

# Mild to Moderate Intellectual Disability and Significant Speech and Language Deficits in Patients with *FOXP1* Deletions and Mutations

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## Key Words

Developmental delay · *FOXP1* · Intellectual disability · Speech deficit

## Abstract

Very recently, *FOXP1* deficiency was shown to result in a phenotype of intellectual disability with significant speech and language impairment. Behavioral abnormalities should be considered as part of the clinical spectrum. Mild craniofacial abnormalities found in half of the described patients expand the clinical spectrum associated with *FOXP1* mutations.

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## History of the Syndrome

Neurodevelopmental disorders that disturb speech and language are highly heritable. Rare heterozygous mutations of the *FOXP2* gene have been identified as one cause of hereditary developmental dyspraxia [Lai et al., 2001]. The most closely related member of the same gene family, the forkhead box P1 gene (*FOXP1*, MIM 605515), has expression patterns that overlap with *FOXP2* in some areas of the brain, and *FOXP1* and *FOXP2* have the ability to form heterodimers. This structural and functional relationship between *FOXP1* and *FOXP2* suggests that *FOXP1* may also contribute to proper speech development. In 2009, a patient was described who presented

with a 3p13–14.1 microdeletion of 4 genes, including *FOXP1*, resulting in speech delay, contractures, muscular hypertonia and blepharophimosis [Pariani et al., 2009]. Recently, a single deletion of *FOXP1* was reported to cause severe speech delay, delayed gross motor skills, Chiari I malformation, and epileptiform discharges in a child [Carr et al., 2010]. Very recently, 3 heterozygous overlapping deletions solely affecting the *FOXP1* gene in unrelated patients affected with moderate intellectual disability (ID) and significant language and speech deficits have been detected by molecular karyotyping [Horn et al., 2010]. Two different de novo heterozygous mutations in the *FOXP1* gene were identified in 2 unrelated children with ID, expressive language deficits, and autistic features [Hamdan et al., 2010].

In total, 6 patients with heterozygous *FOXP1* deficiency have been reported to date.

## Clinical Features

### *Intellectual Disability*

Detailed clinical investigation of these patients revealed that they present mild to moderate ID in combination with a general developmental delay (table 1). In 5 patients, the non-verbal IQ score was assessed as about 50 (3 SD below the mean) [Hamdan et al., 2010; Horn et al., 2010]. Almost all showed retarded gross-motor development with unsupported walking between 18 and 36

**Table 1.** Clinical findings in patients with FOXP1 deletions and mutations

		Carr et al. [2010]	Horn et al. [2010] Pat. 1	Horn et al. [2010] Pat. 2	Horn et al. [2010] Pat. 3	Hamdan et al. [2010] Pat. A	Hamdan et al. [2010] Pat. B
General features	age of last assessment	41 months	7 years	5.5 years	6 years	15 years	9 years
	sex	male	male	female	male	female	male
	occipitofrontal head circumference (SD)	+0.7	+1.2	+0.8	+1.3	n.d.	n.d.
	weight (SD)	-0.2	+0.5	+2.7	+2.5	n.d.	n.d.
	facial gestalt	prominent forehead, ptosis	no dysmorphisms	prominent forehead, frontal hair upsweep	prominent forehead, frontal hair upsweep	n.d.	n.d.
	non-verbal performance IQ	n.d.	<50	<50	50	58	48
	gross motor delay	n.d.	+	+	+	+	+
	age at walking	16 months	24 months	36 months	24 months	18 months	20 months
	first words at age of	3.5 years	3.5 years	3.5 years	3.5 years	3 years	6 years
	combined words at age of	n.d.	7 years	5 years	5.5 years	4 years	n.d.
Speech and language development							
Behavioral anomalies	n.d.	n.d.	+	+	+	+	

**Fig. 1.** Facial features of a 4-year-old girl showing a broad and prominent forehead, frontal hair upsweep, and a short nose (patient 2 reported by Horn et al., 2010).

months [Carr et al., 2010; Hamdan et al., 2010; Horn et al., 2010]. Patients started to speak at ages of 3–6 years and used combinations of 2 words at ages between 4 and 7 years. Expressive language was more affected than receptive abilities. Expressive vocabulary was limited to relatively simple, frequent words or 2–3 word sentences in a

15-year-old and 9-year-old patient, respectively. In terms of expressive communication these 2 patients were scored at an age equivalent of 1 year 11 months at the chronological age of 9 years and about 4.5 years at the chronological age of 15 years, respectively [Hamdan et al., 2010].

Two of them showed oromotor problems including difficulties with lip protrusion. In infancy, some patients had a tendency to keep their mouth open [Horn et al., 2010].

#### *Facial Gestalt*

Mild craniofacial anomalies documented in 3 of 6 patients included broad and prominent forehead, a short nose and a frontal hair upsweep in 2 patients of this cohort (fig. 1) [Carr et al., 2010; Horn et al., 2010]. The remaining patients are not reported to show a distinctive facial phenotype [Hamdan et al., 2010]. Altogether, the facial features alone do not seem to be specific enough to establish the diagnosis.

#### *Growth Parameters*

Patients were born after uneventful pregnancies and deliveries. Growth parameters at birth were normal in all. Also later in childhood, normal growth parameters regarding height and occipitofrontal head circumference were documented in 4 reported cases (table 1) but presence of obesity was striking in 2 patients. Regarding available data, patients show a tendency to head circumferences above mean (+0.7 to +1.3 SD) [Carr et al., 2010; Horn et al., 2010].

### *Behavioral Abnormalities*

Four of 6 patients showed particular behavioral problems [Hamdan et al., 2010; own unpublished results]. The abnormal behaviors were characterized by both internalizing (e.g., anxiety) and externalizing (e.g., mood lability, temper tantrums, impulsivity, physical aggression) behavioral problems. Irritability, stereotypy, hyperactivity and autistic features were rated as the most significant problems on the aberrant behavior checklist [Hamdan et al., 2010]. A number of specific obsessions and compulsions as well as ritualistic behavior (e.g. rigid routines, strong attachment to specific objects) were described by the parents. Self-injurious behavior was also reported for 1 patient [Hamdan et al., 2010]. Common behavioral characteristics in 4 of 6 patients were mood lability, autistic features, and hyperactivity.

### *Other Findings*

Brain magnetic resonance imaging and electroencephalography did not reveal any abnormalities in 3 patients but in 1 further patient a dysmorphic corpus callosum, mild hypoplasia of the cerebellar vermis, and a Chiari I malformation were reported which required suboccipital decompression of this malformation at an age of 30 months [Carr et al., 2010]. An electroencephalogram in this patient disclosed epileptiform discharges in different brain regions [Carr et al., 2010]. Another patient with a *FOXP1* mutation was operated on for atresia of the midjejunum and midileum gut during the neonatal period [Hamdan et al., 2010].

### **Natural History**

In infancy, gross-motor development is delayed in most cases [Carr et al., 2010; Hamdan et al., 2010; Horn et al., 2010]. Speech and language development is significantly retarded with first words spoken after 3 years of age. Expressive vocabulary remains limited to simple and single words. ID is of mild to moderate degree. Behavioral problems, including mood lability and hyperactivity, tend to be frequent in childhood.

### **Recommendations for Management**

Not much information about treatment is available. In the reported patient with epileptiform discharges, oxcarbazepine therapy was initiated [Carr et al., 2010].

### **Genetics**

#### *Information about the FOXP1 Gene, the Corresponding Protein, and Relationship to FOXP2*

*FOXP1* consists of 16 coding exons spanning about 600 kb on chromosome 3p14.1. De novo deletions identified by copy number analysis included all coding exons of *FOXP1* in 3 patients and are intragenic deletions in 2 reported patients [Carr et al., 2010; Hamdan et al., 2010; Horn et al., 2010]. By sequencing of the longest *FOXP1* isoform, a de novo nonsense mutation was found in a further patient [Hamdan et al., 2010]. This mutation was predicted to abolish the last 152 residues of the protein, including part of the forkhead domain. Expression studies showed that this mutant impaired the transcriptional repression ability of *FOXP1*, consistent with a loss of function [Hamdan et al., 2010].

*FOXP1* belongs to a functionally diverse family of forkhead box (FOX) transcription factors that are all characterized by a highly conserved FOX domain. *FOX* genes have been shown to play important roles in diverse cellular functions including metabolic and developmental processes [Carlsson and Mahlapuu, 2002]. While the function of *FOXP1* during blood cell, lung and heart formation has already been addressed [Shu et al., 2001; Shi et al., 2004; Wang et al., 2004; Hu et al., 2006], the role of *FOXP1* in neuronal processes, in particular brain development, is still unclear. In a mouse mutant model, *Foxp1* has recently been shown to be an important accessory factor in Hox transcriptional output, thus regulating motor neuron diversification and connectivity to target muscles [Dasen et al., 2008; Rouso et al., 2008]. These findings are of particular interest with regard to the gross-motor deficits seen in patients with *FOXP1* deletions and mutations.

With regard to structure and expression profiles, the most interesting gene related to *FOXP1* is *FOXP2* (MIM 605317). Rare mutations of *FOXP2* have been described in individuals having expressive and receptive language and speech deficits generally described as developmental verbal dyspraxia [Hurst et al., 1990; Lai et al., 2001; MacDermot et al., 2005; Feuk et al., 2006]. A functional relationship between *Foxp1* and *Foxp2* has been previously demonstrated in mouse, as they form homo- and heterodimers necessary for efficient DNA binding [Li et al., 2004]. *FOXP1* and *FOXP2* also show overlapping expression patterns within brains of zebra finches and fetal human brains, particularly in subcortical regions that play important roles in sensorimotor integration and coordinated movements important for vocalization and speech, respectively [Teramitsu et al., 2004].

Non-verbal intellectual impairment could not be considered characteristic of the phenotype associated with *FOXP2* mutations [Lai et al., 2001]. This is in contrast to the clinical findings in patients with *FOXP1* mutations who, in addition to their speech and language disabilities, exhibit significantly reduced non-verbal IQ scores. This may indicate that additional distinct functions of *FOXP1* exist, presumably acting on a more global level in neuronal development compared to *FOXP2*. Thus, haploinsufficiency of *FOXP1* leads to abnormal development of neural structures that coordinate general cognitive and psychomotor as well as verbal abilities.

#### Mode of Inheritance

Up to now, all reported patients are sporadic cases, resulting from a de novo heterozygous deletion or mutation of *FOXP1*. Therefore, the *FOXP1* related phenotype is inherited in an autosomal dominant manner.

#### Frequency of *FOXP1* Mutations and Deletions

The frequency of these mutations has not been estimated, but these mutations seem to be a rare cause of ID and speech and language deficits. In a cohort of about 1,500 patients with ID, 3 cases with *FOXP1* deletions were identified by copy number analysis [Horn et al., 2010]. Search for point mutations in 883 patients with ID did not discover a clear pathogenic variant, but a few coding variants were detected which have to be further investigated to assess their neurobiological significance [Horn et al., 2010]. Using array based genomic hybridization, 1 intra-genic deletion of *FOXP1* was found in a cohort of 30 patients with nonsyndromic ID and 80 patients with autism spectrum disorders [Hamdan et al., 2010]. Sequencing of *FOXP1* in 110 sporadic cases with nonsyndromic ID and 135 cases with autism spectrum disorders revealed the presence of one de novo nonsense mutation [Hamdan et al., 2010].

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