CLINICAL REPORT

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FOXP1 Mutations Cause Intellectual Disability and a Recognizable Phenotype†

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Mutations in *FOXP1*, located at 3p13, have been reported in patients with global developmental delay (GDD), intellectual disability (ID), and speech defects. Mutations in *FOXP2*, located at 7q31, are well known to cause developmental speech and language disorders, particularly developmental verbal dyspraxia (DVD). FOXP2 has been shown to work co-operatively with FOXP1 in mouse development. An overlap in *FOXP1* and *FOXP2* expression, both in the songbird and human fetal brain, has suggested that *FOXP1* may also have a role in speech and language disorders. We report on a male child with a 0.19 MB intragenic deletion that is predicted to result in haploinsufficiency of *FOXP1*. Review of our patient and others reported in the literature reveals an emerging phenotype of GDD/ID with moderate to severe speech delay where expressive speech is most severely affected. DVD appears not to be a distinct feature in this group. Facial features include a broad forehead, downslanting palpebral fissures, a short nose with broad tip, relative or true macrocephaly, a frontal hair upsweep and prominent digit pads. Autistic traits and other behavioral problems are likely to be associated with haploinsufficiency of *FOXP1*. Congenital malformations may be associated.

Key words: *FOXP1*; intellectual disability; chromosomal microdeletion; 3p13; speech-language pathology

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INTRODUCTION

Microarray testing in global developmental delay (GDD) and intellectual disability (ID) yields a copy number variant result in on average 7.8% of patients with non-syndromic GDD/ID, and in 10.2% presenting with syndromic features [Michelson et al., 2011].

The FOXP proteins (FOXP1–4) are a group of transcription factors important in embryological, immunological, hematological, and speech and language development [Shi et al., 2008; Hannenhalli

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and Kaestner, 2009; Benayoun et al., 2011]. Associated human diseases include speech and language disorders, severe immunological defects and cancer. Although mutations in *FOXP1* (OMIM *605515) have been reported in patients with GDD/ID and speech defects [Pariani et al., 2009; Carr et al., 2010; Hamdan et al., 2010; Horn et al., 2010; O'Roak et al., 2011; Talkowski et al., 2012], the physical phenotype requires further characterization. *FOXP1* is known to be associated with monocyte differentiation and macrophage function [Shi et al., 2008], decreased overall survival with B-cell lymphoma (BCL) [Banham et al., 2005; Yu et al., 2011], failure to produce anti-HBs antibodies after hepatitis B vaccine administration [Davila et al., 2010], generalized vitiligo [Jin et al., 2010], and possibly inflammatory bowel disease (IBD) [Franke et al., 2010]. Mutations in *FOXP2* (OMIM *605317) are well known to cause developmental speech and language disorders, particularly developmental verbal dyspraxia (DVD) [Lai et al., 2001; MacDermot et al., 2005; Liégeois et al., 2011]. FOXP2 has been shown to work cooperatively with FOXP1 in mouse development [Shu et al., 2007]. An overlap in *FOXP1* and *FOXP2* expression in the songbird and human fetal brain has suggested that *FOXP1* may also have a role in speech and language disorders [Teramitsu et al., 2004]. We report a 6-year-old boy with a deletion in *FOXP1* and review the literature for deletions or inactivating mutations of *FOXP1*.

CLINICAL REPORT

We report a male, first-born child of nonconsanguineous parents. There was no significant family history. He was born after a normal pregnancy, at term, by caesarean. His birth weight was 3.2 kg (25th centile), length 48 cm (25th centile), and OFC 36.5 cm (75th centile). His mother was 34 and his father 39 years old at the time of his birth. After successful early breastfeeding, the patient developed feeding problems, and failure-to-thrive at 11 weeks of age. This resolved with the introduction of solids by 6 months. He had oro-motor dysfunction with excessive drooling, difficulty sipping from a cup and ongoing problems with chewing some solids.

Development was globally delayed, most notably in the area of speech and language acquisition. First words appeared at 17 months. At 2.5 years, he had 6 words, but understood approximately 50. Sentences were not spoken until 4 years 4 months. Receptive and expressive language was severely delayed, though receptive language appeared more advanced. Articulation problems included moderate to severe difficulty pronouncing consonants. His speech was not dyspraxic. Motor milestones were delayed. He rolled and sat unsupported at 12 months, cruised from 16 months, and did not walk until 25 months. A coarse pincer grasp developed at 17 months. Occupational therapy resulted in significant improvement, but at age 7 years his Miller Function and Participation Scales (M-FUN) motor development score was in the low range. At age 7 years, he was partially toilet trained. He remained incontinent of urine at day and night. Hearing and vision were normal. There were no behavioral problems or autistic features. He did not have developmental regression or seizures. He had a past history of moderate, well-controlled asthma. Growth parameters have followed the 25–50th centiles for height and weight.

At 6.5 years his height was 115.3 cm (25th centile), weight 21 kg (40th centile), and OFC 55 cm (0.5 cm above the 98th centile). Maternal and paternal OFC measurements were 55 cm (50th centile) and 58 cm (98th centile), respectively. Facial features included prominent forehead, down slanting palpebral fissures, and a flat malar region. His nose was short with a broad tip (Fig. 1). There were prominent digit pads and clinodactyly of his fourth toes bilaterally. Neurological examination was normal.

Investigations with normal results included fragile X testing (19 CGG repeats in *FMR1*) and urine metabolic screen (including urine amino acid, organic acid, and glycosaminoglycan screen). Cerebral MRI at age16 months showed prominent ventricles, but no other abnormality. Renal ultrasound scan at age 6.5 years was normal. The family declined an echocardiogram.

G-Banded karyotype showed normal 46,XY banding. CGH microarray using 60k Oligo ISCA design (BlueGnome), analyzed with BlueMulti v2.3, revealed a deletion at 3p13 (71,041,636–71,229,421, GRCh37/HG19), 190 kb in size. FISH studies with probe RP11–90H15 (The Centre for Applied Genomics, Toronto, Canada) confirmed the copy number change. The deleted region includes exons 6–13 of *FOXP1*. This is expected to result in a severely truncated protein, likely non-functional or not produced at all (due to nonsense-mediated mRNA decay of its premature termination codon containing mRNA). Parental FISH studies showed this to be a de novo occurrence in our patient.

DISCUSSION

From review of our patient and nine others reported in the literature [Pariani et al., 2009; Carr et al., 2010; Hamdan et al., 2010; Horn et al., 2010; O'Roak et al., 2011; Talkowski et al., 2012], we find an emerging phenotype in patients with *FOXP1* haploinsufficiency. To our knowledge this is the largest cohort of patients with *FOXP1* mutations and it defines the associated phenotype of global DD/ID with moderate to severe speech delay, with expressive speech most severely affected. Facial features include a broad forehead, downslanting palpebral fissures, a short nose with broad tip, relative or true macrocephaly, frontal hair upsweep, and prominent digit pads.

The features of 10 patients are outlined in Tables I and II. Pariani et al. [2009] did not describe Patient 1 as having a short nose with broad tip, but the authors feel that this is a fair description of the patient depicted photographically. Many of the common features are seen clearly in the patient images (Figs. 1–3). These show our patient and previously unpublished images of patients reported by Carr et al. [2010], Horn et al. [2010] and Horn [2012].

Though we noted a trend towards relative macrocephaly, only our patient developed an OFC above the 98th centile. Paternal OFC measurement was at the top end of the normal range, suggesting that that this familial trait, in combination with the *FOXP1* mutation, may have resulted in true macrocephaly. Less common features included widely spaced eyes, ptosis of the eyelids and a smooth philtrum [Carr et al., 2010]; sparse lateral eyebrows [Horn et al., 2010]; blepharophimosis, epicanthus, and undescended testes in a child with a multiple gene deletion [Pariani et al., 2009].

The most consistent feature of *FOXP1* haploinsufficiency in this cohort was GDD/ID with prominent speech delay [Pariani et al., 2009; Carr et al., 2010; Hamdan et al., 2010; Horn et al., 2010; Talkowski et al., 2012]. Neurodevelopment can be impaired by mutations affecting a diverse range of cellular functions. These

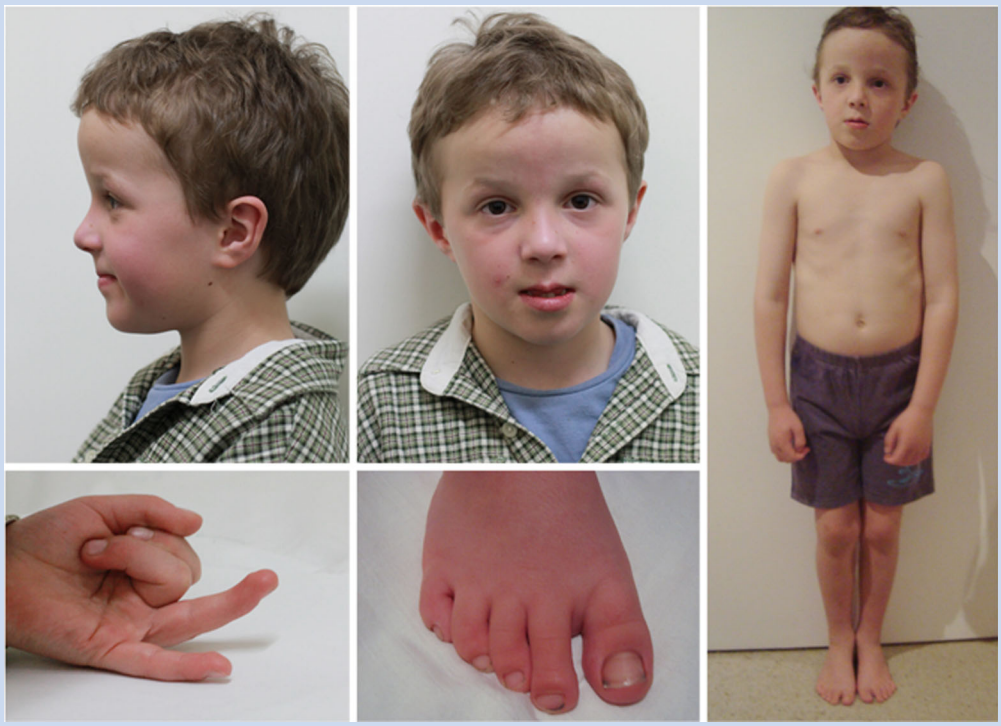

FIG. 1. Patient 10 (patient reported in this paper). Note prominent forehead, downslanting palpebral fissures, short nose with broad tip, prominent digit pads, and clinodactily of fourth toe.

include axon guidance, synapse formation and epigenetic regulation of gene expression and methylation, among others [Franklin and Mansuy, 2011; Schaefer et al., 2011]. More than one member of a particular gene family is often identified in the search for causative mutations [Mitchell, 2011; Topper et al., 2011].

FOXP1 is expressed throughout the human central nervous system [Teramitsu et al., 2004]. FOXP1 appears to have a role in the control of motor neuron migration and axon trajectory choice in mice [Palmesino et al., 2010]. It has been demonstrated to regulate *Pitx3* transcription in mammalian stem cells. Pitx3 is required for the differentiation of mouse midbrain dopaminergic neurons [Konstantoulas et al., 2010]. The finding of developmental delay in all the patients in our series further supports *FOXP1's* role in neurodevelopment. FOXP1's role in motor neuron development [Dasen et al., 2008; Pfaff, 2008; Rousso et al., 2008] is of particular interest considering the consistent finding of gross motor delay.

Considering FOXP1's role in *Pitx3* transcription, it is worth noting that no patients in this series had visual problems other than refractive errors. Our patient did not have opthalmologic evaluation. Mutations in *PITX3* have been implicated in anterior segmental mesenchymal dysgenesis and congenital cataract [Burdon et al., 2006; Summers et al., 2008]. *PITX3* polymorphism has also been associated with Parkinson disease [Tang et al., 2012]. There were no reports of Parkinsonian features in our cohort, though children may not be expected to show these.

FOXP1 appears to have a more global influence on neurodevelopment than *FOXP2*. Patients in this series were delayed in speech/language, motor and intellectual domains. FOXP2 has been shown to work co-operatively with FOXP1 in mouse development [Shu et al., 2007]. The activity of these proteins is regulated by homo and heterodimerization and this appears to be required for transcriptional activity and DNA binding [Li et al., 2004]. Although there is apparent co-operation between these two genes, the difference in phenotype with haploinsufficiency is considerable [Bacon and Rappold, 2012]. *Foxp1* and *Foxp2* are expressed in different subpopulations of cortical projection neurons during development in mice [Hisaoka et al., 2010]. Other possible explanations for phenotypic differences may include different regulatory targets of FOXP1-FOXP2 heterodimers and homodimers [Hamdan et al., 2010].

Mutations in *FOXP2*, located at 7q31, 113,726,365–114,333,827 (GRCh37/HG19) are a rare cause of developmental speech and language disorders, particularly DVD [Lai et al., 2001; MacDermot et al., 2005; Liégeois et al., 2011]. There are no consistent findings of either ID or gross motor delay in patients with mutations in *FOXP2* [Lai et al., 2001; Fisher and Scharff, 2009]. The speech and language delay in patients with *FOXP1* haploinsufficiency is moderate to severe. Expressive skills are consistently more severely affected than receptive skills. Particular difficulty with articulation of consonants is described in the majority of patients. Some patients in this series had oro-motor dysfunction and/or articulation problems, but DVD, a problem in cerebral planning of speech, was not described. The clinical distinction between articulation problems and DVD can be difficult in patients with ID/DD, but often becomes clear over

TABLE I. Physical Features of Reported Patients With Mutations Resulting in Haploinsufficiency of *FOXP1*

	Pariani et al. [2009]	Horn et al. [2010, 2011] Patient 1	Horn et al. [2010, 2011] Patient 2	Horn et al. [2010, 2011] Patient 3	Hamdan et al. [2010] Patient A	Hamdan et al. [2010] Patient B	Carr et al. [2010]	O'Roak et al. [2010]	Talkowski et al. [2012]	Current patient	Total
Patient	1	2	3	4	5	6	7	8	9	10	
Sex	M	M	F	M	F	M	M		M	M	
Type of mutation involving FOXP1	Deletion, multiple genes[a]	Deletion, intragenic	Deletion, whole gene	Deletion, whole gene	Deletion, intragenic	Point mutation, nonsense	Deletion, whole gene	Point mutation, Nonsense[b]	Balanced chromosomal rearrangement[c]	Deletion, intragenic	
Inheritance	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	
Affected allele of paternal origin	N/A	+	+	+	N/A	N/A	N/A	+	N/A	+[d]	5/5
Growth											
LBW	+	N/A	N/A	N/A	N/A	N/A	−	N/A	N/A	−	1/3
FTT or small for age	+	−	−	−	N/A	N/A	−	N/A	N/A	+[e]	2/6
Height (PC)	<2nd	80th	45th	30th	N/A	N/A	10th	N/A	N/A	25th	
Weight (PC)	<10th	40th	>98th	>98th	N/A	N/A	10th–25th	N/A	N/A	40th	
Obesity	−	−	+	+	N/A	N/A	−	N/A	N/A	−	2/6
OFC (PC)	50th	75th	60th	80th	N/A	N/A	50th–75th	N/A	N/A	>98th	3/6
Morphology											
Prominent forehead	−	−	+	+	−	−	+	N/A	N/A	+	4/8
Down slanted palpebral fissures	−	−	−	+	−	−	+	N/A	N/A	+	3/8
Short nose with broad tip	+[f]	−	+	+	−	−	+	N/A	N/A	+	5/8
Frontal hair upsweep	−	−	+	+	−	−	−	N/A	N/A	−	2/8
Prominent digit pads	−	−	−	−	−	−	+	N/A	N/A	+	2/8
Single palmar creases	+	−	−	−	−	−	+	N/A	N/A	−	2/8
Clinodactlly	+	−	−	−	−	−	−	N/A	N/A	+[g]	2/8
Congenital malformation	Contractures hands and feet	−	−	−	−	Jejunal and ileal atresia	Chiari 1 malformation	N/A	Spina Bifida Occulta, bilateral inguinal hernia	−	4/9

Key: N, normal; N/A, not available; +, present; −, not present; LBW, low birth weight; FTT, failure to thrive; OFC, occipito-frontal circumference.
[a]*FOXP1*, *EIF4E3*, *PROK2*, *GPR27*.
[b]Additional missense variant in *CNTNAP2*.
[c]Breakpoints *FOXP1* and *ANK3*.
[d]Potentially paternal.
[e]Up to age 6 months.
[f]Described by authors as "small upturned alaenasi."
[g]Clinodactily of fourth toes bilaterally.

TABLE II. Neurodevelopmental Features of Reported Patients With Mutations Resulting in Haploinsufficiency of *FOXP1*

Patient	1	2	3	4	5	6	7	8	9	10	Total
Development											
Pregnancy	N	N/A	N/A	N/A	N	N	N	N/A	N/A	N	
Global delay	+	+	+	+	+	+	+	+	+	+	10/10
Regression	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	−	1/2
Intellectual delay	N/A	+	+	+	+	+	N/A	+	+	+	8/8
Gross motor delay	+	+	+	+	+	+	+	N/A	+	+	9/9
Speech											
Speech and language delay	+	+	+	+	+	+	+	+	+	+	10/10
Expressive language more severely affected than receptive language	N/A	+	+	+	+	+	+	N/A	N/A	+	7/7
First words (years)	Nil at 2	3.5	3.5	3.5	3	6	3.5	N/A	N/A	1.5	
Combined words (years)	N/A	7	5	5.5	4	N/A	N/A	N/A	N/A	4.5	
Articulation problems, particularly consonants	N/A	+	+	+	N/A	N/A	+	N/A	N/A	+	5/5
Poor grammar	N/A	+	+	+	N/A	N/A	N/A	N/A	N/A	+	4/4
Oro-motor dysfunction	N/A	+	+	−	−	−	−	N/A	N/A	+	3/7
Behavior											
Autistic features	N/A	N/A	N/A	N/A	+	+	N/A	+	N/A	−	3/4
Autism	N/A	N/A	N/A	N/A	−	+	N/A	+	N/A	−	2/4
Behavioral problems	N/A	N/A	+	+	+	+	N/A	N/A	N/A	−	4/5
Neurological Examination											
Tone	↑	N/A	N/A	N/A	N/A	N/A	[a]	N/A	N/A	N	2/3
Reflexes	N	N/A	N/A	N/A	N/A	N/A	↑	N/A	N/A	N	1/3
Seizures	−	−	−	−	N/A	N/A	+	+	N/A	−	2/7
MRI	Minor atrophy	N	N	N	N/A	N/A	Dysmorphic corpus callosum. Mild hypoplasia cerebellar vermis. Chiari 1 malformation	N/A	N/A	Prominent ventricles	
EEG	N	N	N	N	N/A	N/A	Epileptiform discharges	N/A	N/A	N/A	

Key: N, normal; N/A, not available; +, present; −, not present; ↑, increased; ↓, decreased.
[a]Decreased axial, increased peripheral.

FIG. 2. Patient 7. Note prominent forehead, downslanted palpebral fissures, and short nose with broad tip. This patient was described by Carr et al. [2010]. We thank the authors for these previously unpublished images.

time. Although a study of 49 patients with DVD identified no causative *FOXP1* mutations, that cohort excluded patients with ID, as it was previously used to identify *FOXP2* mutations [Vernes et al., 2009].

Autistic behavioral traits were described in three patients in this series and *FOXP1* haploinsufficiency may well be associated with ASDs [Hamdan et al., 2010; O'Roak et al., 2011]. Though these patients were selected on the basis of this trait, suggesting possible selection bias, autistic behavior appears to be a common feature. O'Roak et al. [2011] reported a patient with severe autism, developmental regression, language delay, moderate ID, and non-febrile seizures. The more severe phenotype in this patient was hypothesized to be due to an additive effect of the second mutation in *CNTNAP2*, located at 7q35 (OMIM *604569). *FOXP2* may, at least indirectly, be associated with autism, though research has been inconclusive [Newbury et al., 2002; Mukamel et al., 2011; Bowers and Konopka, 2012; Casey et al., 2012]. Other behavioral problems described in this patient series included hyperactivity, aggression, mood lability, and specific obsessions and compulsions [Hamdan et al., 2010; Horn, 2012].

FOXP1 appears to have a role in organogenesis in mice [Pohl et al., 2005; Shu et al., 2007; Zhang et al., 2010]. Reported patients with congenital malformation may indicate *FOXP1*'s effect. Contiguous gene deletion may well explain some of the malformations [Pariani et al., 2009] but not others, such as Chiari I malformation [Carr et al., 2010] and intestinal atresia [Hamdan et al., 2010]. *FOXP1* was affected in isolation in these cases. Jejunal and ileal atresia was reported in a patient with a point mutation in *FOXP1* [Hamdan et al., 2010]. FOXP1 may be involved in the development of the mouse foregut, but midgut structures were not described [Shu et al., 2007]. Only Carr et al. [2010] reported echocardiogram or renal ultrasound results and no abnormalities were detected. Our patient had a normal renal ultrasound.

No patient in this cohort had significant immunological problems, though formal testing of immune function was not reported and not performed in our patient. FOXP1 appears to play a significant role in immune development [Shi et al., 2008; Feng et al., 2011] and defects in *FOXP3*, a close relative, are known to cause immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) (OMIM #304790) [Bennett et al., 2001; Brunkow et al., 2001]. Downregulation of FOXP1 is required for monocyte differentiation and macrophage function [Shi et al., 2008]. FOXP1 has recently been shown to regulate T-cell quiescence in mice [Feng et al., 2011]. A single-nucleotide polymorphism (SNP) in the 3′ downstream region of *FOXP1* has been found to be associated with failure to produce anti-HBs antibodies 18 months after hepatitis B

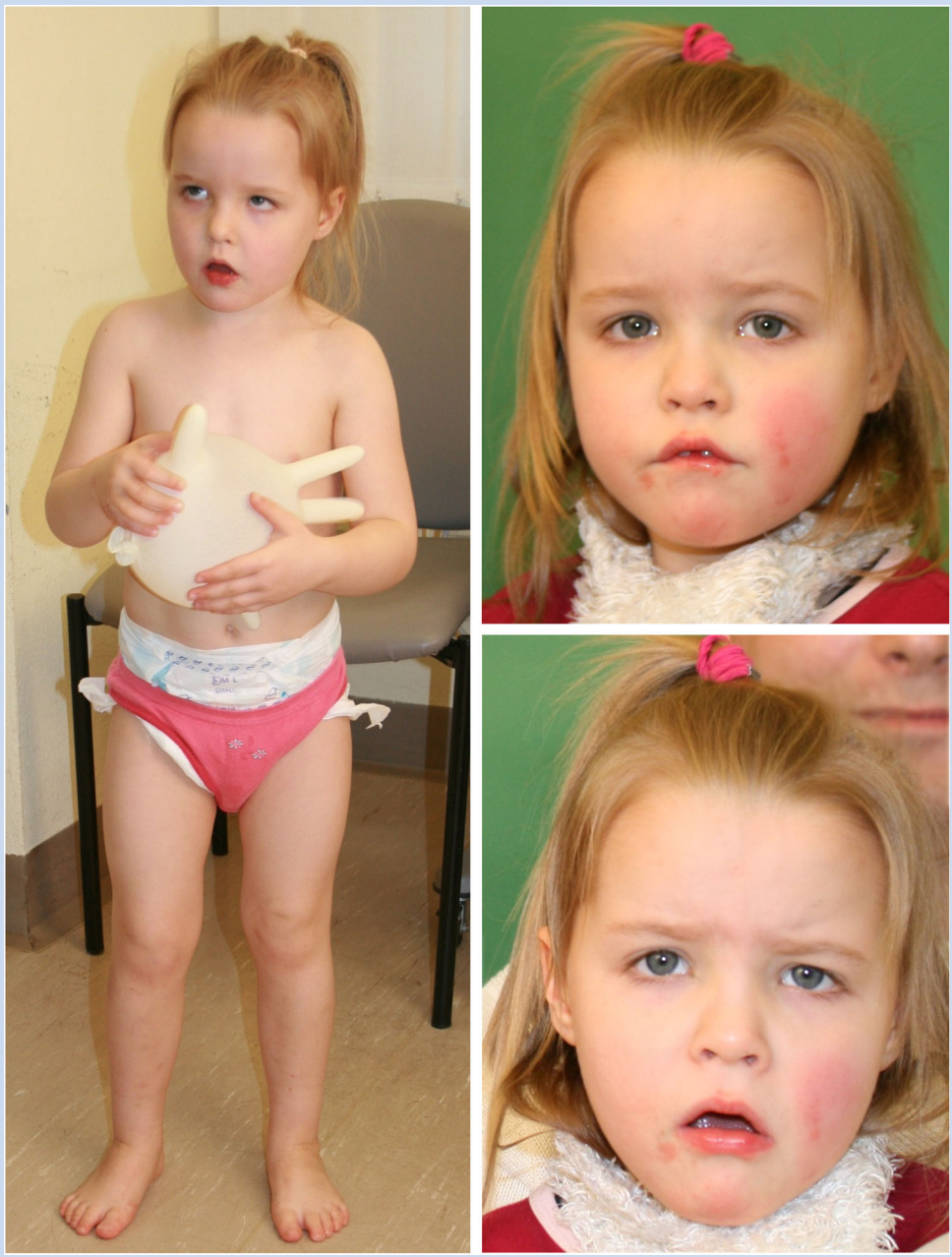

FIG. 3. Patient 3. Note prominent forehead, frontal hair upsweep and short nose with broad tip. This patient was described by Horn et al. [2010, 2012]. We thank the authors for these previously unpublished images.

vaccine administration [Davila et al., 2010]. Variants in *FOXP1* have been associated with generalized vitiligo [Jin et al., 2010] and there may be an association with IBD [Franke et al., 2010]. There has been much recent interest in the role of *FOXP1* in cancer. FOXP1 expression had an adverse effect on survival of patients with extra-nodal diffuse large BCL [Banham et al., 2005; Yu et al., 2011]. There was no neoplasia in our patient series.

FOXP1 mutations were on the paternal allele in three patients reported by Horn et al. [2010]. The great majority of *FOXP2* mutations are of paternal origin [Feuk et al., 2006]. Differential allelic expression and maternal imprinting may be important in disease development involving defects in both, *FOXP2* and *FOXP1*. Genotype analyses were performed on patient and parental DNA samples to determine whether the *FOXP1* deletion in our patient was maternally or paternally derived. Microsatellite marker analysis was inconclusive. A SNP trio analysis [Ting et al., 2007] was performed using genotyping generated from the Illumina Human-CytoSNP—12 v2.1 microarray. This showed one informative marker (rs3846030; chr3:71,148,387–71,148,887 GRCh36) of the twenty-eight markers present within the region of interest, suggest-

ing the mutation was on the paternally derived chromosome 3. The remaining 27 markers were uninformative. While this is not conclusive, it is consistent with the paternal origin of *FOXP1* mutations reported previously [Horn et al., 2010].

Horn et al. [2010] identified one 1.3 MB deletion affecting *FOXP1*, *EIF4E3* (MIM# 609896), *PROK2* (MIM# 607002), and *GPR27* (MIM# 605187) in an individual from the long-lived individuals study with no indications of an ID phenotype. Incomplete penetrance may explain this.

Many patients with larger 3p interstitial deletions including *FOXP1* have been reported. Though phenotypes are understandably varied in this group due to the involvement of other genes, it is interesting that many features overlap with those seen in isolated *FOXP1* mutations. Facial features such as a broad forehead and a short broad nose are commonly noted. Not surprisingly, a broad range of malformations is frequent in patients with these larger deletions [Ţuţulan-Cunită et al., 2012]. We are aware of a patient with a large 3p interstitial deletion, including *FOXP1* and many other genes. This patient has ASDs and a Chiari 1 malformation (Dr. Timothy Bohan, personal communication). The patient shares facial features with patients in our series, such as broad forehead and macrocephaly. We propose that these features may be due to *FOXP1* mutations.

CONCLUSION

We conclude that *FOXP1* haploinsufficiency is a cause of ID/DD with a particular profile of marked speech and language delay. Expressive language is more severely affected than receptive, and particular difficulty in expression of consonants is experienced. DVD was not seen in this cohort. Distinctive facial features are associated with *FOXP1* mutations. These include a broad forehead, down slanting palpebral fissures, a short nose with broad tip, frontal hair upsweep, and relative or true macrocephaly. Autistic behavioral traits and other behavioral problems are common. Congenital malformations may be associated with *FOXP1* mutations. The association of *FOXP1* haploinsufficiency with immune dysfunction or cancer survival needs further evaluation.

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