1+/-

mice.

Proc Natl Acad Sci U S A.

2019;116:22237-45.

[PMC free article: PMC6825283] [PubMed: 31611379]Fu

J, Wang

T, Fu

Z, Li

T, Zhang

X, Zhao

J, Yang

G.

Case report: a case report and literature review of 3p deletion syndrome.

Front Pediatr.

2021;9:618059.

[PMC free article: PMC7902511] [PubMed: 33643973]Hamdan

FF, Daoud

H, Rochefort

D, Piton

A, Gauthier

J, Langlois

M, Foomani

G, Dobrzeniecka

S, Krebs

MO, Joober

R, Lafrenière

RG, Lacaille

JC, Mottron

L, Drapeau

P, Beauchamp

MH, Phillips

MS, Fombonne

E, Rouleau

GA, Michaud

JL. De novo mutations in FOXP1 in cases with intellectual disability, autism, and language

impairment.

Am J Hum Genet.

2010;87:671-8.

[PMC free article: PMC2978954] [PubMed: 20950788]Iossifov

I, O'Roak

BJ, Sanders

SJ, Ronemus

M, Krumm

N, Levy

D, Stessman

HA, Witherspoon

KT, Vives

L, Patterson

KE, Smith

JD, Paeper

B, Nickerson

DA, Dea

J, Dong

S, Gonzalez

LE, Mandell

JD, Mane

SM, Murtha

MT, Sullivan

CA, Walker

MF, Waqar

Z, Wei

L, Willsey

AJ, Yamrom

B, Lee

YH, Grabowska

E, Dalkic

E, Wang

Z, Marks

S, Andrews

P, Leotta

A, Kendall

J, Hakker

I, Rosenbaum

J, Ma

B, Rodgers

L, Troge

J, Narzisi

G, Yoon

S, Schatz

MC, Ye

K, McCombie

WR, Shendure

J, Eichler

EE, State

MW, Wigler

M. The contribution of de novo coding mutations to autism spectrum disorder.

Nature.

2014;515:216-21.

[PMC free article: PMC4313871] [PubMed: 25363768]Le Fevre

AK, Taylor

S, Malek

NH, Horn

D, Carr

CW, Abdul-Rahman

OA, O'Donnell

S, Burgess

T, Shaw

M, Gecz

J, Bain

N, Fagan

K, Hunter

MF. FOXP1 mutations cause intellectual disability and a recognizable phenotype.

Am J Med Genet A.

2013;161A:3166-75.

[PubMed: 24214399]Lloveras

E, Vendrell

T, Fernández

A, Castells

N, Cueto

A, del Campo

M, Hernando

C, Villa

O, Plaja

A.

Intrachromosomal 3p insertion as a cause of reciprocal pure interstitial deletion and duplication in two siblings: further delineation of the emerging proximal 3p deletion syndrome.

Cytogenet Genome Res.

2014;144:290-3.

[PubMed: 25720458]Lozano

R, Gbekie

C, Siper

PM, Srivastava

S, Saland

JM, Sethuram

S, Tang

L, Drapeau

E, Frank

Y, Buxbaum

JD, Kolevzon

A. FOXP1 syndrome: a review of the literature and practice parameters for medical assessment and monitoring.

J Neurodev Disord.

2021;13:18.

[PMC free article: PMC8066957] [PubMed: 33892622]Lozano

R, Vino

A, Lozano

C, Fisher

SE, Deriziotis

P. A de novo FOXP1 variant in a patient with autism, intellectual disability and severe speech and language impairment.

Eur J Hum Genet.

2015;23:1702-7.

[PMC free article: PMC4795189] [PubMed: 25853299]Meerschaut

I, Rochefort

D, Revençu

N, Pètre

J, Corsello

C, Rouleau

GA, Hamdan

FF, Michaud

JL, Morton

J, Radley

J, Ragge

N, García-Miñaúr

S, Lapunzina

P, Bralo

MP, Mori

MÁ, Moortgat

S, Benoit

V, Mary

S, Bockaert

N, Oostra

A, Vanakker

O, Velinov

M, de Ravel

TJ, Mekahli

D, Sebat

J, Vaux

KK, DiDonato

N, Hanson-Kahn

AK, Hudgins

L, Dallapiccola

B, Novelli

A, Tarani

L, Andrieux

J, Parker

MJ, Neas

K, Ceulemans

B, Schoonjans

AS, Prchalova

D, Havlovicova

M, Hancarova

M, Budisteanu

M, Dheedene

A, Menten

B, Dion

PA, Lederer

D, Callewaert

B. FOXP1-related intellectual disability syndrome: a recognisable entity.

J Med Genet.

2017;54:613-23.

[PubMed: 28735298]Morgan

AT, Dodrill

P, Ward

EC. Interventions for oropharyngeal dysphagia in children with neurological impairment.

Cochrane Database Syst Rev.

2012;10:CD009456.

[PubMed: 23076958]Morgan AT, Murray E, Liégeois FJ. 2018. Intervention for childhood

apraxia of speech. Cochrane Database Syst Rev. 30;5:CD006278. [PMC free article: PMC6494637]

[PubMed: 29845607]Myers

A, du Souich

C, Yang

CL, Borovik

L, Mwenifumbo

J, Rupps

R, Study

C, Lehman

A, Boerkoel

CF. FOXP1 haploinsufficiency: phenotypes beyond behavior and intellectual disability?

Am J Med Genet A.

2017;173:3172-81.

[PubMed: 28884888]O'Roak

BJ, Deriziotis

P, Lee

C, Vives

L, Schwartz

JJ, Girirajan

S, Karakoc

E, Mackenzie

AP, Ng

SB, Baker

C, Rieder

MJ, Nickerson

DA, Bernier

R, Fisher

SE, Shendure

J, Eichler

EE. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations.

Nat Genet.

2011;43:585-9.

[PMC free article: PMC3115696] [PubMed: 21572417]Palumbo

O, D'Agruma

L, Minenna

AF, Palumbo

P, Stallone

R, Palladino

T, Zelante

L, Carella

M. 3p14.1 de novo microdeletion involving the FOXP1 gene in an adult patient with autism, severe speech delay and deficit of motor coordination.

Gene.

2013;516:107-13.

[PubMed: 23287644]Rahbari

R, Wuster

A, Lindsay

SJ, Hardwick

RJ, Alexandrov

LB, Turki

SA, Dominiczak

A, Morris

A, Porteous

D, Smith

B, Stratton

MR, Hurles

ME, et al.

Timing, rates and spectra of human germline mutation.

Nat Genet.

2016;48:126-33.

[PMC free article: PMC4731925] [PubMed: 26656846]Richards

S, Aziz

N, Bale

S, Bick

D, Das

S, Gastier-Foster

J, Grody

WW, Hegde

M, Lyon

E, Spector

E, Voelkerding

K, Rehm

HL, et al.

Standards and guidelines for the interpretation of sequence variants: a joint consensus

recommendation of the American College of Medical Genetics and Genomics and the Association

for Molecular Pathology.

Genet Med.

2015;17:405-24.

[PMC free article: PMC4544753] [PubMed: 25741868]Schluth-Bolard

C, Diguet

F, Chatron

N, Rollat-Farnier

PA, Bardel

C, Afenjar

A, Amblard

F, Amiel

J, Blesson

S, Callier

P, Capri

Y, Collignon

P, Cordier

MP, Coubes

C, Demeer

B, Chaussenot

A, Demurger

F, Devillard

F, Doco-Fenzy

M, Dupont

C, Dupont

JM, Dupuis-Girod

S, Faivre

L, Gilbert-Dussardier

B, Guerrot

AM, Houlier

M, Isidor

B, Jaillard

S, Joly-Hélas

G, Kremer

V, Lacombe

D, Le Caignec

C, Lebbar

A, Lebrun

M, Lesca

G, Lespinasse

J, Levy

J, Malan

V, Mathieu-Dramard

M, Masson

J, Masurel-Paulet

A, Mignot

C, Missirian

C, Morice-Picard

F, Moutton

S, Nadeau

G, Pebrel-Richard

C, Odent

S, Paquis-Flucklinger

V, Pasquier

L, Philip

N, Plutino

M, Pons

L, Portnoï

MF, Prieur

F, Puechberty

J, Putoux

A, Rio

M, Rooryck-Thambo

C, Rossi

M, Sarret

C, Satre

V, Siffroi

JP, Till

M, Touraine

R, Toutain

A, Toutain

J, Valence

S, Verloes

A, Whalen

S, Edery

P, Tabet

AC, Sanlaville

D. Whole genome paired-end sequencing elucidates functional and phenotypic consequences of balanced chromosomal rearrangement in patients with developmental disorders.

J Med Genet.

2019;56:526-35.

[PubMed: 30923172]Siper

PM, De Rubeis

S, Trelles

MDP, Durkin

A, Di Marino

D, Muratet

F, Frank

Y, Lozano

R, Eichler

EE, Kelly

M, Beighley

J, Gerdts

J, Wallace

AS, Mefford

HC, Bernier

RA, Kolevzon

A, Buxbaum

JD. Prospective investigation of FOXP1 syndrome.

Mol Autism.

2017;8:57.

[PMC free article: PMC5655854] [PubMed: 29090079]Sollis

E, Graham

SA, Vino

A, Froehlich

H, Vreeburg

M, Dimitropoulou

D, Gilissen

C, Pfundt

R, Rappold

GA, Brunner

HG, Deriziotis

P, Fisher

SE. Identification and functional characterization of de novo FOXP1 variants provides novel insights into the etiology of neurodevelopmental disorder.

Hum Mol Genet.

2016;25:546-57.

[PubMed: 26647308]Song

H, Makino

Y, Noguchi

E, Arinami

T.

A case report of de novo missense FOXP1 mutation in a non-Caucasian patient with global developmental delay and severe speech impairment.

Clin Case Rep.

2015;3:110-3.

[PMC free article: PMC4352365] [PubMed: 25767709]Srivastava

S, Cohen

JS, Vernon

H, Barañano

K, McClellan

R, Jamal

L, Naidu

S, Fatemi

A. Clinical whole exome sequencing in child neurology practice.

Ann Neurol.

2014;76:473-83.

[PubMed: 25131622]Talkowski

ME, Rosenfeld

JA, Blumenthal

I, Pillalamarri

V, Chiang

C, Heilbut

A, Ernst

C, Hanscom

C, Rossin

E, Lindgren

AM, Pereira

S, Ruderfer

D, Kirby

A, Ripke

S, Harris

DJ, Lee

JH, Ha

K, Kim

HG, Solomon

BD, Gropman

AL, Lucente

D, Sims

K, Ohsumi

TK, Borowsky

ML, Loranger

S, Quade

B, Lage

K, Miles

J, Wu

BL, Shen

Y, Neale

B, Shaffer

LG, Daly

MJ, Morton

CC, Gusella

JF. Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries.

Cell.

2012;149:525-37.

[PMC free article: PMC3340505] [PubMed: 22521361]Trelles

MP, Levy

T, Lerman

B, Siper

P, Lozano

R, Halpern

D, Walker

H, Zweifach

J, Frank

Y, Foss-Feig

J, Kolevzon

A, Buxbaum

J. Individuals with FOXP1 syndrome present with a complex neurobehavioral profile with high rates of ADHD, anxiety, repetitive behaviors, and sensory symptoms.

Mol Autism.

2021;12:61.

[PMC free article: PMC8482569] [PubMed: 34588003]Vuillaume

ML, Cogné

B, Jeanne

M, Boland

A, Ung

DC, Quinquis

D, Besnard

T, Deleuze

JF, Redon

R, Bézieau

S, Laumonnier

F, Toutain

A. Whole genome sequencing identifies a de novo 2.1 Mb balanced paracentric inversion disrupting FOXP1 and leading to severe intellectual disability.

Clin Chim Acta.

2018;485:218-23.

[PubMed: 29969624]Zimmer

MH. Not ready for prime time: policy cautions against using sensory processing disorder as a diagnosis.

AAP News.

2012;33:30.Zimmer

M, Desch

L, et al.

Sensory integration therapies for children with developmental and behavioral disorders.

Pediatrics.

2012;129:1186-9.

[PubMed: 22641765]

Literature CitedBacon

C, Rappold

GA. The distinct and overlapping phenotypic spectra of FOXP1 and FOXP2 in cognitive disorders.

Hum Genet.

2012;131:1687-98.

[PMC free article: PMC3470686] [PubMed: 22736078]Bekheirnia

MR, Bekheirnia

N, Bainbridge

MN, Gu

S, Coban Akdemir

ZH, Gambin

T, Janzen

NK, Jhangiani

SN, Muzny

DM, Michael

M, Brewer

ED, Elenberg

E, Kale

AS, Riley

AA, Swartz

SJ, Scott

DA, Yang

Y, Srivaths

PR, Wenderfer

SE, Bodurtha

J, Applegate

CD, Velinov

M, Myers

A, Borovik

L, Craigen

WJ, Hanchard

NA, Rosenfeld

JA, Lewis

RA, Gonzales

ET, Gibbs

RA, Belmont

JW, Roth

DR, Eng

C, Braun

MC, Lupski

JR, Lamb

DJ. Whole-exome sequencing in the molecular diagnosis of individuals with congenital anomalies of the kidney and urinary tract and identification of a new causative gene.

Genet Med.

2017;19:412-20.

[PMC free article: PMC5362362] [PubMed: 27657687]Biesecker

LG, Adam

MP, Alkuraya

FS, Amemiya

AR, Bamshad

MJ, Beck

AE, Bennett

JT, Bird

LM, Carey

JC, Chung

B, Clark

RD, Cox

TC, Curry

C, Dinulos

MBP, Dobyns

WB, Giampietro

PF, Girisha

KM, Glass

IA, Graham

JM

Jr, Gripp

KW, Haldeman-Englert

CR, Hall

BD, Innes

AM, Kalish

JM, Keppler-Noreuil

KM, Kosaki

K, Kozel

BA, Mirzaa

GM, Mulvihill

JJ, Nowaczyk

MJM, Pagon

RA, Retterer

K, Rope

AF, Sanchez-Lara

PA, Seaver

LH, Shieh

JT, Slavotinek

AM, Sobering

AK, Stevens

CA, Stevenson

DA, Tan

TY, Tan

WH, Tsai

AC, Weaver

DD, Williams

MS, Zackai

E, Zarate

YA. A dyadic approach to the delineation of diagnostic entities in clinical genomics.

Am J Hum Genet.

2021;108:8-15.

[PMC free article: PMC7820621] [PubMed: 33417889]Braden

RO, Amor

DJ, Fisher

SE, Mei

C, Myers

CT, Mefford

H, Gill

D, Srivastava

S, Swanson

LC, Goel

H, Scheffer

IE, Morgan

AT. Severe speech impairment is a distinguishing feature of FOXP1-related disorder.

Dev Med Child Neurol.

2021;63:1417-26.

[PubMed: 34109629]Carr

CW, Moreno-De-Luca

D, Parker

C, Zimmerman

HH, Ledbetter

N, Martin

CL, Dobyns

WB, Abdul-Rahman

OA. Chiari I malformation, delayed gross motor skills, severe speech delay, and epileptiform discharges in a child with FOXP1 haploinsufficiency.

Eur J Hum Genet.

2010;18:1216-20.

[PMC free article: PMC2987472] [PubMed: 20571508]Chang

SW, Mislankar

M, Misra

C, Huang

N, Dajusta

DG, Harrison

SM, McBride

KL, Baker

LA, Garg

V. Genetic abnormalities in FOXP1 are associated with congenital heart defects.

Hum Mutat.

2013;34:1226-30.

[PMC free article: PMC5717756] [PubMed: 23766104]Fröhlich

H, Kollmeyer

ML, Linz

VC, Stuhlinger

M, Groneberg

D, Reigl

A, Zizer

E, Friebe

A, Niesler

B, Rappold

G. Gastrointestinal dysfunction in autism displayed by altered motility and achalasia in Foxp1+/- mice.

Proc Natl Acad Sci U S A.

2019;116:22237-45.

[PMC free article: PMC6825283] [PubMed: 31611379]Fu

J, Wang

T, Fu

Z, Li

T, Zhang

X, Zhao

J, Yang

G.

Case report: a case report and literature review of 3p deletion syndrome.

Front Pediatr.

2021;9:618059.

[PMC free article: PMC7902511] [PubMed: 33643973]Hamdan

FF, Daoud

H, Rochefort

D, Piton

A, Gauthier

J, Langlois

M, Foomani

G, Dobrzeniecka

S, Krebs

MO, Joober

R, Lafrenière

RG, Lacaille

JC, Mottron

L, Drapeau

P, Beauchamp

MH, Phillips

MS, Fombonne

E, Rouleau

GA, Michaud

JL. De novo mutations in FOXP1 in cases with intellectual disability, autism, and language impairment.

Am J Hum Genet.

2010;87:671-8.

[PMC free article: PMC2978954] [PubMed: 20950788]Iossifov

I, O'Roak

BJ, Sanders

SJ, Ronemus

M, Krumm

N, Levy

D, Stessman

HA, Witherspoon

KT, Vives

L, Patterson

KE, Smith

JD, Paeper

B, Nickerson

DA, Dea

J, Dong

S, Gonzalez

LE, Mandell

JD, Mane

SM, Murtha

MT, Sullivan

CA, Walker

MF, Waqar

Z, Wei

L, Willsey

AJ, Yamrom

B, Lee

YH, Grabowska

E, Dalkic

E, Wang

Z, Marks

S, Andrews

P, Leotta

A, Kendall

J, Hakker

I, Rosenbaum

J, Ma

B, Rodgers

L, Troge

J, Narzisi

G, Yoon

S, Schatz

MC, Ye

K, McCombie

WR, Shendure

J, Eichler

EE, State

MW, Wigler

M. The contribution of de novo coding mutations to autism spectrum disorder.

Nature.

2014;515:216-21.

[PMC free article: PMC4313871] [PubMed: 25363768]Le Fevre

AK, Taylor

S, Malek

NH, Horn

D, Carr

CW, Abdul-Rahman

OA, O'Donnell

S, Burgess

T, Shaw

M, Gecz

J, Bain

N, Fagan

K, Hunter

MF. FOXP1 mutations cause intellectual disability and a recognizable phenotype.

Am J Med Genet A.

2013;161A:3166-75.

[PubMed: 24214399]Lloveras

E, Vendrell

T, Fernández

A, Castells

N, Cueto

A, del Campo

M, Hernando

C, Villa

O, Plaja

A.

Intrachromosomal 3p insertion as a cause of reciprocal pure interstitial deletion and duplication in two siblings: further delineation of the emerging proximal 3p deletion syndrome.

Cytogenet Genome Res.

2014;144:290-3.

[PubMed: 25720458]Lozano

R, Gbekie

C, Siper

PM, Srivastava

S, Saland

JM, Sethuram

S, Tang

L, Drapeau

E, Frank

Y, Buxbaum

JD, Kolevzon

A. FOXP1 syndrome: a review of the literature and practice parameters for medical assessment and monitoring.

J Neurodev Disord.

2021;13:18.

[PMC free article: PMC8066957] [PubMed: 33892622]Lozano

R, Vino

A, Lozano

C, Fisher

SE, Deriziotis

P. A de novo FOXP1 variant in a patient with autism, intellectual disability and severe speech and language impairment.

Eur J Hum Genet.

2015;23:1702-7.

[PMC free article: PMC4795189] [PubMed: 25853299]Meerschaut

I, Rochefort

D, Revençu

N, Pètre

J, Corsello

C, Rouleau

GA, Hamdan

FF, Michaud

JL, Morton

J, Radley

J, Ragge

N, García-Miñaúr

S, Lapunzina

P, Bralo

MP, Mori

MÁ, Moortgat

S, Benoit

V, Mary

S, Bockaert

N, Oostra

A, Vanakker

O, Velinov

M, de Ravel

TJ, Mekahli

D, Sebat

J, Vaux

KK, DiDonato

N, Hanson-Kahn

AK, Hudgins

L, Dallapiccola

B, Novelli

A, Tarani

L, Andrieux

J, Parker

MJ, Neas

K, Ceulemans

B, Schoonjans

AS, Prchalova

D, Havlovicova

M, Hancarova

M, Budisteanu

M, Dheedene

A, Menten

B, Dion

PA, Lederer

D, Callewaert

B. FOXP1-related intellectual disability syndrome: a recognisable entity.

J Med Genet.

2017;54:613-23.

[PubMed: 28735298]Morgan

AT, Dodrill

P, Ward

EC. Interventions for oropharyngeal dysphagia in children with neurological impairment.

Cochrane Database Syst Rev.

2012;10:CD009456.

[PubMed: 23076958]Morgan AT, Murray E, Liégeois FJ. 2018. Intervention for childhood apraxia of speech. Cochrane Database Syst Rev. 30;5:CD006278. [PMC free article: PMC6494637] [PubMed: 29845607]Myers

A, du Souich

C, Yang

CL, Borovik

L, Mwenifumbo

J, Rupps

R, Study

C, Lehman

A, Boerkoel

CF. FOXP1 haploinsufficiency: phenotypes beyond behavior and intellectual disability?

Am J Med Genet A.

2017;173:3172-81.

[PubMed: 28884888]O'Roak

BJ, Deriziotis

P, Lee

C, Vives

L, Schwartz

JJ, Girirajan

S, Karakoc

E, Mackenzie

AP, Ng

SB, Baker

C, Rieder

MJ, Nickerson

DA, Bernier

R, Fisher

SE, Shendure

J, Eichler

EE. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations.

Nat Genet.

2011;43:585-9.

[PMC free article: PMC3115696] [PubMed: 21572417]Palumbo

O, D'Agruma

L, Minenna

AF, Palumbo

P, Stallone

R, Palladino

T, Zelante

L, Carella

M. 3p14.1 de novo microdeletion involving the FOXP1 gene in an adult patient with autism, severe speech delay and deficit of motor coordination.

Gene.

2013;516:107-13.

[PubMed: 23287644]Rahbari

R, Wuster

A, Lindsay

SJ, Hardwick

RJ, Alexandrov

LB, Turki

SA, Dominiczak

A, Morris

A, Porteous

D, Smith

B, Stratton

MR, Hurles

ME, et al.

Timing, rates and spectra of human germline mutation.

Nat Genet.

2016;48:126-33.

[PMC free article: PMC4731925] [PubMed: 26656846]Richards

S, Aziz

N, Bale

S, Bick

D, Das

S, Gastier-Foster

J, Grody

WW, Hegde

M, Lyon

E, Spector

E, Voelkerding

K, Rehm

HL, et al.

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.

Genet Med.

2015;17:405-24.

[PMC free article: PMC4544753] [PubMed: 25741868]Schluth-Bolard

C, Diguet

F, Chatron

N, Rollat-Farnier

PA, Bardel

C, Afenjar

A, Amblard

F, Amiel

J, Blesson

S, Callier

P, Capri

Y, Collignon

P, Cordier

MP, Coubes

C, Demeer

B, Chaussenot

A, Demurger

F, Devillard

F, Doco-Fenzy

M, Dupont

C, Dupont

JM, Dupuis-Girod

S, Faivre

L, Gilbert-Dussardier

B, Guerrot

AM, Houlier

M, Isidor

B, Jaillard

S, Joly-Hélas

G, Kremer

V, Lacombe

D, Le Caignec

C, Lebbar

A, Lebrun

M, Lesca

G, Lespinasse

J, Levy

J, Malan

V, Mathieu-Dramard

M, Masson

J, Masurel-Paulet

A, Mignot

C, Missirian

C, Morice-Picard

F, Moutton

S, Nadeau

G, Pebrel-Richard

C, Odent

S, Paquis-Flucklinger

V, Pasquier

L, Philip

N, Plutino

M, Pons

L, Portnoï

MF, Prieur

F, Puechberty

J, Putoux

A, Rio

M, Rooryck-Thambo

C, Rossi

M, Sarret

C, Satre

V, Siffroi

JP, Till

M, Touraine

R, Toutain

A, Toutain

J, Valence

S, Verloes

A, Whalen

S, Edery

P, Tabet

AC, Sanlaville

D. Whole genome paired-end sequencing elucidates functional and phenotypic consequences of balanced chromosomal rearrangement in patients with developmental disorders.

J Med Genet.

2019;56:526-35.

[PubMed: 30923172]Siper

PM, De Rubeis

S, Trelles

MDP, Durkin

A, Di Marino

D, Muratet

F, Frank

Y, Lozano

R, Eichler

EE, Kelly

M, Beighley

J, Gerdts

J, Wallace

AS, Mefford

HC, Bernier

RA, Kolevzon

A, Buxbaum

JD. Prospective investigation of FOXP1 syndrome.

Mol Autism.

2017;8:57.

[PMC free article: PMC5655854] [PubMed: 29090079]Sollis

E, Graham

SA, Vino

A, Froehlich

H, Vreeburg

M, Dimitropoulou

D, Gilissen

C, Pfundt

R, Rappold

GA, Brunner

HG, Deriziotis

P, Fisher

SE. Identification and functional characterization of de novo FOXP1 variants provides novel insights into the etiology of neurodevelopmental disorder.

Hum Mol Genet.

2016;25:546-57.

[PubMed: 26647308]Song

H, Makino

Y, Noguchi

E, Arinami

T.

A case report of de novo missense FOXP1 mutation in a non-Caucasian patient with global developmental delay and severe speech impairment.

Clin Case Rep.

2015;3:110-3.

[PMC free article: PMC4352365] [PubMed: 25767709]Srivastava

S, Cohen

JS, Vernon

H, Barañano

K, McClellan

R, Jamal

L, Naidu

S, Fatemi

A. Clinical whole exome sequencing in child neurology practice.

Ann Neurol.

2014;76:473-83.

[PubMed: 25131622]Talkowski

ME, Rosenfeld

JA, Blumenthal

I, Pillalamarri

V, Chiang

C, Heilbut

A, Ernst

C, Hanscom

C, Rossin

E, Lindgren

AM, Pereira

S, Ruderfer

D, Kirby

A, Ripke

S, Harris

DJ, Lee

JH, Ha

K, Kim

HG, Solomon

BD, Gropman

AL, Lucente

D, Sims

K, Ohsumi

TK, Borowsky

ML, Loranger

S, Quade

B, Lage

K, Miles

J, Wu

BL, Shen

Y, Neale

B, Shaffer

LG, Daly

MJ, Morton

CC, Gusella
JF. Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries.
Cell.
2012;149:525-37.
[PMC free article: PMC3340505] [PubMed: 22521361]Trelles
MP, Levy
T, Lerman
B, Siper
P, Lozano
R, Halpern
D, Walker
H, Zweifach
J, Frank
Y, Foss-Feig
J, Kolevzon
A, Buxbaum
J. Individuals with FOXP1 syndrome present with a complex neurobehavioral profile with high rates of ADHD, anxiety, repetitive behaviors, and sensory symptoms.
Mol Autism.
2021;12:61.
[PMC free article: PMC8482569] [PubMed: 34588003]Vuillaume
ML, Cogné
B, Jeanne
M, Boland
A, Ung
DC, Quinquis

D, Besnard

T, Deleuze

JF, Redon

R, Bézieau

S, Laumonnier

F, Toutain

A. Whole genome sequencing identifies a de novo 2.1 Mb balanced paracentric inversion disrupting FOXP1 and leading to severe intellectual disability.

Clin Chim Acta.

2018;485:218-23.

[PubMed: 29969624]Zimmer

MH. Not ready for prime time: policy cautions against using sensory processing disorder as a diagnosis.

AAP News.

2012;33:30.Zimmer

M, Desch

L, et al.

Sensory integration therapies for children with developmental and behavioral disorders.

Pediatrics.

2012;129:1186-9.

[PubMed: 22641765]

Bacon

C, Rappold

GA. The distinct and overlapping phenotypic spectra of FOXP1 and FOXP2 in cognitive disorders.

Hum Genet.

2012;131:1687-98.

[PMC free article: PMC3470686] [PubMed: 22736078]

Bekheirnia

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N, Bainbridge

MN, Gu

S, Coban Akdemir

ZH, Gambin

T, Janzen

NK, Jhangiani

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AA, Swartz

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DA, Yang

Y, Srivaths

PR, Wenderfer

SE, Bodurtha

J, Applegate

CD, Velinov

M, Myers

A, Borovik

L, Craigen

WJ, Hanchard

NA, Rosenfeld

JA, Lewis

RA, Gonzales

ET, Gibbs

RA, Belmont

JW, Roth

DR, Eng

C, Braun

MC, Lupski

JR, Lamb

DJ. Whole-exome sequencing in the molecular diagnosis of individuals with congenital anomalies of the kidney and urinary tract and identification of a new causative gene.

Genet Med.

2017;19:412-20.

[PMC free article: PMC5362362] [PubMed: 27657687]

Biesecker

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MP, Alkuraya

FS, Amemiya

AR, Bamshad

MJ, Beck

AE, Bennett

JT, Bird

LM, Carey

JC, Chung

B, Clark

RD, Cox

TC, Curry

C, Dinulos

MBP, Dobyns

WB, Giampietro

PF, Girisha

KM, Glass

IA, Graham

JM

Jr, Gripp

KW, Haldeman-Englert

CR, Hall

BD, Innes

AM, Kalish

JM, Keppler-Noreuil

KM, Kosaki

K, Kozel

BA, Mirzaa

GM, Mulvihill

JJ, Nowaczyk

MJM, Pagon

RA, Retterer

K, Rope

AF, Sanchez-Lara

PA, Seaver

LH, Shieh

JT, Slavotinek

AM, Sobering

AK, Stevens

CA, Stevenson

DA, Tan

TY, Tan

WH, Tsai

AC, Weaver

DD, Williams

MS, Zackai

E, Zarate

YA. A dyadic approach to the delineation of diagnostic entities in clinical genomics.

Am J Hum Genet.

2021;108:8-15.

[PMC free article: PMC7820621] [PubMed: 33417889]

Braden

RO, Amor

DJ, Fisher

SE, Mei

C, Myers

CT, Mefford

H, Gill

D, Srivastava

S, Swanson

LC, Goel

H, Scheffer

IE, Morgan

AT. Severe speech impairment is a distinguishing feature of FOXP1-related disorder.

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2021;63:1417-26.

[PubMed: 34109629]

Carr

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D, Parker

C, Zimmerman

HH, Ledbetter

N, Martin

CL, Dobyns

WB, Abdul-Rahman

OA. Chiari I malformation, delayed gross motor skills, severe speech delay, and epileptiform

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Eur J Hum Genet.

2010;18:1216-20.

[PMC free article: PMC2987472] [PubMed: 20571508]

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M, Misra

C, Huang

N, Dajusta

DG, Harrison

SM, McBride

KL, Baker

LA, Garg

V. Genetic abnormalities in FOXP1 are associated with congenital heart defects.

Hum Mutat.

2013;34:1226-30.

[PMC free article: PMC5717756] [PubMed: 23766104]

Fröhlich

H, Kollmeyer

ML, Linz

VC, Stuhlinger

M, Groneberg

D, Reigl

A, Zizer

E, Friebe

A, Niesler

B, Rappold

G. Gastrointestinal dysfunction in autism displayed by altered motility and achalasia in Foxp1+/-

mice.

Proc Natl Acad Sci U S A.

2019;116:22237-45.

[PMC free article: PMC6825283] [PubMed: 31611379]

Fu

J, Wang

T, Fu

Z, Li

T, Zhang

X, Zhao

J, Yang

G.

Case report: a case report and literature review of 3p deletion syndrome.

Front Pediatr.

2021;9:618059.

[PMC free article: PMC7902511] [PubMed: 33643973]

Hamdan

FF, Daoud

H, Rochefort

D, Piton

A, Gauthier

J, Langlois

M, Foomani

G, Dobrzeniecka

S, Krebs

MO, Joober

R, Lafrenière

RG, Lacaille

JC, Mottron

L, Drapeau

P, Beauchamp

MH, Phillips

MS, Fombonne

E, Rouleau

GA, Michaud

JL. De novo mutations in FOXP1 in cases with intellectual disability, autism, and language

impairment.

Am J Hum Genet.

2010;87:671-8.

[PMC free article: PMC2978954] [PubMed: 20950788]

Iossifov

I, O'Roak

BJ, Sanders

SJ, Ronemus

M, Krumm

N, Levy

D, Stessman

HA, Witherspoon

KT, Vives

L, Patterson

KE, Smith

JD, Paeper

B, Nickerson

DA, Dea

J, Dong

S, Gonzalez

LE, Mandell

JD, Mane

SM, Murtha

MT, Sullivan

CA, Walker

MF, Waqar

Z, Wei

L, Willsey

AJ, Yamrom

B, Lee

YH, Grabowska

E, Dalkic

E, Wang

Z, Marks

S, Andrews

P, Leotta

A, Kendall

J, Hakker

I, Rosenbaum

J, Ma

B, Rodgers

L, Troge

J, Narzisi

G, Yoon

S, Schatz

MC, Ye

K, McCombie

WR, Shendure

J, Eichler

EE, State

MW, Wigler

M. The contribution of de novo coding mutations to autism spectrum disorder.

Nature.

2014;515:216-21.

[PMC free article: PMC4313871] [PubMed: 25363768]

Le Fevre

AK, Taylor

S, Malek

NH, Horn

D, Carr

CW, Abdul-Rahman

OA, O'Donnell

S, Burgess

T, Shaw

M, Gecz

J, Bain

N, Fagan

K, Hunter

MF. FOXP1 mutations cause intellectual disability and a recognizable phenotype.

Am J Med Genet A.

2013;161A:3166-75.

[PubMed: 24214399]

Lloveras

E, Vendrell

T, Fernández

A, Castells

N, Cueto

A, del Campo

M, Hernando

C, Villa

O, Plaja

A.

Intrachromosomal 3p insertion as a cause of reciprocal pure interstitial deletion and duplication in two siblings: further delineation of the emerging proximal 3p deletion syndrome.

Cytogenet Genome Res.

2014;144:290-3.

[PubMed: 25720458]

Lozano

R, Gbekie

C, Siper

PM, Srivastava

S, Saland

JM, Sethuram

S, Tang

L, Drapeau

E, Frank

Y, Buxbaum

JD, Kolevzon

A. FOXP1 syndrome: a review of the literature and practice parameters for medical assessment and monitoring.

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2021;13:18.

[PMC free article: PMC8066957] [PubMed: 33892622]

Lozano

R, Vino

A, Lozano

C, Fisher

SE, Deriziotis

P. A de novo FOXP1 variant in a patient with autism, intellectual disability and severe speech and language impairment.

Eur J Hum Genet.

2015;23:1702-7.

[PMC free article: PMC4795189] [PubMed: 25853299]

Meerschaut

I, Rochefort

D, Revençu

N, Pètre

J, Corsello

C, Rouleau

GA, Hamdan

FF, Michaud

JL, Morton

J, Radley

J, Ragge

N, García-Miñaúr

S, Lapunzina

P, Bralo

MP, Mori

MÁ, Moortgat

S, Benoit

V, Mary

S, Bockaert

N, Oostra

A, Vanakker

O, Velinov

M, de Ravel

TJ, Mekahli

D, Sebat

J, Vaux

KK, DiDonato

N, Hanson-Kahn

AK, Hudgins

L, Dallapiccola

B, Novelli

A, Tarani

L, Andrieux

J, Parker

MJ, Neas

K, Ceulemans

B, Schoonjans

AS, Prchalova

D, Havlovicova

M, Hancarova

M, Budisteanu

M, Dheedene

A, Menten

B, Dion

PA, Lederer

D, Callewaert

B. FOXP1-related intellectual disability syndrome: a recognisable entity.

J Med Genet.

2017;54:613-23.

[PubMed: 28735298]

Morgan

AT, Dodrill

P, Ward

EC. Interventions for oropharyngeal dysphagia in children with neurological impairment.

Cochrane Database Syst Rev.

2012;10:CD009456.

[PubMed: 23076958]

Morgan AT, Murray E, Liégeois FJ. 2018. Intervention for childhood apraxia of speech. Cochrane Database Syst Rev. 30;5:CD006278. [PMC free article: PMC6494637] [PubMed: 29845607]

Myers

A, du Souich

C, Yang

CL, Borovik

L, Mwenifumbo

J, Rupps

R, Study

C, Lehman

A, Boerkoel

CF. FOXP1 haploinsufficiency: phenotypes beyond behavior and intellectual disability?

Am J Med Genet A.

2017;173:3172-81.

[PubMed: 28884888]

O'Roak

BJ, Deriziotis

P, Lee

C, Vives

L, Schwartz

JJ, Girirajan

S, Karakoc

E, Mackenzie

AP, Ng

SB, Baker

C, Rieder

MJ, Nickerson

DA, Bernier

R, Fisher

SE, Shendure

J, Eichler

EE. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations.

Nat Genet.

2011;43:585-9.

[PMC free article: PMC3115696] [PubMed: 21572417]

Palumbo

O, D'Agruma

L, Minenna

AF, Palumbo

P, Stallone

R, Palladino

T, Zelante

L, Carella

M. 3p14.1 de novo microdeletion involving the FOXP1 gene in an adult patient with autism, severe speech delay and deficit of motor coordination.

Gene.

2013;516:107-13.

[PubMed: 23287644]

Rahbari

R, Wuster

A, Lindsay

SJ, Hardwick

RJ, Alexandrov

LB, Turki

SA, Dominiczak

A, Morris

A, Porteous

D, Smith

B, Stratton
MR, Hurles
ME, et al.
Timing, rates and spectra of human germline mutation.
Nat Genet.
2016;48:126-33.
[PMC free article: PMC4731925] [PubMed: 26656846]

Richards
S, Aziz
N, Bale
S, Bick
D, Das
S, Gastier-Foster
J, Grody
WW, Hegde
M, Lyon
E, Spector
E, Voelkerding
K, Rehm
HL, et al.
Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.
Genet Med.
2015;17:405-24.
[PMC free article: PMC4544753] [PubMed: 25741868]

Schluth-Bolard

C, Diguet

F, Chatron

N, Rollat-Farnier

PA, Bardel

C, Afenjar

A, Amblard

F, Amiel

J, Blesson

S, Callier

P, Capri

Y, Collignon

P, Cordier

MP, Coubes

C, Demeer

B, Chaussenot

A, Demurger

F, Devillard

F, Doco-Fenzy

M, Dupont

C, Dupont

JM, Dupuis-Girod

S, Faivre

L, Gilbert-Dussardier

B, Guerrot

AM, Houlier

M, Isidor

B, Jaillard

S, Joly-Hélas

G, Kremer

V, Lacombe

D, Le Caignec

C, Lebbar

A, Lebrun

M, Lesca

G, Lespinasse

J, Levy

J, Malan

V, Mathieu-Dramard

M, Masson

J, Masurel-Paulet

A, Mignot

C, Missirian

C, Morice-Picard

F, Moutton

S, Nadeau

G, Pebrel-Richard

C, Odent

S, Paquis-Flucklinger

V, Pasquier

L, Philip

N, Plutino

M, Pons

L, Portnoï

MF, Prieur

F, Puechberty

J, Putoux

A, Rio

M, Rooryck-Thambo

C, Rossi

M, Sarret

C, Satre

V, Siffroi

JP, Till

M, Touraine

R, Toutain

A, Toutain

J, Valence

S, Verloes

A, Whalen

S, Edery

P, Tabet

AC, Sanlaville

D. Whole genome paired-end sequencing elucidates functional and phenotypic consequences of balanced chromosomal rearrangement in patients with developmental disorders.

J Med Genet.

2019;56:526-35.

[PubMed: 30923172]

Siper

PM, De Rubeis

S, Trelles

MDP, Durkin

A, Di Marino

D, Muratet

F, Frank

Y, Lozano

R, Eichler

EE, Kelly

M, Beighley

J, Gerdts

J, Wallace

AS, Mefford

HC, Bernier

RA, Kolevzon

A, Buxbaum

JD. Prospective investigation of FOXP1 syndrome.

Mol Autism.

2017;8:57.

[PMC free article: PMC5655854] [PubMed: 29090079]

Sollis

E, Graham

SA, Vino

A, Froehlich

H, Vreeburg

M, Dimitropoulou

D, Gilissen

C, Pfundt

R, Rappold

GA, Brunner

HG, Deriziotis

P, Fisher

SE. Identification and functional characterization of de novo FOXP1 variants provides novel insights into the etiology of neurodevelopmental disorder.

Hum Mol Genet.

2016;25:546-57.

[PubMed: 26647308]

Song

H, Makino

Y, Noguchi

E, Arinami

T.

A case report of de novo missense FOXP1 mutation in a non-Caucasian patient with global developmental delay and severe speech impairment.

Clin Case Rep.

2015;3:110-3.

[PMC free article: PMC4352365] [PubMed: 25767709]

Srivastava

S, Cohen

JS, Vernon

H, Barañano

K, McClellan

R, Jamal

L, Naidu

S, Fatemi

A. Clinical whole exome sequencing in child neurology practice.

Ann Neurol.

2014;76:473-83.

[PubMed: 25131622]

Talkowski

ME, Rosenfeld

JA, Blumenthal

I, Pillalamarri

V, Chiang

C, Heilbut

A, Ernst

C, Hanscom

C, Rossin

E, Lindgren

AM, Pereira

S, Ruderfer

D, Kirby

A, Ripke

S, Harris

DJ, Lee

JH, Ha

K, Kim

HG, Solomon

BD, Gropman

AL, Lucente

D, Sims

K, Ohsumi

TK, Borowsky

ML, Loranger

S, Quade

B, Lage

K, Miles

J, Wu

BL, Shen

Y, Neale

B, Shaffer

LG, Daly

MJ, Morton

CC, Gusella

JF. Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries.

Cell.

2012;149:525-37.

[PMC free article: PMC3340505] [PubMed: 22521361]

Trelles

MP, Levy

T, Lerman

B, Siper

P, Lozano

R, Halpern

D, Walker

H, Zweifach

J, Frank

Y, Foss-Feig

J, Kolevzon

A, Buxbaum

J. Individuals with FOXP1 syndrome present with a complex neurobehavioral profile with high rates of ADHD, anxiety, repetitive behaviors, and sensory symptoms.

Mol Autism.

2021;12:61.

[PMC free article: PMC8482569] [PubMed: 34588003]

Vuillaume

ML, Cogné

B, Jeanne

M, Boland

A, Ung

DC, Quinquis

D, Besnard

T, Deleuze

JF, Redon

R, Bézieau

S, Laumonnier

F, Toutain

A. Whole genome sequencing identifies a de novo 2.1 Mb balanced paracentric inversion disrupting FOXP1 and leading to severe intellectual disability.

Clin Chim Acta.

2018;485:218-23.

[PubMed: 29969624]

Zimmer

MH. Not ready for prime time: policy cautions against using sensory processing disorder as a diagnosis.

AAP News.

2012;33:30.

Zimmer

M, Desch

L, et al.

Sensory integration therapies for children with developmental and behavioral disorders.

Pediatrics.

2012;129:1186-9.

[PubMed: 22641765]