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FOXP2-Related Speech and Language Disorder

Angela Morgan, BSpPath (Aud Hons), PhD,[1] Simon E Fisher, DPhil,[2] Ingrid Scheffer, MBBS, PhD, FRACP, FAA,[3] and Michael Hildebrand, PhD[4]

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Summary

Clinical characteristics

FOXP2-related speech and language disorder (*FOXP2*-SLD) is caused by heterozygous *FOXP2* pathogenic variants (including whole- or partial-gene deletions). The core phenotype of *FOXP2*-SLD is childhood apraxia of speech (CAS), a disorder of speech motor programming or planning that affects the production, sequencing, timing, and stress of sounds, and the accurate sequencing of speech sounds into syllables and syllables into words. CAS also interferes nonselectively with multiple other aspects of language, including phonology, grammar, and literacy. Additional findings in *FOXP2*-SLD can include oral-motor dyspraxia (difficulty planning or programming oral movements on command); dysarthria; moderate-to-severe receptive and expressive language disorder; reading and spelling impairments; and fine motor difficulties. Nonverbal (performance) IQ is typically relatively preserved compared to verbal IQ; gross motor skills are normal. Autistic features or a diagnosis of autism spectrum disorder have been reported in some individuals.

Diagnosis/testing

The diagnosis of *FOXP2*-SLD is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *FOXP2* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no cure for *FOXP2*-SLD. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by

Author Affiliations: 1 Head, Speech & Language, Murdoch Children's Research Institute; Professor, Department of Audiology and Speech Pathology, University of Melbourne; Director, Genetics of Speech Clinic, Royal Children's Hospital, Melbourne, Victoria, Australia; Email: amor@unimelb.edu.au. 2 Language and Genetics Department, Max Planck Institute for Psycholinguistics; Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands; Email: simon.fisher@mpi.nl. 3 Epilepsy Research Centre, Department of Medicine and Paediatrics, University of Melbourne; Austin Health, Melbourne, Victoria, Australia; Email: i.scheffer@unimelb.edu.au. 4 Epilepsy Research Centre, Melbourne Brain Centre, Department of Medicine, University of Melbourne; Austin Health; Neuroscience Group, Murdoch Children's Research Institute, Melbourne, Victoria, Australia; Email: michael.hildebrand@unimelb.edu.au.

speech-language pathologists (to individualize care, which may include use of nonverbal support or alternative means of communication), developmental pediatricians (to help guide parents through appropriate behavior management strategies and individualized education plans), occupational therapists (to address fine motor impairments), and mental health specialists (to address issues such as anxiety and depression, which can occur).

Surveillance: To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the following evaluations are recommended: follow-up evaluations with standardized tests by a speech-language pathologist; review of educational progress/needs; review of mental health if anxiety and/or depression have been issues or have emerged as issues.

Genetic counseling

FOXP2-SLD is inherited in an autosomal dominant manner. About half of individuals diagnosed with *FOXP2*-SLD have the disorder as the result of a *de novo* pathogenic variant. If a parent of the proband has the *FOXP2* pathogenic variant identified in the proband, the risk to sibs of inheriting the pathogenic variant is 50%. Once the *FOXP2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

This chapter addresses the core phenotype (speech and language disorder) and additional (variable) findings associated with intragenic *FOXP2* pathogenic variants. The generally more severe phenotype associated with large copy number variants (i.e., contiguous gene deletions), structural variants (i.e., translocations or inversions), or maternal uniparental disomy of chromosome 7 involving *FOXP2* and additional adjacent genes – referred to in this *GeneReview* as *FOXP2*-plus-related disorder – is outside the scope of this chapter. (See also Genetically Related Disorders.)

Diagnosis

No consensus clinical diagnostic criteria for *FOXP2*-related speech and language disorder (*FOXP2*-SLD) have been published.

Suggestive Findings

FOXP2-SLD **should be suspected** in a child with the following clinical findings and family history.

Clinical Findings

Childhood apraxia of speech (CAS) [American Speech-Language-Hearing Association 2007] (also known as developmental verbal dyspraxia, verbal dyspraxia, or speech dyspraxia)

- Children with CAS have difficulties in automatically and accurately sequencing speech sounds into words with the correct prosody.
- The diagnosis of CAS is made by assessment by a speech-language pathologist (also known as a speech and language therapist in the UK or speech pathologist in Australia). CAS is challenging to diagnose in a child younger than age three years; speech development is delayed in these children, and thus key manifestations are typically not seen or able to be elicited until the child has acquired sufficient speech to complete the verbal assessment tasks.

Additional Clinical Findings

- Delayed speech development
- Poor oral-motor function (e.g., excessive drooling, early feeding difficulties)

- Oral-motor difficulties and/or oral-motor dyspraxia
- Dysarthria
- Receptive and expressive language impairment
- Low average IQ, typically with poorer verbal IQ compared to nonverbal IQ (and average nonverbal IQ reported in some)
- Reading and spelling impairment
- Fine and gross motor impairment

Family History

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *FOXP2*-SLD **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *FOXP2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *FOXP2* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel, single-gene testing) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires the clinician to determine which gene(s) are likely involved (see Option 1), whereas genomic testing may not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *FOXP2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

An inherited disorders of speech delay and developmental delay / intellectual disability multigene panel that includes *FOXP2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

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 *FOXP2*-Related Speech and Language Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FOXP2	Sequence analysis [3]	~70% [4]
	Gene-targeted deletion/duplication analysis [5]	~30% [4, 5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. This percentage is an estimate derived from data regarding intragenic deletion and duplications as well as whole gene deletions from the Human Gene Mutation Database [Stenson et al 2020]. This may not necessarily distinguish between large intragenic deletions and contiguous gene deletions involving *FOXP2* (*FOXP2*-plus-related disorder). Thus, if the individual's phenotype suggests *FOXP2*-plus-related disorder, a chromosomal microarray is recommended.

Clinical Characteristics

Clinical Description

Available evidence to date suggests that *FOXP2*-related speech and language disorder (*FOXP2*-SLD) is caused by heterozygous *FOXP2* pathogenic variants (including whole- or partial-gene deletions). *FOXP2*-SLD has a core phenotype: childhood apraxia of speech (CAS), a disorder of speech motor programming or planning that affects the production, sequencing, timing, and stress of sounds, and the accurate sequencing of speech sounds into syllables and syllables into words. In addition, CAS interferes nonselectively with multiple other aspects of language, including phonology, grammar, and literacy.

The interactions between these communication disorder subtypes are not well understood. Language and literacy difficulties may be influenced by or even result from CAS, or these phenotypes may actually be features of the same broad communication disorder.

Additional findings in *FOXP2*-SLD can include oral-motor dyspraxia (difficulty planning or programming oral movements on command); dysarthria (a neuromuscular-based speech disorder that may affect nasal resonance, voice quality, prosody, and breath support for speech); moderate-to-severe receptive and expressive language disorder; reading and spelling impairments; and fine motor difficulties. "Autistic features" or a diagnosis of autism spectrum disorder have been reported in a quarter of affected individuals. Typically mild dysmorphology has been reported in a few individuals.

In *FOXP2*-SLD nonverbal IQ (performance) is typically relatively preserved compared to verbal IQ; gross motor skills are delayed or impaired in the early years of development.

Sleep issues are present in some.

To date, *FOXP2*-SLD has been described in approximately 30 families (see Supplementary Table 1 in Morison et al [2022] for a summary of all reported families). The following description is based on the findings in these families.

Childhood apraxia of speech. First words typically appear between ages 18 months and seven years in children with *FOXP2*-SLD [Vargha-Khadem et al 1995, MacDermot et al 2005, Laffin et al 2012, Reuter et al 2017, Morison et al 2022]. *FOXP2*-SLD is typically diagnosed around age three to four years, but may be considered earlier when the family history is positive.

In the first decade of life, speech is highly unintelligible, even to close friends and family. Although speech development and intelligibility improve over time, speech never develops to the same level as age-matched peers, and intelligibility may remain reduced in adulthood [Morison et al 2022]. In contrast, for typically developing children, speech sound acquisition is mastered by around age eight years [Dodd et al 2003], with intelligibility as high as 97% as early as age three years [Flipsen 2006].

Although CAS comprises certain core features, it is important to note that the severity and features of CAS change across the life span [Royal College of Speech and Language Therapists 2011], and while referred to as "core" features, they are not necessarily present in all individuals with CAS [American Speech-Language-Hearing Association 2007]. Core features, agreed upon by a consensus panel, include the following:

- Inconsistent speech errors (e.g., producing the same syllable or word differently across repetitions of the same word, such as "ubella," "umbrella," and "umbarella" for umbrella)
- Lengthened and disrupted coarticulatory transitions (e.g., oral groping behaviors during speech; difficulty sequencing phonemes and syllables; difficulty maintaining syllable integrity; hypernasality, thought to be due to incoordination of the velum for denoting oral-nasal contrasts; slowed and disrupted diadochokinetic sequences, e.g., when asked to repeat "pa-ta-ka")
- Inappropriate prosody (e.g., lexical stress errors, equal stress across words giving a robotic-sounding presentation)

In addition, children with CAS tend to lag behind their peers in acquiring the sounds of their language system; hence, their phonetic inventory may be reduced for the child's age. Children with CAS may use a more restricted range of consonants and vowels than age-matched peers. For example, they will simplify syllable shapes, reducing a consonant-consonant-vowel (CCV) shape (e.g., "sta") or a consonant-consonant-consonant-vowel (CCCV) shape ("stra") to a consonant-vowel (CV) shape ("sa").

Although CAS is distinct from other speech disorders (e.g., stuttering, phonologic disorder) and language disorders (e.g., developmental language disorder), these additional diagnoses can co-occur with CAS [Morison et al 2022].

Additional common speech- and language-related comorbidities in *FOXP2*-SLD can include the following, irrespective of underlying genetic alteration:

- **Oral-motor dyspraxia,** an inability or difficulty in planning or programming of oral movements on command, including single movements in isolation (e.g., commands such as "blow," "bite," "stick out your tongue") or sequences of oral movements (e.g., commands such as "bite and blow," "touch your bottom lip with your tongue and then blow a kiss"). Both oral dyspraxia [Vargha-Khadem et al 1998, Alcock et al 2000, Lai et al 2000, MacDermot et al 2005, Turner et al 2013] and more general oral-motor deficits (e.g., difficulty performing isolated tongue movements) have been reported in *FOXP2*-SLD [Morison et al 2022].
- **Dysarthria** is infrequent relative to CAS and phonologic errors [Morison et al 2022]. Typical dysarthric features include hypernasality, impaired laryngeal quality, and difficulties modulating pitch and loudness [Turner et al 2013, Morison et al 2022].
- **Moderate-to-severe receptive and expressive language disorder** [Vargha-Khadem et al 1995, Morison et al 2022]. Expressive language is usually poorer than receptive language, with expressive language likely confounded by the presence of CAS. Impaired performance across both semantic and syntactic language domains has been reported in *FOXP2*-SLD [Watkins et al 2002, Vargha-Khadem et al 2005, Turner et al

2013, Morison et al 2022]. Affected semantic domains include naming accuracy and lexical decision making; affected syntactic domains include past tense production for regular and irregular verbs.
- **Reading and spelling impairments** are typically evident once literacy develops [Vargha-Khadem et al 2005]. Difficulties with real word and nonword reading, spelling, and phonologic awareness skills are common in *FOXP2*-SLD [Watkins et al 2002, Turner et al 2013, Morison et al 2022].

Other features of *FOXP2*-SLD

- **IQ.** Generally stronger nonverbal (performance) IQ compared to verbal IQ [Vargha-Khadem et al 1995, Watkins et al 2002, Turner et al 2013, Reuter et al 2017, Morison et al 2022], although both verbal and nonverbal (performance) IQ may be impaired [Watkins et al 2002, Reuter et al 2017, Morison et al 2022].
- **Fine or gross motor impairments** are highly prevalent in the early years of life but typically improve and even resolve with physiotherapy and occupational therapy input. These motor impairments are relatively mild compared to the marked speech production deficits [Lai et al 2000, Morison et al 2022].
- **Autism spectrum disorder** or features of autism have been observed in about 25% of affected individuals [Reuter et al 2017, Morison et al 2022].
- **Mental health.** Some individuals report anxiety and depression, but it is not clear whether this is part of *FOXP2*-SLD or occurs secondary to the other communication and developmental challenges [Morison et al 2022].
- **Mild physical features or dysmorphology** have been reported in a small number of individuals, although no clear pattern has been identified [Morison et al 2022]. Physical features have included: high-arched palate; horizontal eyebrows; ear features (i.e., simply folded ears, prominent ears, anteverted ears); periorbital fullness; nasal features (i.e., upturned nose, prominent nose, hypoplastic alae nasi, high nasal root, rounded, fleshy, or prominent nasal tip); short/flat philtrum; prominent eyes; retrognathia; full lips or thin upper lip [Reuter et al 2017, Morison et al 2022]. In individual instances, mild finger pads, tapering fingers, single palmar crease, and clinodactyly were also noted [Morison et al 2022]. Submucous cleft palate was reported in one individual [Liégeois et al 2016].

Neuroimaging. Routine clinical brain MRIs of individuals with *FOXP2*-SLD typically appear normal on visual inspection [Vargha-Khadem et al 1998].

Genotype-Phenotype Correlations

The specific genetic alteration responsible for *FOXP2*-SLD does not predict clinical severity.

Of note, large copy number abnormalities and more complex variants (including deletions, translocations, and inversions) affecting one allele also lead to speech and language issues as well as other features similar to *FOXP2*-plus-related disorder (see Genetically Related Disorders).

Penetrance

The penetrance for *FOXP2*-SLD is high – close to 100% – based on the findings in individuals reported to date [Morison et al 2022].

Nomenclature

Prior to the discovery of causative pathogenic variants in *FOXP2*, the locus "speech language disorder-1 (SPCH1)" was assigned to the chromosome region linked to the CAS phenotype [Fisher et al 1998].

FOXP2-SLD may also be referred to as "*FOXP2*-only speech and language disorder" to distinguish the condition from *FOXP2*-plus-related disorder (a generally more severe phenotype associated with large copy number variants, structural variants, or maternal uniparental disomy of chromosome 7 involving *FOXP2* and additional adjacent genes; see Genetically Related Disorders).

"Speech and language impairment" is a synonymous term for "speech and language disorder." The term "speech and language delay" should be avoided unless there is a clear clinical justification for use of this term, which implies a child will "catch up" to peers.

Prevalence

The population prevalence of CAS has not been determined by any epidemiologic study. The most commonly referenced estimate of prevalence is 1-2:1,000 [Shriberg et al 1997].

In a cohort with a severe speech disorder, one of 49 individuals had a confirmed *FOXP2* pathogenic variant [MacDermot et al 2005].

Three recent studies performed molecular genetic testing on probands clinically diagnosed with CAS [Eising et al 2019, Hildebrand et al 2020, Kaspi et al 2022]. Within these three cohorts (total: 121 individuals), none of the probands had a pathogenic *FOXP2* variant. Hence, pathogenic *FOXP2* variants are rare, even in cohorts selected for CAS.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline intragenic *FOXP2* pathogenic variants.

Large copy number variants (i.e., contiguous gene deletions), structural variants (i.e., translocations or inversions), or maternal uniparental disomy of chromosome 7 involving *FOXP2* and additional adjacent genes are associated with a generally more severe phenotype referred to in this *GeneReview* as *FOXP2*-plus-related disorder.

Like children with *FOXP2*-related speech and language disorder (*FOXP2*-SLD), children with *FOXP2*-plus-related disorder have childhood apraxia of speech (CAS), and their first words are reported to appear between ages 18 months and seven years [Feuk et al 2006, Zeesman et al 2006, Lennon et al 2007, Rice et al 2012, Zilina et al 2012]. No data are available to determine what proportion of CAS is caused by disruption of *FOXP2* only (*FOXP2*-SLD) or large copy number variants or structural variants involving *FOXP2* (*FOXP2*-plus-related disorder).

In addition to CAS, clinical features reported in *FOXP2*-plus-related disorder include:

- Oral-motor deficits (commonly reported) [Lennon et al 2007, Laffin et al 2012, Zilina et al 2012]
- "Global" developmental delay (presumably involving speech, cognitive, gross, and fine motor abilities) [Feuk et al 2006]
- Autism spectrum disorder (ASD) [Feuk et al 2006, Zilina et al 2012] or presence of features of autism such as repetitive behaviors and unusual interests [Zeesman et al 2006]. Of note, many individuals with *FOXP2*-SLD are explicitly stated not to meet diagnostic criteria for ASD [Feuk et al 2006, Lennon et al 2007, Rice et al 2012], suggesting that these features may relate to disruption of neighboring genes on chromosome 7.
- Facial dysmorphology [Zeesman et al 2006, Lennon et al 2007, Zilina et al 2012, Reuter et al 2017]. Oral structures are typically intact in the absence of a cleft lip or palate, but a high-arched palate has been reported in one individual [Palka et al 2012].

Sporadic tumors occurring as single tumors in the absence of any other findings of *FOXP2*-SLD frequently harbor a somatic pathogenic variant in *FOXP2* that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable.

Differential Diagnosis

The prelinguistic developmental history of children with childhood apraxia of speech (CAS) (e.g., restricted babbling or feeding difficulties) is very similar to that seen in other neurodevelopmental speech or language conditions (e.g., developmental language disorder, phonologic disorder) or even other neurodevelopmental disorders in which language impairment may occur such as autism spectrum disorder. Hence, early signs are not usually sufficiently discriminating to enable a differential diagnosis prior to a child gaining some speech production abilities.

While CAS is rare, it may also be observed in a range of other conditions. The following chromosomal and single-gene disorders may be considered in the differential diagnosis.

Chromosomal disorders associated with CAS include:

- **16p11.2 recurrent deletion.** The 16p11.2 recurrent deletion phenotype is characterized by motor speech disorder, language disorder (broadly impaired receptive, expressive, and pragmatic domains), motor coordination difficulties, psychiatric conditions, and autistic features. While most, if not all, individuals with the 16p11.2 recurrent deletion experience some degree of developmental delay, the severity varies significantly. The majority of children (~80%) with the 16p11.2 recurrent deletion present with a motor speech disorder, such as CAS and dysarthria. CAS is particularly prevalent (found in 77% of affected children) and often co-occurs with other speech sound disorders, such as articulation and phonologic disorders. Additional features include epilepsy or recurrent seizures and dysmorphic features (e.g., low-set ears, partial syndactyly).
- **7q11.23 duplication syndrome** is characterized by delayed motor, speech, and social skills in early childhood; neurologic abnormalities (hypotonia, adventitious movements, and abnormal gait and station); speech sound disorders including motor speech disorders (CAS and/or dysarthria) and phonologic disorders; behavior issues (especially social anxiety disorder / social phobia); autism spectrum disorder; and, in some individuals, intellectual disability. Distinctive craniofacial features (macrocephaly, brachycephaly, broad forehead, straight eyebrows, deep-set eyes, long eyelashes, broad nasal tip, low insertion of the columella, short philtrum, thin vermilion of the upper lip, high-arched palate, and minor ear anomalies) are common.
- **Koolen-de Vries syndrome** (KdVS) is characterized by developmental delay / intellectual disability, neonatal/childhood hypotonia, dysmorphisms, congenital malformations, and behavioral features. Psychomotor developmental delay is noted in all individuals from an early age. Communication disorder is a core feature of KdVS, with a common speech and language phenotype seen. This includes an overriding "double hit" of oral hypotonia and apraxia in infancy and preschool, associated with severely delayed speech development. CAS is common in the preschool years. KdVS is caused by either a heterozygous 500- to 650-kb deletion at chromosome 17q21.31 that includes *KANSL1* (~95% of affected individuals) or a heterozygous intragenic pathogenic variant in *KANSL1*. Note: The 17q21.31 deletion cannot be identified by analysis of G-banded chromosomes or other cytogenetic banding techniques.

Single-gene disorders with robust evidence of CAS involvement are summarized in Table 2.

Table 2. Single-Gene Disorders with Childhood Apraxia of Speech in the Differential Diagnosis of *FOXP2*-Related Speech and Language Disorder

Gene	Disease Name	MOI	Speech & Language Phenotype	Other Features
CDK13	*CDK13*-related disorder	AD	• Nearly all persons age >1 yr display impaired verbal language skills (either absent or restricted speech). • CAS seen in more than half of persons w/verbal impairment.	• DD/ID • Other common findings are recognizable facial features in some persons, behavioral findings, feeding difficulties in infancy, structural cardiac defects, & seizures.
CHD3	Snijders Blok-Campeau syndrome (OMIM 618205)	AD	• Delayed speech acquisition • Expressive language deficits w/CAS & dysarthria	• DD/ID • Macrocephaly, characteristic facial features (prominent forehead, hypertelorism, hypotonia, joint laxity) • Severity of neurologic deficits & presence of nonneurologic features are variable. [1]
DDX3X	*DDX3X*-related neurodevelopmental disorder	XL	• Speech disorder incl CAS [2] • Mild to severely affected receptive & expressive language • ~50% of affected females remain nonverbal after age 5 yrs (*DDX3X*-NDD typically occurs in females & very rarely in males).	• DD/ID • Hypotonia that can be assoc w/ feeding difficulty in infancy • Behavioral issues (e.g., ASD, ADHD, self-injurious behavior, poor impulse control, & aggression)
GALT	Classic galactosemia	AR	• CAS & dysarthria (Prevalence of motor speech disorder is high; in 1 study ~25% of children had CAS. [3]) • Expressive/receptive language impairment	• Life-threatening complications in untreated infants • If lactose-restricted diet is provided during 1st 10 days of life, neonatal signs usually quickly resolve & neonatal death is prevented; however, despite adequate treatment from an early age, affected children are at ↑ risk for DD & abnormalities of motor function.
GRIN2A	*GRIN2A*-related speech disorders & epilepsy	AD	• Severe speech disorders incl dysarthria & speech dyspraxia, & both receptive & expressive language delay/regression. • More mildly affected persons may display subtly impaired intelligibility of conversational speech.	Epilepsy (present in ~90% of affected persons)
KANSL1 [4]	Koolen-de Vries syndrome	AD	See **Chromosomal disorders**.	See **Chromosomal disorders**.

Table 2. continued from previous page.

Gene	Disease Name	MOI	Speech & Language Phenotype	Other Features
KAT6A	*KAT6A* syndrome [5]	AD	• Majority of affected persons are minimally verbal & rely on alternate communication methods. • Verbal persons have speech disorder incl CAS. • Severe expressive & receptive language impairment	• Moderate-to-severe ID, vision, GI function, sleep issues • ASD present in 30% of affected persons • Mainly truncating variants reported [5]
POGZ	White-Sutton syndrome (*POGZ*-related disorder)	AD	Severe speech & language acquisition delays or difficulties incl CAS	NDD w/wide spectrum of cognitive dysfunction, DD, hypotonia, ASD, & behavioral issues
PURA	*PURA* syndrome (See *PURA*-Related Neurodevelopmental Disorders.)	AD	• Delayed speech & language • Expressive language is more severely affected than receptive language. • Most affected persons are unable to speak. • CAS [2]	• ID, delayed motor skills (severely delayed walking; some persons never walk), hypotonia, feeding difficulties, dysphagia • Infants: hypersomnolence, low body temperature, apnea, slow breathing • Recurrent seizures, heart abnormalities, urogenital, GI, & skeletal anomalies, hormone disorders
SETBP1	*SETBP1* haploinsufficiency disorder	AD	• Delayed speech in early years • CAS, receptive & expressive language impairments across domains of function	• Mild motor DD & hypotonia, ID • ADHD • Refractive errors & strabismus
SETD1B	*SETD1B*-related neurodevelopmental disorder	AD	• Speech & language delay • CAS [2]	• DD (precedes seizure onset), ID, ASD, variable epilepsy phenotypes • Males are overrepresented. • Behavioral issues are more common in males.
SHANK3	*SHANK3*-related absent or severely delayed speech (See Phelan-McDermid syndrome.)	AD	• Absent to severely delayed speech • CAS [2]	22q13.3 deletions involving *SHANK3* & *SHANK3* pathogenic variants are known to be assoc w/Phelan-McDermid syndrome. In the authors' experience, children w/ intragenic *SHANK3* pathogenic variants are much more mildly affected than children w/22q13.3 deletions. [6]
SRCAP	Floating-Harbor syndrome	AD	• Dysarthria & verbal dyspraxia w/phoneme imprecision • Hypernasality, high-pitched voice • Severe receptive & expressive language impairment across all domains of function	• Craniofacial features • Low birth weight, normal head circumference, & short stature • Bone age delay that normalizes between ages 6-12 yrs • Skeletal anomalies • ID that is typically mild to moderate
TNRC6B	*TNRC6B*-related syndrome [7]	AD	• Delayed speech • CAS	• ID/DD, fine & gross motor delay • ASD, ADHD, or other behavioral findings • Musculoskeletal findings [7]

Table 2. continued from previous page.

Gene	Disease Name	MOI	Speech & Language Phenotype	Other Features
ZNF142	*ZNF142*-related NDD w/ impaired speech & hyperkinetic movements (OMIM 618425)	AR	Speech impairment ranging from severely affected (minimally verbal) to verbal (w/CAS)	• ID • Variable manifestation of seizures, tremor, dystonia • 24 families reported [8]

AD = autosomal dominant; ADHD = attention-deficit/hyperactivity disorder; AR = autosomal recessive; ASD = autism spectrum disorder; CAS = childhood apraxia of speech; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; NDD = neurodevelopmental disorder

1. Snijders Blok et al [2018], Eising et al [2019]

2. Kaspi et al [2022]

3. Shriberg et al [2011]

4. A heterozygous intragenic pathogenic variant in *KANSL1* is identified in ~5% of affected individuals. Most individuals with Koolen-de Vries syndrome have the disorder as the result of a heterozygous deletion at chromosome 17q21.31 that includes *KANSL1* [St John et al 2022b].

5. St John et al [2022a]

6. Author, personal observation; Brignell et al [2021]

7. Eising et al [2019], Granadillo et al [2020]

8. Khan et al [2019], Christensen et al [2022], Kamal et al [2022]

Management

No clinical practice guidelines for *FOXP2*-related speech and language disorder (*FOXP2*-SLD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and management needs for an individual with *FOXP2*-SLD, the following evaluations conducted by a trained and specialized speech-language pathologist are recommended:

- Detailed developmental history including early oral-motor and feeding abilities, speech sound development, motor milestones, and cognitive development
- Family history of speech disorder
- Oral-facial structural examination to determine if any structural abnormalities are present
- Speech sound assessment including a test of single words, sounds in isolation, and connected speech to determine the child's phonetic inventory (i.e., has the child acquired age-appropriate speech sounds) and to determine if the child has phonologic errors, apraxic errors, dysfluency (stuttering), dysarthric errors, or a combination of these speech disorder diagnoses. The presence of resonance or nasality deficits signals the need to consider whether structurally based velopharyngeal port incompetence is present by referral to an ear, nose, and throat specialist and possibly videopalatography.
- Assessment of oral-motor function including:
  - Examination of facial asymmetry, reduced or increased oral-facial tone, and/or poor coordination of neuromuscular oral movements (e.g., "try to lick your nose with your tongue," "move your tongue quickly side to side," "blow a kiss" [lip protrusion], "smile" [lip retraction], etc.)
  - Examination for evidence of oral-motor dyspraxia (i.e., can the individual perform oral movements on command in isolation [e.g., "bite" or "blow"] or in sequence [e.g., "kiss and blow"; "kiss, blow, and bite"])
- Language assessment to determine the presence of receptive and/or expressive language impairments across the domains of semantics, syntax, and morphology
- Literacy assessment or preliteracy (phonologic awareness) for evidence of reading and spelling difficulties so that appropriate support can be arranged

Additional evaluations include the following:

- Referral to a neuropsychologist or clinical psychologist to determine the extent of any coexisting cognitive and learning impairments and to assess for the presence of behaviors associated with autism spectrum disorder, attention-deficit/hyperactivity disorder, anxiety, or depression
- Referral to a physical therapist if gross motor movement difficulties are reported and to an occupational therapist if fine motor movement difficulties are observed
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of *FOXP2*-SLD to facilitate medical and personal decision making
- Assessment of the need for family support (see Resources and Parent to Parent)

Treatment of Manifestations

There is no cure for *FOXP2*-SLD.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields.

Speech and language disorder. A speech-language pathologist will utilize treatments targeted to the specific findings in an affected individual; thus, a thorough initial assessment to establish the extent of the condition and management needs for an individual is important.

No single recommended treatment exists. The optimal approach should be determined based on the individual's presentation, but guidance on CAS therapies is as follows [American Speech-Language-Hearing Association 2007, Royal College of Speech and Language Therapists 2011, Murray et al 2014, Murray et al 2015, Morgan et al 2018].

- 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) are 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.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech-language, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended and results from referral to Child Find programs. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
  - Vocational opportunities and programming including vocational rehabilitation should be considered early with a focus on achievement of meaningful employment
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

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

Oral motor dysfunction. Feeding therapy (typically from a speech-language pathologist or occupational therapist) is recommended to help improve coordination of oral movement skills for feeding or sensory-related feeding issues using relevant approaches including postural modification and altering the consistency of food and fluid [Morgan et al 2012]. Mothers 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.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social,

and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about anxiety can be addressed by a developmental specialist or psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the following evaluations are recommended:

- Routine care by a general pediatrician
- Follow-up evaluations with standardized tests by a speech-language pathologist
- Review educational progress/needs
- Review mental health if anxiety and/or depression have been issues or have emerged as issues

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic sibs of an affected individual by molecular genetic testing for the *FOXP2* pathogenic variant in the family to identify as early as possible those who would benefit from prompt evaluation by a speech-language pathologist and initiation of treatment.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

FOXP2-related speech and language disorder (*FOXP2*-SLD) is caused by a heterozygous pathogenic variant in *FOXP2* and inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About half of individuals diagnosed with *FOXP2*-SLD have the disorder as the result of a *de novo* pathogenic variant. In a cohort of 17 families with *FOXP2*-SLD, eight individuals represented simplex cases (i.e., the only affected family member) and had the disorder as the result of a *de novo* pathogenic variant [Morison et al 2022].

- About half of individuals diagnosed with *FOXP2*-SLD have an affected parent [Morison et al 2022].
- If the proband appears to be the only affected family member, molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent 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 a proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the *FOXP2* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- The penetrance of *FOXP2*-SLD in heterozygous family members approaches 100% [Morison et al 2022]. Although interfamilial variability is observed in *FOXP2*-SLD, minimal clinical variability is observed among affected family members [Morison et al 2022].
- If the *FOXP2* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental mosaicism [Morison et al 2022].

Offspring of a proband. Each child of an individual with *FOXP2*-SLD has a 50% chance of inheriting the *FOXP2* pathogenic variant.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of having a child with *FOXP2*-SLD.

Prenatal Testing and Preimplantation Genetic Testing

Once the *FOXP2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **Apraxia Kids**
  Phone: 412-785-7072
  Email: info@apraxia-kids.org
  apraxia-kids.org
- **Dyspraxia Foundation**
  United Kingdom
  Phone: 01462 454986; 01462 454986
  dyspraxiafoundation.org.uk

Molecular Genetics

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

Table A. FOXP2-Related Speech and Language Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FOXP2	7q31.1	Forkhead box protein P2	FOXP2 database	FOXP2	FOXP2

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 FOXP2-Related Speech and Language Disorder (View All in OMIM)

602081	SPEECH-LANGUAGE DISORDER 1; SPCH1
605317	FORKHEAD BOX P2; FOXP2

Molecular Pathogenesis

FOXP2 encodes the Forkhead box protein P2, a transcription factor with zinc finger (residues 346 to 371) and DNA-binding (residues 504 to 594) functional domains. *FOXP2* is thought to form homodimers (and heterodimers with *FOXP1* or *FOXP4*) via a protein region that includes a leucine zipper and zinc finger. Forkhead box proteins are transcription factors that likely regulate hundreds of downstream target genes, some of which will be critical for development of speech and language. *FOXP2* pathogenic missense variants, including those that disrupt the DNA-binding domain (e.g., p.Arg553His [Vernes et al 2006]), produce abnormal gene products that cannot bind DNA targets properly, as shown by functional studies of some variants that cause *FOXP2*-related speech and language disorder [Deriziotis et al 2014, Estruch et al 2018, Hickey et al 2019, den Hoed et al 2021].

Other pathogenic missense variants may be associated with dominant-negative effects, which to date have not been demonstrated in published reports.

Mechanism of disease causation. Loss of function, haploinsufficiency

***FOXP2*-specific laboratory technical considerations.** Missense variants that directly affect the DNA-binding domain are likely to be pathogenic, while missense variants outside this domain are unlikely to be pathogenic.

Chapter Notes

Author Notes

Angela T Morgan is a speech pathologist with more than 25 years of experience in speech phenotyping in genetic conditions. She works closely with the coauthors of this review both in identifying genes that cause severe speech disorder and in characterizing speech and language in known genetic conditions.

- University of Melbourne profile
- Murdoch Children's Research Institute profile and publications

Prof Morgan (angela.morgan@mcri.edu.au) is actively involved in clinical research regarding individuals with speech disorder. She would be happy to communicate with persons who have any questions regarding diagnosis of genetic conditions related to severe speech presentations.

Prof Morgan (angela.morgan@mcri.edu.au) is also interested in hearing from clinicians treating families affected by severe speech disorder or speech apraxia in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Simon Fisher (simon.fisher@mpi.nl) to inquire about review of *FOXP2* variants of uncertain significance.

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