ARTICLE

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

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Human *FOXP2* deficiency has been identified as a cause of hereditary developmental verbal dyspraxia. Another member of the same gene family, *FOXP1*, has expression patterns that overlap with *FOXP2* in some areas of the brain, and *FOXP1* and *FOXP2* have the ability to form heterodimers. These findings suggest the possibility that *FOXP1* may also contribute to proper speech development. However, no such role of *FOXP1* has been established to date. Recently, a child was reported who presented with a 3p13-14.1 deletion of four genes, including *FOXP1*, and a constellation of deficits that included speech delay. In this study, we report the case of a patient with a single deletion of *FOXP1*. This patient presented with speech and motor developmental delays, a Chiari I malformation, and epileptiform discharges. The nature of the speech deficit is different from the primary oromotor verbal dyspraxia found in patients with *FOXP2* deficiency. The patient's developmental deficits may support a role for *FOXP1* in the development of verbal and motor skills.

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INTRODUCTION

FOXP1, located on 3p14.1, is a member of the *FOX* gene family of winged-helix/forkhead DNA-binding proteins.¹ To date, the association of *FOXP1* with human pathology has been confined to B-cell development and lymphomas.² In comparison, more is known about the role of *Foxp1* in murine pathology. In the last decade, *Foxp1* deficiency has been associated with defective lymphopoiesis³ and cardiac development.⁴ Murine models have also uncovered the role of *Foxp1* as an accessory factor of Hox transcription factors that regulate the projection and connection of motor neurons to target muscles.^{5,6} The absence of *Foxp1* causes disordered, random connection of motor neurons to muscles.^{7,8}

FOXP2 belongs to the same family of genes as *FOXP1*. *FOXP2* haploinsufficiency has been implicated in the etiology of a familial verbal dyspraxia (ie, impairments in learning and producing sequences of mouth movements involved in fluent speech). This discovery began with the characterization of a three-generation family who had deficits in orofacial praxis, expressive language, receptive vocabulary and grammar, and nonverbal coding skills.^{9–11} Subsequently, an unrelated individual with a similar dyspraxia was identified, and molecular studies revealed disruptions in the *FOXP2* gene of all affected individuals.¹² Since then, additional cases of verbal dyspraxia caused by *FOXP2* mutations and chromosomal rearrangements have been reported.^{13–16} Recent *FOXP2* studies have focused on the identification of cerebral structures influenced by the *FOXP2* transcription factor,^{17,18} and multiple transcriptional targets

in the human basal ganglia and inferior frontal cortex have been identified.^{19,20}

The association of human *FOXP2* with speech deficits is mirrored in animal models. Similar to humans, songbirds possess the ability to modify innate vocalizations. Haesler *et al*²¹ found that the knockdown of *Foxp2* in the basal ganglia of zebra finches resulted in incomplete and inaccurate vocal imitation, a finding that likely parallels the verbal dyspraxia seen in *FOXP2*-haploinsufficient humans. Interestingly, in zebra finches and humans, *Foxp1* and *Foxp2* have some overlapping expression in subcortical structures that contribute to the coordination of movement, including those needed for complex vocalization.²² With this colocalization of *Foxp1* and *Foxp2* expression in some regions of the brain, Teramitsu *et al*²² hypothesized that these genes function together to regulate the development of neurological structures required for fluent vocal control. Furthermore, *Foxp1* and *Foxp2* can interact with one another, forming heterodimers.²³ This ability to interact lends support to the hypothesis that both *FOXP1* and *FOXP2* may collaborate in a common pathway that influences the proper formation and function of circuits used in learned articulation.

Although *FOXP2* has been formally associated with deficits in verbal expression, the role of *FOXP1* deficiency in speech deficits remains to be established. In 2009, Vernes *et al*²⁴ analyzed *FOXP1* in 49 patients with developmental verbal dyspraxia (DVD). A non-synonymous coding change was discovered in only one patient, and, although the same mutation was present in a control sample, the possibility that the mutation contributed to the patient's DVD could

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not be ruled out. Although finding that *FOXP1* mutations were not likely a major cause of DVD, Vernes *et al*²⁴ did posit that *FOXP1* remains a candidate for involvement in neurodevelopmental disease. A recent case report described a patient with speech delay, contractures, blepharophimosis, hypertonia, and a deletion of four genes in 3p13-14.1, including *FOXP1*.²⁵ This case is consistent with the hypothesis of a potential role of *FOXP1* in speech development. In this study, we report a patient with a deletion involving only the *FOXP1* gene whose deficits support a role of *FOXP1* in human motor and speech development.

CLINICAL REPORT

The proband, a male born at 37 weeks of gestation, is the second child of a 32-year-old Caucasian mother and a 33-year-old Caucasian father. The prenatal course was unremarkable. After delivery, the infant had a 'puffy' left face, but otherwise appeared normal. Growth parameters were normal.

Subsequently, gross motor skills were delayed; the patient did not walk until 16 months of age. A neurological evaluation at 26 months was undertaken because of speech delays. An MRI revealed a normal gyral pattern, a dysmorphic but intact corpus callosum, mild hypoplasia of the cerebellar vermis, and a Chiari I malformation (herniation of the cerebellar tonsils through the foramen magnum) (Figure 1). At 30 months, the patient underwent suboccipital decompression of the malformation, with some improvement in motor development thereafter.

At 41 months, the patient was found to be imitating sounds and attempting words. The patient had difficulty articulating entire words, and was only able to verbalize one or two syllables of multisyllabic words. Most often, he could verbalize vowels but not consonants. For example, an attempt to repeat the word 'dad' yielded only the short 'a' sound. The patient exhibited no deficits of oromotor coordination that could explain this deficit, as he had no feeding difficulty, was able to suck through a straw, and did not dribble excessively. The patient compensated for his speech deficit using rudimentary sign language, using ~25 signs with some phrase formation. Given the patient's effective use of sign language, the patient's speech deficit appears to

be a problem of verbal expression and not a failure of language development. No formal language, intelligence, nor praxis testing was made available for this patient.

Physical examination at 41 months demonstrated a height of 100 cm (10th centile), weight of 15.6 kg (10th–25th centile), and head circumference of 52 cm (50th–75th centile). Dysmorphic features were noted as indicated in Figure 2. The neurological examination showed intact cranial nerves except for mild ptosis and mildly decreased facial expression. There was decreased tone axially and a slightly increased tone of the extremities. Reflexes were slightly increased as well. The patient developed staring spells with motor arrest at the age of 4 years. An electroencephalogram noted epileptiform discharges in the left frontocentral region and the right posterior region. Oxcarbazepine was initiated.

A review of the patient's family history revealed that several of the proband's relatives, including his mother, suffered from a mild sensorineural hearing loss of unknown etiology. In addition, the proband's maternal uncle has an auditory processing problem (no further detail about this deficit is available). No hearing difficulty has been detected in the patient. The mother has normal speech and language abilities, so no deficiencies in her communication skills have been contributing to the patient's developmental deficits.

An echocardiogram and renal ultrasound were normal. Chromosome analysis showed a normal 46,XY karyotype at a band resolution of 600. Cytogenetic array analysis followed with notable results discussed below.

MOLECULAR CYTOGENETIC ANALYSIS

Whole-genome cytogenetic array comparative genomic hybridization (aCGH) analysis was carried out using a custom-designed 44K oligonucleotide array with a backbone resolution of ~250 kb.²⁶ An ~1.0 Mb interstitial deletion of 3p14.1 was identified that only involved the *FOXP1* gene (Figure 3)²⁷; FISH analysis confirmed the deletion. No other copy-number abnormalities were found on the 44K

Figure 1 MRI showing the patient's Chiari I malformation.

Figure 2 The patient's dysmorphology includes a broad forehead, orbital hypertelorism, down-slanting palpebral fissures, bilateral ptosis, short nose, broad nasal tip, smooth philtrum, and slightly down-turned corners of the mouth. Facial photos demonstrate the evolution of the facial phenotype from (a) 10 months to (b) 20 months to (c) 46 months.

Figure 3 The deletion of *FOXP1* at 3p14.1. (a) Array results for the proband are shown above the ideogram of chromosome 3. Each dot is an oligonucleotide probe; those with normal copy number have a log2 ratio of ~ 0 , whereas those in the deleted region have a log2 of less than -0.32 . The deleted region is boxed. (b) UCSC Genome Browser view of the *FOXP1* deletion. The deletion described in this report and a similar larger deletion from a previous study²⁵ are shown as red bars. Probes on the whole-genome array and *FOXP1*-targeted array appear as black vertical lines. Deletions (red bars) and duplications (green bars) found in apparently normal control individuals from a previous study²⁷ are also displayed. The minimal deleted region is chr3:70 549 923–71 618 670; the maximum deleted region is chr3:70 508 118–71 618 932. The color reproduction of this figure is available on the html full text version of the manuscript.

oligonucleotide array. High-resolution aCGH was performed for fine mapping using a custom-designed *FOXP1*-targeted array with one exonic probe every 15 bp and one intronic probe every 500 bp. These analyses refined the minimal deleted region to chr3:70 549 923–71 618 670 (hg18). Parental FISH analyses demonstrated that the deletion is *de novo*.

DISCUSSION

Although only *FOXP2* has been associated with neurodevelopmental deficits in humans to date, the patient reported here suggests that *FOXP1* deficiency may cause motor and speech deficits. Similar to the patient reported herein, patients with *FOXP2* haploinsufficiency have normal gross oromotor function (eg, no feeding difficulties, no excessive dribbling). However, this patient's speech deficit is fundamentally different from that seen in *FOXP2* deficiency. This patient has limited verbal output, has greater difficulty verbalizing consonants than vowels, and has difficulty in producing multisyllabic speech. In contrast, patients with *FOXP2* haploinsufficiency have greater verbal output, and these patients' ability to verbalize consonants and vowels is the same. These patients do not have the same difficulty in producing multisyllabic speech as the patient reported herein. *FOXP2*-haploinsufficient patients' deficit lies in the coordination of rapid sequences of articulatory gestures; their verbalizations contain more errors as the length and/or complexity of utterances increases.¹¹ Another significant difference between the *FOXP2*-deficient phenotype and our patient is gross motor skill. The patient reported herein has experienced delays in gross motor skill acquisition. *FOXP2*-haploinsufficient patients feature normal gross motor development.

A previous case report by Pariani *et al*²⁵ described a patient with a deletion of four genes in 3p13-14.1, including *FOXP1*. This patient's constellation of pathology included speech delay, gross motor skill

delay, hypertonia, contractures, and blepharophimosis. Table 1 offers a comparison of key features of Pariani's patient and the patient reported herein. Some similarities between these two *FOXP1*-deficient patients exist, but, on balance, the phenotypic differences are greater. Both patients experienced speech delay; at 23 months of age, Pariani's patient was producing vowel sounds but not words. In addition, both patients also experienced delays in gross motor skill acquisition, although the degree of severity is worse in Pariani's patient. This latter patient only began cruising at the age of 18 months, whereas our patient began walking at 16 months. Contractures present in Pariani's patient were absent in our patient. Hypertonia was a key finding in Pariani's patient, whereas our patient only exhibited slightly increased extremity muscle tone. The nature of facial dysmorphism also differs between the two patients. These disparate findings suggest that the previously reported patient's phenotype was influenced by the deletion of not just *FOXP1* but also *EIF4E3*, *PROK2*, and *GPR27*. Alternatively, these phenotypic differences could be due to a highly variable expressivity of *FOXP1* haploinsufficiency.

In the current patient, *FOXP1* is the only deleted gene, and rearrangements involving *FOXP1* are absent from the Database of Genomic Variants.^{28,29} Therefore, *FOXP1* is a likely etiological basis of the patient's constellation of developmental deficits. However, Chiari I malformations can adversely affect sensory and motor development, and so the possibility exists that the patient's symptoms may have been exacerbated or even caused by his Chiari I malformation. Possibly, the surgical treatment of the patient's Chiari I malformation, combined with the dynamic plasticity of the young central nervous system, may explain the patient's relatively late improvement in motor function, as has been reported in other cases.³⁰ Alternatively, the patient's late improvement in motor function may suggest that the impact of *FOXP1* on human motor neuron development is modified

Table 1 A comparison of the phenotypes of two patients with *FOXP1* deletions

	<i>Pariani et al</i> ²⁵	<i>Current report</i>
Deleted genes	<i>FOXP1, EIF4E3, PROK2, GPR27</i>	<i>FOXP1</i>
<i>Development</i>		
Speech delay	Producing vowel sounds, but no words at 23 months	Producing almost exclusively vowel sounds, but no words at the age of 41 months
Gross motor skill delay	Sat upright unassisted at 15 months Cruising at 18 months	Walking at 16 months
<i>Neurological features</i>		
Muscle tone	Hypertonia	Slightly increased extremity tone Decreased axial tone
Reflexes	Normal	Slightly increased
Other	Intermittent daily muscle spasms since birth	Staring spells with motor arrest Mild ptosis
Facial dysmorphology	Upturned alae nasi Blepharophimosis Epicanthal folds Prominent cheeks	Alae nasi unremarkable Broad forehead Hypertelorism Down-slanting palpebral fissures Smooth philtrum Slightly down-turned corners of mouth
Musculoskeletal	Contractures Persistent flexion of phalanges	No contractures Normal positioning of phalanges
Genitalia	Bilateral cryptorchidism	Descended testes bilaterally
Hands	Bilateral single transverse palmar crease	Bridged palmar creases Persistent fetal pads
MRI	Mild asymmetric enlargement of ventricles and sulci, consistent with minor atrophy	Dysmorphic but intact corpus callosum Mild hypoplasia of the cerebellar vermis Chiari I malformation

by other factors not found in animal models. Indeed, attribution of the patient's full complement of deficits to the Chiari I malformation would be difficult. Previous studies have identified an association between Chiari I malformations and speech delays,^{31–33} suggesting that these abnormalities may be clustering together in some instances and might have a common pathogenetic background. Our report may support this association, identifying *FOXP1* haploinsufficiency as one possible origin for this particular phenotype. At the least, the Chiari malformation is an important confounder that complicates the interpretation of the effect of *FOXP1* deficiency on the patient's speech and motor development.

The patient reported herein developed seizures after decompression of his Chiari malformation. Although cerebellar fits have been demonstrated in children with Chiari malformation, epilepsy is thought to be rare.³⁴ However, one case series suggests that some patients with Chiari I malformation may have cerebral microdysgenesis as evidenced by single-photon emission computed tomography.³⁵ *FOXP1* haploinsufficiency may also contribute to aberrations in cerebral–cerebellar networking, resulting in seizure activity, although this hypothesis requires investigation.

Even with the Chiari I confounder, the concurrence of a *FOXP1* deletion and the patient's constellation of deficits is compelling enough to merit genetic studies of persons with gross motor developmental delay and/or verbal deficits. With respect to the latter, the identification of only one *FOXP1* mutation among 49 patients with DVD and the inability to assign causality to this single mutation suggest that larger sample sizes may be needed to identify *FOXP1* mutations, especially if such mutations have a frequency less than

FOXP2 gene anomalies, in which ~2% of patients carry a deleterious genetic change.²⁴

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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- Shu W, Yang H, Zhang L, Lu MM, Morrissey EE: Characterization of a new subfamily of winged-helix/forkhead (Fox) genes that are expressed in the lung and act as transcriptional repressors. *J Biol Chem* 2001; **276**: 27488–27497.
- Banham AH, Connors JM, Brown PJ *et al*: Expression of the *FOXP1* transcription factor is strongly associated with inferior survival in patients with diffuse large B-cell lymphoma. *Clin Cancer Res* 2005; **11**: 1065–1072.
- Hu H, Wang B, Borde M *et al*: Foxp1 is an essential transcriptional regulator of B cell development. *Nat Immunol* 2006; **7**: 819–826.
- Wang B, Weindenfeld J, Lu MM *et al*: Foxp1 regulates cardiac outflow tract endocardial cushion morphogenesis and myocyte proliferation and maturation. *Development* 2004; **131**: 4477–4487.
- Dasen JS, Liu JP, Jessell TM: Motor neuron columnar fate imposed by sequential phases of Hox-c activity. *Nature* 2003; **425**: 926–933.
- Dasen JS, Tice BC, Brenner-Morton S, Jessell TM: A Hox regulatory network establishes motor neuron pool identity and target-muscle connectivity. *Cell* 2005; **123**: 477–491.
- Dasen JS, De Camilli A, Wang B, Tucker PW, Jessell TM: Hox repertoires for motor neuron diversity and connectivity gated by a single accessory factor, FoxP1. *Cell* 2008; **134**: 304–316.
- Rouso DL, Gaber ZB, Wellik D, Morrissey EE, Novitsch BG: Coordinated actions of the forkhead protein Foxp1 and Hox proteins in the columnar organization of spinal motor neurons. *Neuron* 2008; **59**: 226–240.

- 9 Watkins KE, Dronkers NF, Vargha-Khadem F: Behavioral analysis of an inherited speech and language disorder: comparison with acquired aphasia. *Brain* 2002; **125**: 452–464.
- 10 Hurst JA, Baraitser M, Auger E, Graham F, Norel SV: An extended family with a dominantly inherited speech disorder. *Dev Med Child Neurol* 1990; **32**: 352–355.
- 11 Vargha-Khadem F, Watkins K, Alcock K, Fletcher P, Passingham R: Praxic and nonverbal cognitive deficits in a large family with a genetically transmitted speech and language disorder. *Proc Natl Acad Sci USA* 1995; **92**: 930–933.
- 12 Lai CSL, Fisher SE, Hurst JA, Vargha-Khadem F, Monaco AP: A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature* 2001; **413**: 519–523.
- 13 MacDermot KD, Bonora E, Sykes N *et al*: Identification of *FOXP2* truncation as a novel cause of developmental speech and language deficits. *Am J Hum Genet* 2005; **76**: 1074–1080.
- 14 Feuk L, Kalervo A, Lipsanen-Nyman M *et al*: Absence of a paternally inherited *FOXP2* gene in developmental verbal dyspraxia. *Am J Hum Genet* 2006; **79**: 965–972.
- 15 Lennon PA, Cooper ML, Peiffer DA *et al*: Deletion of 7q31.1 supports involvement of *FOXP2* in language impairment: clinical report and review. *Am J Med Genet A* 2007; **143**: 791–798.
- 16 Shriberg LD, Ballard KJ, Tomblin JB, Duffy JR, Odell KH, Williams CA: Speech, prosody, and voice characteristics of a mother and daughter with a 7;13 translocation affecting *FOXP2*. *J Speech Lang Hear Res* 2006; **49**: 500–525.
- 17 Lai CS, Gerrelli D, Monaco AP, Fisher SE, Copp AJ: *FOXP2* expression during brain development coincides with adult sites of pathology in a severe speech and language disorder. *Brain* 2003; **126**: 2455–2462.
- 18 Liégeois F, Baldeweg T, Connelly A, Gadian DG, Mishkin M, Vargha-Khadem F: Language fMRI abnormalities associated with *FOXP2* gene mutation. *Nat Neurosci* 2003; **6**: 1230–1237.
- 19 Spiteri E, Konopka G, Coppola G *et al*: Identification of the transcriptional targets of *FOXP2*, a gene linked to speech and language, in developing human brain. *Am J Hum Genet* 2007; **81**: 1144–1157.
- 20 Vernes SC, Spiteri E, Nicod J: High-throughput analysis of promoter occupancy reveals direct neural targets of *FOXP2*, a gene mutated in speech and language disorders. *Am J Hum Genet* 2007; **81**: 1232–1250.
- 21 Haesler S, Rochefort C, Georgi B, Licznarski P, Osten P, Scharff C: Incomplete and inaccurate vocal imitation after knockdown of *FoxP2* in songbird basal ganglia nucleus Area X. *PLoS Biol* 2007; **5**: 2885–2897.
- 22 Teramitsu I, Kudo LC, London SE, Geschwind DH, White SA: Parallel *FoxP1* and *FoxP2* expression in songbird and human brain predicts functional interaction. *J Neurosci* 2004; **24**: 3152–3163.
- 23 Li S, Weindenfeld J, Morrissey EE: Transcriptional and DNA binding activity of the *Foxp1/2/4* family is modulated by heterotypic and homotypic protein interactions. *Mol Cell Biol* 2004; **24**: 809–822.
- 24 Vernes SC, Macdermot KD, Monaco AP, Fisher SE: Assessing the impact of *FOXP1* mutations on developmental verbal dyspraxia. *Eur J Hum Genet* 2009; **17**: 1354–1358.
- 25 Pariani MJ, Spencer A, Graham JM, Rimoin DL: A 785 kb deletion of 3p14.1p13, including the *FOXP1* gene, associated with speech delay, contractures, hypertonias and blepharophimosis. *Eur J Med Genet* 2009; **52**: 123–127.
- 26 Baldwin EL, Lee JY, Blake DM *et al*: Enhanced detection of clinically relevant genomic imbalances using a targeted plus whole genome oligonucleotide microarray. *Genet Med* 2008; **10**: 415–429.
- 27 Shaikh TH, Gai X, Perin JC *et al*: High-resolution mapping and analysis of copy number variations in the human genome: a data resource for clinical and research applications. *Genome Res* 2009; **19**: 1682–1690.
- 28 Lafrate AJ, Feuk L, Rivera MN *et al*: Detection of large-scale variation in the human genome. *Nat Genet* 2004; **36**: 949–951.
- 29 Database of Genomic Variants <http://projects.tcag.ca/variation>. Accessed on 20 May 2009.
- 30 Ahmed AU, Mackenzie I, Das VK, Chatterjee S, Ly RH: Audio-vestibular manifestations of Chiari I malformation and outcome of surgical decompression: a case report. *J Laryngol Otol* 1996; **110**: 1060–1064.
- 31 Grosso S, Scattolini R, Paolo G, DiBartolo RM, Morgese G, Balestri P: Association of Chiari I malformation, mental retardation, speech delay, and epilepsy: a specific disorder? *Neurosurgery* 2001; **49**: 1099–1103; discussion 1103–1104.
- 32 de Vasconcelos Hage SR, Cendes F, Montenegro MA, Abramides DV, Guimarães CA, Guerreiro MM: Specific language impairment: linguistic and neurobiological aspects. *Arq Neuropsiquiatr* 2006; **64** (2A): 173–180.
- 33 Haapanen ML: CHERI: time to identify the syndrome? *J Craniofac Surg* 2007; **18**: 369–373.
- 34 Pandey A, Robinson S, Cohen AR: Cerebellar fits in children with Chiari I malformation. *Neurosurg Focus* 2001; **11**: E4.
- 35 Iannetti P, Spalice A, De Felice Ciccoli C, Bruni O, Festa A, Maini CL: Seizures in paediatric Chiari type I malformation: the role of single-photon emission computed tomography. *Acta Paediatr* 2002; **91**: 313–317.