

ORIGINAL ARTICLE

FOXP1-related intellectual disability syndrome: a recognisable entity

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ABSTRACT

Background Mutations in forkhead box protein P1 (*FOXP1*) cause intellectual disability (ID) and specific language impairment (SLI), with or without autistic features (MIM: 613670). Despite multiple case reports no specific phenotype emerged so far.

Methods We correlate clinical and molecular data of 25 novel and 23 previously reported patients with *FOXP1* defects. We evaluated *FOXP1* activity by an in vitro luciferase model and assessed protein stability in vitro by western blotting.

Results Patients show ID, SLI, neuromotor delay (NMD) and recurrent facial features including a high broad forehead, bent downslanting palpebral fissures, ptosis and/or blepharophimosis and a bulbous nasal tip. Behavioural problems and autistic features are common. Brain, cardiac and urogenital malformations can be associated. More severe ID and NMD, sensorineural hearing loss and feeding difficulties are more common in patients with interstitial 3p deletions (14 patients) versus patients with monogenic *FOXP1* defects (34 patients). Mutations result in impaired transcriptional repression and/or reduced protein stability.

Conclusions *FOXP1*-related ID syndrome is a recognisable entity with a wide clinical spectrum and frequent systemic involvement. Our data will be helpful to evaluate genotype–phenotype correlations when interpreting next-generation sequencing data obtained in patients with ID and/or SLI and will guide clinical management.

heterogeneous phenotypes, making gestalt diagnosis complicated and challenging. In the majority of patients, no molecular defect has been identified thus far, arguing for a genetic heterogeneous and probably multifactorial aetiology.^{1–4}

Meanwhile, over 700 genes have been identified in both isolated ID and ID-associated disorders, and several genes have been associated with speech and language disorders, including *FOXP1*, *FOXP2*, *SHANK3* and *TM4SF20*.^{1–4} Additional loci for specific language impairment (SLI), a specific form of speech and language disorders defined by an isolated delayed or absent language acquisition that may however be associated with autism and/or oromotor dyspraxia, have been mapped to chromosomal regions 16q (SLI1; OMIM#606711), 19q (SLI2; OMIM#606712), 13q21 (SLI3; OMIM#607134) and 7q35–q36 (SLI4; OMIM#612514).

The first gene implicated in the pathogenesis of developmental speech and language disorders was *FOXP2*.⁶ Later on, similar expression patterns of *FOXP2* and *FOXP1* in songbird and human brain suggested a functional relationship.⁷ Since then, several case reports have confirmed *FOXP1* defects in language impairment other than verbal dyspraxia,^{8–9} including both monogenic *FOXP1* mutations and more extensive 3p chromosomal deletions encompassing *FOXP1*. However, until now, no specific phenotype has emerged. The absence of a clear ‘gestalt’ in monogenic causes of SLI, including *FOXP1*-related SLI, complicates the work-up and delays the diagnosis.

With the introduction of array comparative genome hybridisation (arrayCGH) and next-generation sequencing (NGS) in clinical practice, the concept of reverse genetics allows to identify a recurrent phenotype in patients with similar molecular defects, delineating novel conditions and

INTRODUCTION

Intellectual disability (ID) and speech and language disorders are common problems in the paediatric population and frequent reasons for encounter with child neurologists and clinical geneticists. They cover a wide range of conditions with



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providing useful information for prognosis, management guidelines and recurrence risk to other family members.

FOXP1 encodes forkhead box protein P1, which belongs to the family of the winged helix/forkhead transcription factors that regulate embryogenesis and maintenance of differentiated tissues through transcriptional repression.^{10–11} *FOXP1* is widely expressed.^{12–17} Hence, reduced *FOXP1* functioning may perturb the development of multiple organ systems.

We report on the molecular and clinical data of 25 novel patients with a *FOXP1* defect and compare the data with 23 previously reported patients. This comprehensive description evidences a recognisable ‘gestalt’ for *FOXP1*-related ID syndrome. Based on the relative frequent occurrence of non-neurological anomalies, we provide recommendations for clinical management and follow-up. We further show that both missense and premature truncation mutations reduce *FOXP1* repression activity and/or interfere with protein stability.

METHODS

Patients

All patients were evaluated by experienced clinical geneticists and recruited through direct referral or through the Decipher website. Patient 19 (Decipher 252324) was already published by Thevenon *et al.*¹⁸ although a more detailed phenotypic description is presented here. Previously published patients with *FOXP1* mutations were identified through a National Center for Biotechnology Information (NCBI) PubMed literature search (www.ncbi.nlm.nih.gov/pubmed).^{9–18–29} We excluded the four patients reported by Chang *et al.*¹² and Srivastava *et al.*³⁰ because of the unavailability of phenotypic data. We also excluded patients with interstitial 3p deletions if the precise chromosomal breakpoints were not provided and therefore the involvement of *FOXP1* unknown.

The study was approved by the Ethics Committee of the Ghent University Hospital. For the publication of clinical and molecular data, we obtained informed consent from all individuals or their legal representatives. For publication of clinical pictures, we obtained a specific consent.

Phenotypic analysis

A clinical summary, photographs and a checklist were provided by the referring clinicians. To reduce interobserver variability, all data were re-evaluated by IM and BCa. Missing data were excluded from statistical analyses. Subgroup analysis, comparing patients with 3p deletions and monogenic *FOXP1* defects, and patients with *FOXP1* deletions or truncating mutations (nonsense, frameshift and splice site mutations) and *FOXP1* missense mutations, was performed using Fisher’s exact tests (SPSS Statistics V.22).

Molecular analysis

Molecular analysis was performed at each referring centre with varying methodologies for arrayCGH analysis, direct Sanger sequencing and NGS of ID gene panels. All NGS detected *FOXP1* mutations were confirmed by Sanger sequencing. Sequences were compared with the wild-type sequence as submitted to NM_032682.5 (Ensembl Accession number ENST00000318789.4). Nucleotides were numbered starting from the first base of the initiation codon (ATG) of the cDNA reference sequence. Amino acid residues are numbered from the first methionine residue of the reference sequence. CNVs were mapped against the human genome build hg19/GRCh37.

Functional analysis

Luciferase assay

To evaluate transcriptional repression activity, we used a standard luciferase assay.^{9–23–26} Mutations were introduced into the full length coding sequence of *FOXP1* longest isoform (*FOXP1a*; obtained from Kazusa DNA Research Institute, Kisarazu, Japan) and subcloned into the mammalian expression vector pcDNA4His (Invitrogen). HEK293 cells were then cotransfected using Fugene 6 (Roche), in 24-well plates, with 400 ng of pcDNA4His without an insert or containing the wild-type *FOXP1* (wt-*FOXP1*) or the mutant *FOXP1* cDNA, along with 50 ng of pGL3-promoter construct (Promega) (in which the SV40 promoter drives a firefly luciferase reporter). To normalise for transfection efficiency and variation in cell number, cells were also cotransfected with 50 ng of a *Renilla* luciferase construct (pRL-TK; Promega) driven by the HSV-thymidine kinase promoter which is not affected by *FOXP1*. Cells were lysed 48 hours after transfection. Firefly and *Renilla* luciferase activities were quantified using the *Synergy H4 Hybrid Multiplate Reader* (BioTek). Protein expression was verified by western blotting (see below). Student’s t-test was performed to evaluate statistical significance.

Western blotting

Expression of the different exogenously expressed proteins was evaluated using standard western blotting. To enable monitoring and detection of *FOXP1*, we fused it to an n-terminal tag (Xpress) and used Xpress Monoclonal Antibody (Thermo Fisher Scientific) for detection, thereby avoiding simultaneous detection of endogenous *FOXP1*. Ten micrograms of total protein were loaded per lane of a 12% acrylamide gel (Bio-Rad). Transfer onto a low fluorescence polyvinylidene difluoride (PVDF) membrane was done using turbo blot.

Splicing efficiency

Splice site mutations were tested in the pSPL3 splicing vector.^{31–32} The *FOXP1* exons flanked by 200bp of intronic sequence containing the putative splice mutation were cloned in between two b-globin exons. HEK293 cells were transfected with these constructs and RNA was collected 48 hours post-transfection. Splicing was analysed by sequencing the RT-PCR fragment generated by the fused b-globin mini-gene.

RESULTS

Molecular characteristics

The molecular data of 25 novel and 23 previously reported patients are shown in figure 1 and see online supplementary table 1. In our cohort, all defects originated de novo (22/22) (in three patients the analysis of parents was not possible). Six patients have an interstitial 3p deletion (6/25) affecting more proximally and/or more distally located genes with sizes of the deleted region ranging from ~3 Mb to ~6 Mb. Nineteen patients have a monogenic *FOXP1* defect (19/25), including five partial *FOXP1* deletions (5/19) (~120 kb to ~630 kb) and 14 point mutations (14/19), comprising nonsense (6/14), missense (2/14), frameshift (3/14) or splice site (3/14) alterations. Three patients harbour the c.1573C>T, p.(Arg525*) mutation, previously reported by Hamdan *et al.*⁹

Comparable, all previously reported cases have de novo (19/19) defects (data were missing for four patients), including extended 3p deletions (8/23) (~800 kb to ~27.2 Mb), whole *FOXP1* deletions (1/15) (~200 kb to ~1 Mb), partial

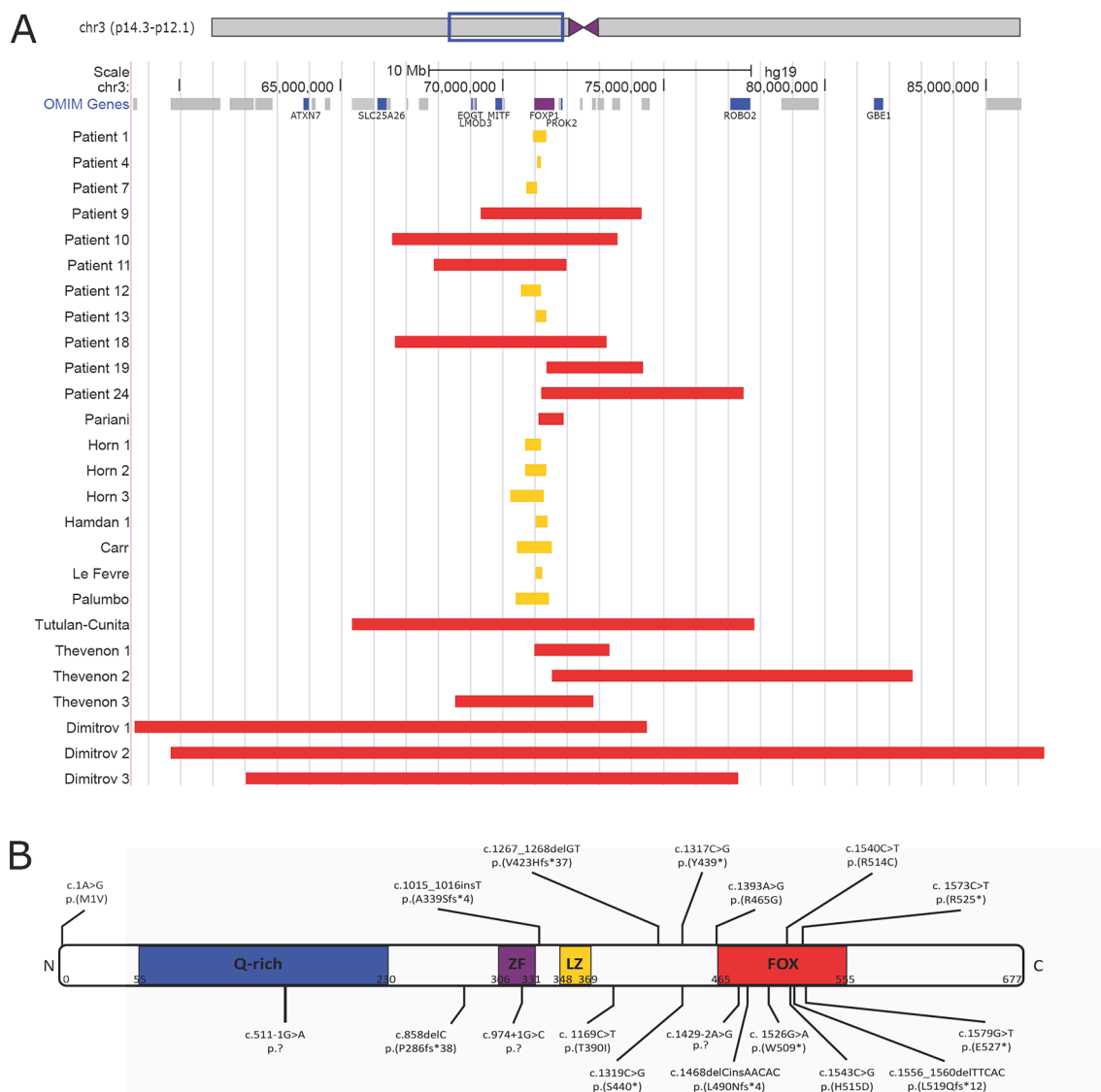


Figure 1 Molecular data of 25 novel and 23 previously reported patients with *FOXP1* defects. (A) CNVs affecting *FOXP1*. Interstitial 3p deletions encompassing *FOXP1* are depicted in red, CNVs restricted to *FOXP1* are shown in yellow. (B) Small indels and point mutations identified in *FOXP1*. Previously reported mutations are shown above the schematic representation of the *FOXP1* protein, while novel mutations identified in this study are shown below. Four patients harbour the c.1573C>T, p.(Arg525*) mutation. (Q-rich, glycine-rich domain; ZF, zinc finger domain; LZ, leucine zipper domain; and FOX, DNA-binding forkhead box domain).

FOXP1 deletions (6/15) and seven point mutations (7/15) (2 nonsense, 3 missense and 2 frameshift). One patient has a balanced chromosomal rearrangement with breakpoints in 3p13 (affecting *FOXP1*) and 10q21.2 (1/15).

Most pathogenic *FOXP1* variants result in premature truncation (10/18). Missense mutations (5/18) and splice site mutations (3/18) are present in a minority of the patients. **Figure 1B** illustrates that nonsense mutations, frameshift mutations and splice site mutations appear throughout the whole protein, while all but one missense mutations are located in or close to the DNA-binding FOX domain.

As shown in **figure 2**, further functional evaluation of p.Arg525*, p.Trp509*, p.His515Asp and p.Thr390Ile mutant proteins shows that *FOXP1*-Arg525* and *FOXP1*-Trp509* (both stably expressed from plasmid cDNA vectors) fail to reduce luciferase levels as compared with wt-*FOXP1* ($p < 0.001$), indicating that both truncating mutations impair *FOXP1*s ability to repress the SV40

promoter. The missense mutation *FOXP1*-His515Asp (also stably expressed in vitro) maintains some residual repressor activity ($p < 0.005$), while *FOXP1*-Thr390Ile (which has limited protein expression in vitro) has rather normal repressor activity.

Furthermore, we evaluated the effects of *FOXP1* c.974+1G>C, c.1429-2A>G and c.551-1G>A mutations on splicing. Failed sequencing of the RT-PCR fragment of the c.974+1G>C donor splice site mutation and the c.1429-2A>G acceptor splice site mutation could result from nonsense-mediated mRNA decay or exon skipping. The c.974+1G>C mutation resulted in normal splicing, although with a lower splicing efficiency. For the c.1429-2A>G mutation, the exon is skipped in 100%, compared with 50% in wt-*FOXP1* in this system. The c.551-1G>A acceptor splice site mutation results in alternative splicing skipping 6 bp of the exon (resulting in deletion of two glutamine residues) (data not shown).

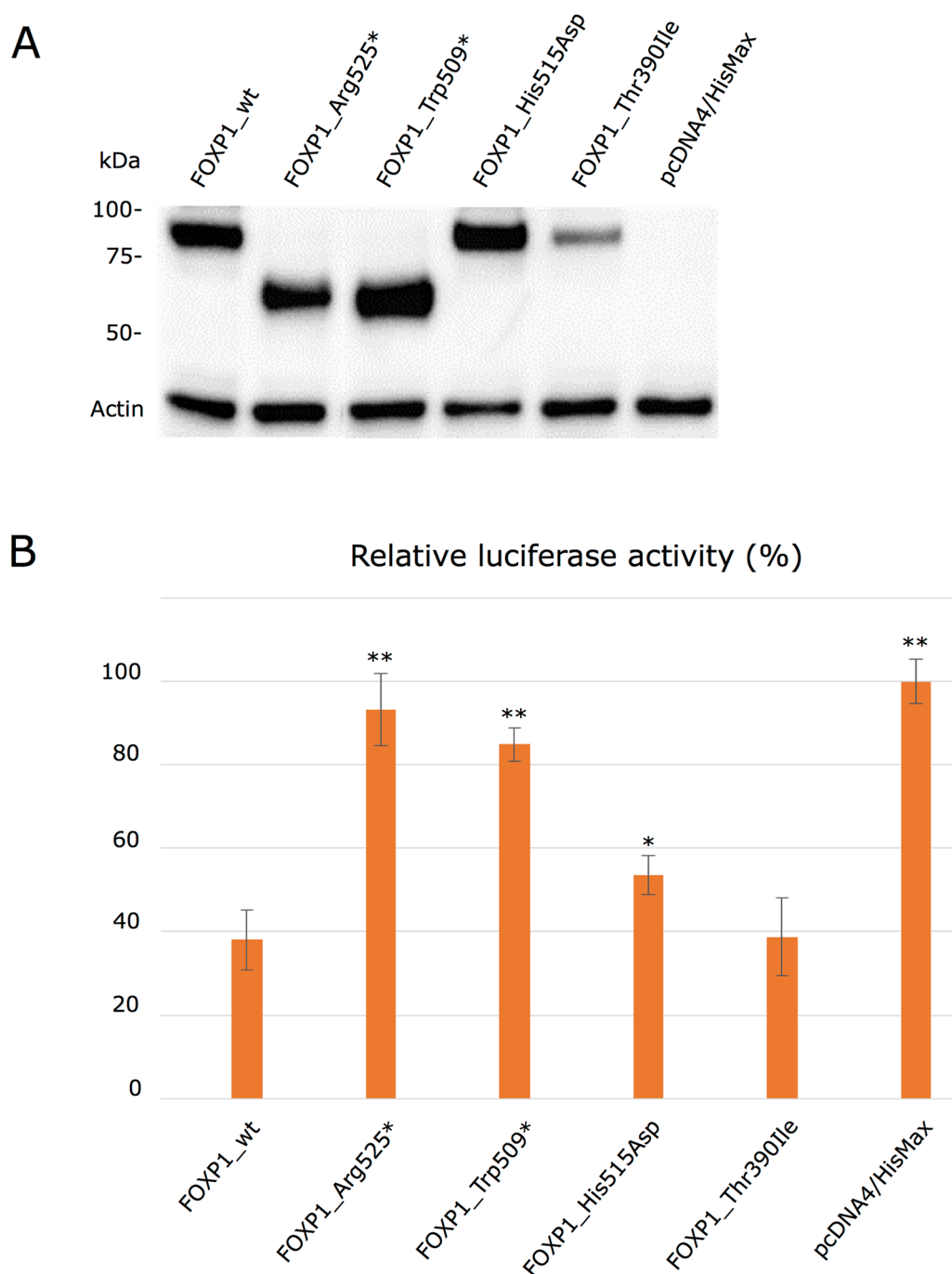


Figure 2 Functional analysis in selected group of *FOXP1* mutations. (A) Results of western blot evaluating the effects of *FOXP1* variants on protein expression from cDNA plasmid vectors. FOXP1-p.Arg525*, p.Trp509* and p.His515Asp are stably expressed, while p.Trp390Ile results in decreased protein expression. The detection of endogenous produced beta actin insured equivalent loading of protein in all western blot tracks. (B) Luciferase reporter assay assessing the impact of the p.Arg525*, p.Trp509*, p.His515Asp and p.Trp390Ile mutations on FOXP1 transactivation activity in transfected HEK293 cells. Wild-type FOXP1 and FOXP1-Thr390Ile significantly inhibited pGL3-promoter (SV40) transcriptional activity ($p < 0.001$) as compared with empty vector (pcDNA4)-transfected cells only (comparisons for each pair using Student's t-test). In contrast, FOXP1-Arg525* and FOXP1-Trp509* failed to repress the pGL3-promoter activity (** $p < 0.001$). FOXP1-His515Asp had a reduced repression activity compared with FOXP1 (* $p < 0.005$). Results (mean of four independent experiments, each performed in triplicate) are shown as relative firefly luciferase activity, which is driven by SV40 promoter, normalised with *Renilla* luciferase and driven by herpes simplex virus thymidine kinase (HSV-TK) promoter activity. The control signal value was obtained with cells transfected with the empty expression vector (pcDNA4/HisMax) and both pGL3-promoter (firefly luciferase) and pRL-TK (*Renilla* luciferase) constructs.

Phenotypic characteristics

The phenotypic characteristics of all novel and previously reported patients are summarised in [table 1](#). For extended clinical data see online supplementary table 2.

Demographic characteristics

Patients originate from Belgium (9/25), France (1/25), Germany (1/25), the UK (5/25), Spain (3/25), Italy (1/25), the Czech Republic (1/25), the USA (3/25) and New Zealand (1/25).

Table 1 Overview of clinical features in *FOXP1* patients

Characteristics	Our cohort		Literature		Total	
	20:5		14:9		34:14	
Sex (male:female)						
Mild/moderate motor delay	15/24	63%	15/21	71%	30/45	67%
Severe motor delay	7/24	29%	6/21	29%	13/45	29%
Mild/moderate intellectual disability	15/24	63%	13/19	68%	28/43	65%
Severe intellectual disability	8/24	33%	6/19	32%	14/43	33%
Speech and language delay	23/23	100%	19/19	100%	42/42	100%
Expressive language delay	18/19	95%	11/11	100%	29/30	97%
Articulation problems	9/11	82%	10/10	100%	19/21	90%
Poor grammar	5/7	71%	4/4	100%	9/11	82%
Oromotor dysfunction	10/17	59%	4/10	40%	14/27	52%
Behavioural difficulties	12/19	63%	10/13	77%	22/32	69%
Autistic features	14/20	70%	10/12	83%	24/32	75%
Abnormal tonicities	14/21	67%	12/14	86%	26/35	74%
Spasticity/contractures	10/19	53%	8/10	80%	18/29	62%
Abnormal reflexes	3/17	18%	5/8	63%	8/25	32%
Seizures	3/22	14%	4/11	36%	7/33	21%
Abnormal brain imaging	11/23	48%	10/14	71%	21/37	57%
Abnormal electroencephalography	2/12	17%	2/9	22%	4/21	19%
Failure to thrive	8/22	36%	7/15	47%	15/37	41%
Feeding difficulties	16/24	67%	8/11	73%	24/35	69%
Obesity	0/23	0%	2/11	18%	2/34	6%
Broad, prominent forehead	23/24	96%	11/15	73%	34/39	87%
Frontal hair upsweep	10/24	42%	5/14	36%	15/38	39%
Hypertelorism	11/24	46%	9/16	56%	20/40	50%
Downslanting palpebral fissures	14/24	58%	7/14	50%	21/38	55%
Bent palpebral fissures	5/16	31%	–	–	5/16	31%
Ptosis	16/24	67%	6/9	67%	22/33	67%
Blepharophimosis	4/24	17%	1/11	9%	5/35	14%
Short nose	17/24	71%	10/15	67%	27/39	69%
Broad nose tip	19/24	79%	9/15	60%	28/39	72%
Pronounced nasolabial folds	10/24	42%	1/9	11%	11/33	33%
Wide mouth with full lips	14/24	58%	2/14	14%	16/38	42%
Pronounced vermilion border	16/22	73%	–	–	16/22	73%
Downturned corners of the mouth	14/24	58%	4/10	40%	18/34	53%
Open mouth	12/20	60%	6/9	67%	18/29	62%
Prominent chin	9/22	41%	–	–	9/22	41%
Horizontal chin crease	10/22	45%	–	–	10/22	45%
Hypoplastic upper ear helix	5/24	21%	3/13	23%	8/37	22%
Prominent finger pads	2/22	9%	2/10	20%	4/32	13%
Single palmar crease	8/21	38%	5/15	33%	13/36	36%
Clinodactyly	6/21	29%	2/14	14%	8/35	23%
Ophthalmological abnormalities	17/21	81%	10/14	71%	27/35	77%
Auditory abnormalities	2/11	18%	3/9	33%	5/20	25%
Cardiac abnormalities	9/19	47%	5/7	71%	14/26	54%
Renal abnormalities	1/9	11%	0/3	0%	1/12	8%
Genitourinary tract abnormalities	12/23	52%	4/6	67%	16/29	55%

The mean age at last follow-up is 6.48 years, and the median age is 7.25 (range 0.42–23). Two patients died (2/25). Patient 3 died at the age of 16 years due to an aspiration pneumonia. Patient 9 died at the age of 5 months due to complications of a diaphragmatic hernia. The male:female ratio is 20:5.

Neurological phenotype

Common neurological features are developmental language delay (23/23; 100%), neuromotor delay (NMD) (22/24; 92%) and ID (23/24; 96%). ID is mostly mild to moderate although

one-third have severe ID. The severity of the NMD correlates well with ID in this cohort. Of note, two patients (17 and 22) harbouring a frameshift and a splice site mutation, respectively, have a normal neuromotor development, and intellect is normal in patient 22. Behavioural problems (including hyperactivity, aggression, mood lability, obsessions and compulsions) are common (63%). Autistic features occur in 14 out of 20 patients (70%).

Expressive language is more affected than receptive language. One-third of the patients (8/21) were able to speak a single word



Figure 3 Clinical features of patients with monogenic *FOXP1* defects (patient 1 at age 2 years (A), patient 2 at age 2 years (B), patient 6 at age 11 years (C), patient 13 at age 7 years (D), patient 20 at age 3 years (E), patient 22 at age 9 years (F), patient 23 at age 10 years (G), patient 25 at age 8 years (H)) or interstitial 3p deletions (patient 10 at age 4 years (I), patient 18 at age 5 years (J)). Note the high and broad forehead, downslanting and/or bent palpebral fissures, ptosis, bulbous nasal tip and pronounced nasolabial folds. Full red lips are most prominent in patients with monogenic defects (A–H).

by the age of 2 years, and about 60% acquires the ability to speak a few words. Seven patients use short sentences (32%). Poor grammar (5/7) and articulation problems (9/11) are frequent, and more than half of the patients experience oromotor dysfunction (10/17) and/or feeding difficulties (16/24).

Neurological examination reveals hypotonia in half of the patients (10/21), either generalised (6) or axial (4). Hypertonia is present in six patients (6/21; 29%), being generalised in four. Two patients had peripheral hypertonia in combination with axial hypotonia. Spasticity and contractures (10/19; 53%) can be present from birth on and can be progressive or transient. Seizures are documented in three patients (3/22; 14%). Half of the patients show structural brain abnormalities (11/23), including cerebral and/or cerebellar atrophy, cortical, subcortical and deep white matter abnormalities, and/or cerebellar abnormalities.

Staturoponderal evolution

Failure to thrive is reported in eight patients and 30% (6/20) has a body mass index (BMI) \leq 10th centile at last follow-up. None of them are obese (BMI \geq 90th centile). Nine patients (43%) have a head circumference above the 90th centile, and eleven patients have a relative macrocephaly (head circumference more than 25 centiles above the height).

Craniofacial phenotype

Clinical photographs of some of the patients are shown in figure 3. The most common craniofacial features in patients with *FOXP1* mutations include a high, broad and prominent forehead (96%), a frontal hair upsweep (42%), hypertelorism (46%), downslanting palpebral fissures (58%), ptosis (67%), blepharophimosis (17%), bent palpebral fissures (31%) and a short nose (71%) with a broad tip (79%). In most patients, the mouth is wide with full reddish lips (58%), a pronounced vermilion border (73%) and downturned corners (58%). Patients often have an open mouth appearance (60%) with pronounced nasolabial folds (42%). About half of the patients have a prominent chin, mostly with a horizontal crease. Occasionally, unilateral or bilateral hypoplastic upper ear helices (21%), prominent digital

pads (9%), a single palmar crease (38%) and clinodactyly (29%) are reported.

Other organ involvements

Other commonly affected organ systems are the eye (81%), heart (47%) and genitourinary tract (52%). Ophthalmological abnormalities include strabismus and/or refractive errors, mainly hypermetropia. Optic nerve hypoplasia is reported in one patient. Cardiac defects are minor and often restricted to atrial septal defects. More than half of the boys have unilateral or bilateral cryptorchidism. Four patients had an inguinal hernia. Miscellaneous findings that remain to be confirmed in other patients with *FOXP1* mutations are renal malformations (1), diaphragmatic hernia (1), hepatic and bile duct abnormalities (1), transient splenomegaly (1), oesophageal dysmotility (1) and constipation (1), subclinical hypothyroidism (1), hearing impairment (2), developmental dysplasia of the hip (2), spina bifida occulta (1), sacral dimple (2) and anal malformations (1).

Literature review and subgroup analysis

The previously published cases confirm the higher male:female ratio (14:9) and the major neurological features, including variable NMD, ID, SLI (with more severely affected expressive language), behavioural traits and autistic features. Seventy per cent developed speech, but with poor articulation. Oromotor dysfunction (40%) and feeding difficulties (73%) are commonly reported. Hypotonia (50%) and hypertonia (43%) are within similar ranges. Spasticity or contractures are reported in 8 out of 10, and seizures in 4 out of 11 patients (36%). Anatomical brain defects are present in 10 out of 14 (71%) patients. In 15 patients with reported staturoponderal measurements, failure to thrive is reported in 47%, and two patients are obese. Absolute macrocephaly or relative macrocephaly is reported in three patients (3/15; 20%). Associated organ systems in the previously reported cases include the eye (refractive disorders (4), strabismus (3), iris coloboma (2) and aniridia (1)), heart (secundum atrial septal defect (5)) and genitourinary tract (cryptorchidism (3)). Three patients have hearing impairment (3/9; 33%).

Table 2 Subgroup analysis of monogenic *FOXP1* defects versus interstitial deletions

Characteristics	3p deletion		Monogenic		p Value	
Sex (male:female)	9:5		25:9		0.728	NS
Mild/moderate motor delay	3/12	25%	27/33	82%	0.001	<0.05
Severe motor delay	9/12	75%	4/33	12%	0.000	<0.05
Mild/moderate intellectual disability	3/10	30%	25/33	76%	0.019	<0.05
Severe intellectual disability	7/10	70%	7/33	21%	0.007	<0.05
Speech and language delay	9/9	100%	33/33	100%	–	–
Expressive language delay	6/6	100%	23/24	96%	1.000	NS
Articulation problems	3/3	100%	16/18	89%	1.000	NS
Poor grammar	0/1	0%	9/10	90%	0.182	NS
Oromotor dysfunction	3/4	75%	11/23	48%	0.596	NS
Behavioural difficulties	1/3	33%	21/29	72%	0.224	NS
Autistic features	4/5	80%	20/27	74%	1.000	NS
Abnormal tonicities	11/12	92%	15/23	65%	0.121	NS
Spasticity/contractures	12/13	92%	6/16	38%	0.006	<0.05
Abnormal reflexes	5/9	56%	3/16	19%	0.087	NS
Seizures	2/9	22%	5/24	21%	1.000	NS
Abnormal brain imaging	9/12	75%	12/25	48%	0.166	NS
Abnormal electroencephalography	0/7	0%	4/14	29%	0.255	NS
Failure to thrive	9/11	82%	6/26	23%	0.002	<0.05
Feeding difficulties	12/13	92%	12/22	55%	0.027	<0.05
Obesity	0/7	0%	2/27	7%	1.000	NS
Broad, prominent forehead	8/9	89%	26/30	87%	1.000	NS
Frontal hair upsweep	3/9	33%	12/29	41%	1.000	NS
Hypertelorism	9/12	75%	11/28	39%	0.082	NS
Downslanting palpebral fissures	4/8	50%	17/30	57%	1.000	NS
Bent palpebral fissures	1/4	25%	4/12	33%	1.000	NS
Ptosis	5/7	71%	17/26	65%	1.000	NS
Blepharophimosis	3/9	33%	2/26	8%	0.095	NS
Short nose	8/9	89%	19/30	63%	0.228	NS
Broad nose tip	6/9	67%	22/30	73%	0.693	NS
Pronounced nasolabial folds	2/7	29%	9/26	35%	1.000	NS
Wide mouth with full lips	1/12	8%	15/26	58%	0.005	<0.05
Pronounced vermilion border	4/5	80%	12/17	71%	1.000	NS
Downturned corners of the mouth	6/8	75%	12/26	46%	0.233	NS
Open mouth	4/7	57%	14/22	64%	1.000	NS
Prominent chin	3/5	60%	6/17	35%	0.609	NS
Horizontal chin crease	3/5	60%	7/17	41%	0.624	NS
Hypoplastic upper ear helix	5/11	45%	3/26	12%	0.035	<0.05
Prominent finger pads	0/5	0%	4/27	15%	1.000	NS
Single palmar crease	6/10	60%	7/26	27%	0.119	NS
Clinodactyly	4/9	44%	4/26	15%	0.162	NS
Ophthalmological abnormalities	9/11	82%	18/24	75%	1.000	NS
Auditory abnormalities	5/6	83%	0/14	0%	0.000	<0.05
Cardiac abnormalities	8/11	73%	6/15	40%	0.130	NS
Renal abnormalities	0/3	0%	1/9	11%	1.000	NS
Genitourinary tract abnormalities	8/10	80%	8/19	42%	0.114	NS

NS, not significant.

Using data from the total cohort, we compared the occurrence of the studied phenotypic features between the group with more extended 3p deletions and the group with monogenic *FOXP1* defects. Severe NMD, severe ID, feeding difficulties and failure to thrive, spasticity and contractures, and hearing impairment were more frequently encountered in the 3p interstitial deletion group ($p < 0.05$, table 2). Further comparison of phenotypic characteristics between *FOXP1* deletions, truncating mutations and splice site mutations and *FOXP1* missense mutations showed no difference in severity of NMD and/or ID between both groups.

Neither was there any difference in the other evaluated phenotypic features between both groups, except for the presence of prominent finger pads ($p < 0.05$, table 3).

DISCUSSION

Mutations in *FOXP1* are a generally accepted monogenic cause of ID and SLI. In contrast to *FOXP2* mutations they occur de novo.⁶ Our results indicate a loss of function for all tested *FOXP1* mutations. Most of the mutations have the potential to

Table 3 Subgroup analysis of *FOXP1* deletions or truncating mutations versus *FOXP1* missense mutations

Characteristics	Deletion or truncation		Missense mutation		p Value	
Sex (male:female)	21:8		4:1		1.000	NS
Mild/moderate motor delay	22/28	79%	5/5	100%	0.556	NS
Severe motor delay	4/28	14%	0/5	0%	1.000	NS
Mild/moderate intellectual disability	21/28	75%	4/5	80%	1.000	NS
Severe intellectual disability	6/28	21%	1/5	20%	1.000	NS
Speech and language delay	28/28	100%	5/5	100%	–	–
Expressive language delay	22/23	96%	1/1	100%	1.000	NS
Articulation problems	13/14	93%	3/4	75%	0.405	NS
Poor grammar	9/10	90%	–	–	–	–
Oromotor dysfunction	10/20	50%	1/3	33%	1.000	NS
Behavioural difficulties	17/24	71%	4/5	80%	1.000	NS
Autistic features	17/23	74%	3/4	75%	1.000	NS
Abnormal tonicities	12/19	63%	3/4	75%	1.000	NS
Spasticity/contractures	6/16	38%	–	–	–	–
Abnormal reflexes	3/15	20%	0/1	0%	1.000	NS
Seizures	5/22	23%	0/2	0%	1.000	NS
Abnormal brain imaging	10/22	45%	2/3	67%	0.593	NS
Abnormal electroencephalography	4/14	29%	–	–	–	–
Failure to thrive	6/23	26%	0/3	0%	1.000	NS
Feeding difficulties	12/21	57%	0/1	0%	0.455	NS
Obesity	2/24	8%	0/3	0%	1.000	NS
Broad, prominent forehead	23/26	88%	3/4	75%	0.454	NS
Frontal hair upswEEP	11/26	42%	1/3	33%	1.000	NS
Hypertelorism	9/25	36%	2/3	67%	0.543	NS
Downslanting palpebral fissures	14/26	54%	3/4	75%	0.613	NS
Bent palpebral fissures	4/11	36%	0/1	0%	1.000	NS
Ptosis	16/24	67%	1/2	50%	1.000	NS
Blepharophimosis	2/24	8%	0/2	0%	1.000	NS
Short nose	17/26	65%	2/4	50%	0.611	NS
Broad nose tip	20/27	74%	2/3	67%	1.000	NS
Pronounced nasolabial folds	9/24	38%	0/2	0%	0.529	NS
Wide mouth with full lips	14/24	58%	1/2	50%	1.000	NS
Pronounced vermilion border	11/15	73%	1/2	50%	0.515	NS
Downturned corners of the mouth	11/24	46%	1/2	50%	1.000	NS
Open mouth	13/20	65%	1/2	50%	1.000	NS
Prominent chin	5/15	33%	1/2	50%	1.000	NS
Horizontal chin crease	6/15	40%	1/2	50%	1.000	NS
Hypoplastic upper ear helix	2/24	8%	1/2	50%	0.222	NS
Prominent finger pads	2/24	8%	2/3	67%	0.049	<0.05
Single palmar crease	6/24	25%	1/2	50%	0.474	NS
Clinodactyly	4/24	17%	0/2	0%	1.000	NS
Ophthalmological abnormalities	16/21	76%	2/3	67%	0.597	NS
Auditory abnormalities	0/13	0%	–	–	–	–
Cardiac abnormalities	6/14	43%	0/1	0%	1.000	NS
Renal abnormalities	1/9	11%	–	–	–	–
Genitourinary tract abnormalities	6/17	35%	2/2	100%	0.164	NS

NS, not significant.

result in premature truncation and nonsense-mediated mRNA decay.³³ Although western blotting did show the presence of truncated protein if overexpressed from a cDNA plasmid vector, this does not rule out nonsense-mediated mRNA decay in the in vivo situation as this complex process may require the genomic context to be properly activated. Nonetheless, our reporter assay, normalised for transfection efficiency and cell count using an additional *Renilla* reporter, demonstrates that in case the truncated proteins are produced, their transcriptional repression

activity is impaired. A significantly reduced transcriptional repression was also observed for the p.His515Asp missense mutation. This reduced transcriptional repression might be due to impaired DNA-binding of the mutant protein, due to its impact on dimerisation by three-dimensional domain swapping.^{34–36} In contrast, the p.Thr390Ile missense mutation shows normal repression activity compared with wt-*FOXP1*, although the resulting phenotype is typical for *FOXP1*-related ID and the mutation occurred de novo. The p.Thr390Ile locates outside the

DNA-binding FOX domain, in a region where currently only truncating mutations have been identified. We could confirm reduced protein levels for this mutation from Western blot (figure 2A), since the level of protein resulting from the different transfections was normalised according to the *Renilla* level.

Besides the previously reported link of *FOXP1* mutations with ID, SLI and autistic features, our study shows a broader neurological phenotype with more general neurodevelopmental delay (including NMD and ID), spasticity and/or contractures, structural brain abnormalities and epilepsy, as well as involvement of other organ systems including the ocular, cardiovascular and genitourinary systems. Moreover, most patients show a recognisable craniofacial phenotype, that so far has not been routinely recognised. Besides the earlier reported features of relative macrocephaly and a broad and high forehead,^{20 23 37} other distinctive features were downslanting and/or bent palpebral fissures, ptosis and/or blepharophimosis, marked nasolabial folds, and a wide mouth with downturned corners and full red lips. The chin becomes more prominent with advancing age. Hand and foot anomalies, such as single palmar crease, clinodactyly and syndactyly are noted, although finger pads, previously considered part of the syndrome,²⁰ are only observed in two patients of our cohort.

Previous reports were contradictory on the occurrence of autism.^{9 20} In our cohort 70% of patients present with autistic features, confirming this association. It should however be noted that autism remains a difficult diagnosis in patients with ID and SLI, which might be overdiagnosed in these patients. In about two-thirds other behavioural problems are reported, including hyperactivity, aggression, mood lability, obsessions and compulsions.^{9 37} Oromotor dysfunction and articulation problems may aggravate the apparent SLI^{20 37} and correlate well with the feeding difficulties (Fisher's exact test $p=0.006$). Feeding difficulties were also associated with failure to thrive (Fisher's exact test $p<0.001$). The observation of obesity in two previously reported patients²⁵ remains thus far unconfirmed. Remarkably, we observe a male predominance (34:14). Sex predisposition in autosomal disorders remains largely unexplained, although it has been observed in other entities including Wolf-Hirschhorn syndrome, Brugada syndrome, and long QT syndrome.^{38–40} Fisher's exact test comparing the presence of each studied phenotypic characteristic between male and female revealed no statistically significant difference in the severity of the phenotype between both sexes. Therefore, the observed sex difference cannot be explained by either an increased lethality (less likely) or otherwise a higher occurrence of mild unrecognised cases in women.

Of note, all reported frequencies of the phenotypic characteristics are solely based on available data and did not take into account the amount of missing data. Therefore, the presence of a reporting bias cannot be excluded. Initially, most patients were reported as a 3p- syndrome, involving *FOXP1*.^{41–45} However, NGS panel analysis for ID genes and exome analysis clearly shows that monogenic *FOXP1* defects are at least twice as frequent as interstitial 3p- deletions. Five *FOXP1* mutations were found in a cohort of 2000 patients referred for panel analysis because of epilepsy and ID or autism (DL, personal communication). Therefore, mutations in *FOXP1* in this cohort were as frequent as *ARID1B* and *DYRK1A* mutations, establishing it as a relatively frequent, but often unrecognised cause of monogenic ID.

No specific genotype–phenotype correlations emerged considering monogenic *FOXP1* defects only. Indeed, wide phenotypic variation exists between the four patients who harbour exactly the same c.1573C>T, p.(Arg525*) mutation. Moreover, mild phenotypes were observed in association with both frameshift and

splice site mutations. Furthermore, no relevant clinical findings differed significantly between patient groups harbouring missense versus premature truncating mutations. In contrast, patients with extended 3p deletions are at risk of a more severe delay (Fisher's exact test $p<0.05$), anterior eye segment abnormalities and hypogenitalism compared with patients with monogenic *FOXP1* defects, despite the absence of known disease-modifying candidate genes in the overlapping regions of the deletions. In addition, hearing impairment only occurs in patients with extended 3p deletions (Fisher's exact $p<0.001$) for which *MITF*, associated with Waardenburg type IIA syndrome (MIM: 193510), emerges as a plausible candidate gene. One patient with hearing impairment did not show a deletion of *MITF*, but a positional effect cannot be excluded.

The differential diagnosis of SLI is wide (see online supplementary table 3), but the craniofacial 'gestalt' may guide towards an underlying *FOXP1* defect and may be helpful in correlating NGS data with clinical presentation.

In case of unclear pathogenicity and absence of sufficient patient material, in vitro functional assessment of variants is straightforward and feasible, showing loss of function either by alternative splicing, reduced repression activity or reduced protein expression.

Patients with *FOXP1* defects should be screened for associated organ system involvement including a detailed clinical examination, eye and hearing evaluation (especially in those patients with extended 3p interstitial deletions), echocardiography and ultrasound of the genitourinary tract. Indeed, single nucleotide variants (SNVs) in *FOXP1* have recently been associated with congenital anomalies of the kidneys and urinary tract.⁴⁶ An electroencephalogram should be performed if there is any doubt of seizures, and brain MRI should be considered in the presence of epilepsy.

Follow-up should include repeated assessment of the neuro-motor development, oromotor development (especially in case of failure to thrive), language development and behavioural problems in order to enable early initiation of therapy. Physiotherapy might be beneficial to prevent progressive contractures in case of spasticity. The management and follow-up of associated organ system involvements should be adjusted to the specific underlying problems and the patient's needs.

In conclusion, we have delineated the *FOXP1*-related ID syndrome as a recognisable entity that seems to be more frequent than expected based on the rather rare previous case reports. Moreover, the 'gestalt' may help clinicians in interpreting genotype–phenotype correlations.

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Contributors We hereby declare that all authors have contributed to this work: IM and BCa contributed to the conception and design of the article, data acquisition, analysis and interpretation of the clinical, molecular and functional data, and writing of the manuscript. DL contributed to the conception and design of the article and to the acquisition of clinical and molecular patient data. DR, GAR, FFH, JLM and PAD contributed to the acquisition of the functional data, and analysis and interpretation of these data. NRe, JP, CC, JM, JR, NRe, SGM, PL, MPB, MAM, StM, VB, SM, NB, AO, OV, MV, TJLdr, DM, JS, KKV, NDD, AKHK, LH, BD, AN, LT, JA, MJP, KN, BGe, A-SS, DP, MaH, MiH, MB, AD and BM contributed to the acquisition of clinical and molecular patient data. All authors have approved the manuscript and none have reported a conflict of interest.

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Competing interests None declared.

Patient consent Obtained.

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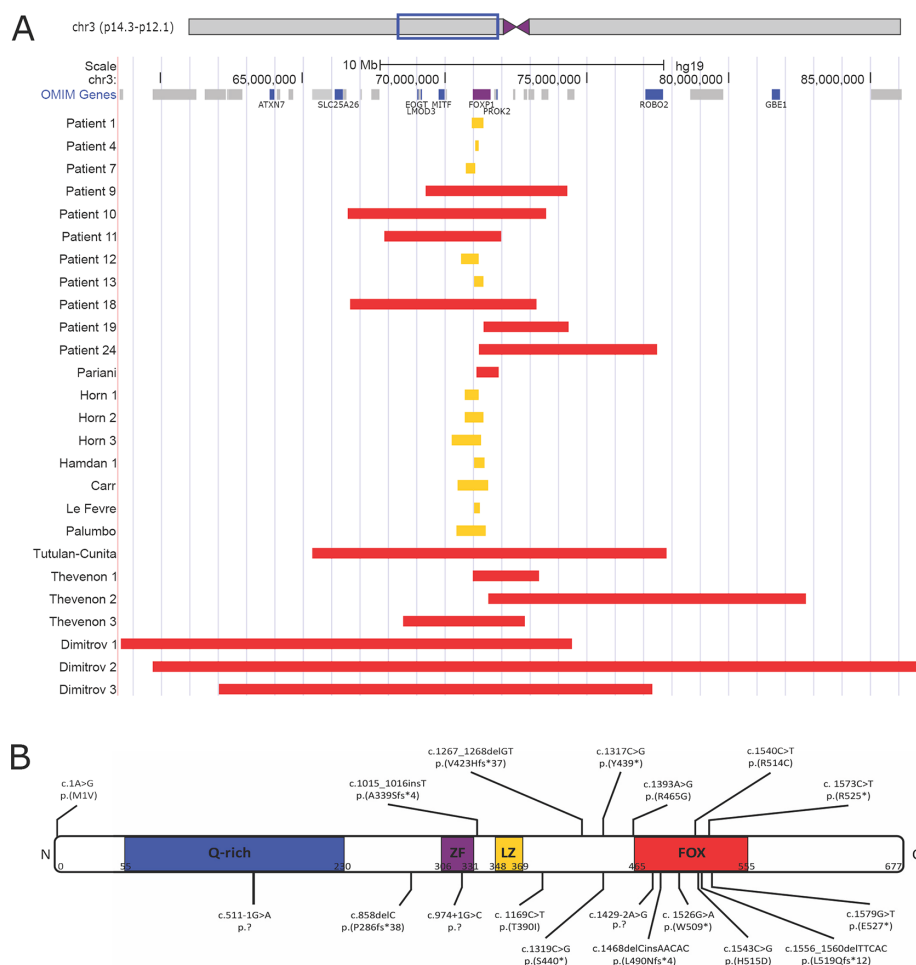
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Erratum: *FOXP1*-related intellectual disability syndrome: a recognisable entity

Meerschaert I, Rochefort D, Revençu N, *et al.* *FOXP1*-related intellectual disability syndrome: a recognisable entity. *Journal of Medical Genetics* 2017;**54**:613-623.

In the original article, the authors noted four mutation annotation errors in figure 1B and supplementary table 1. Correction of the mistakes in the annotations have no impact on the results and conclusions of this article. The authors apologise for all possible inconveniences due to these errors.



The corrected annotations are as follows:

- In patient 5 the correct c. and p. notations for the mutation are c.858delC and p.(R288Gfs*37), instead of c.858delC and p.(P286fs*38)
 - In patient 17 the correct c. and p. notations for the mutation are c.1462delCinsAACAC and p.(L488Nfs*4), instead of c.1468delCinsAACAC and p.(L490Nfs*4)
 - In patient 21 the correct c. and p. notations for the mutation are c.1556_1560delTTCAC and p.(L519Qfs*10), instead of c.1556_1560delTTCAC and p.(L519Qfs*12)
 - For the patient reported in O’Roak *et al* the correct c. and p. notations for the mutation are c.1014_1015insA and p.(A339Sfs*4), instead of c.1015_1016insT and p.(A339Sfs*4)
- These mistakes were corrected in figure 1B and the online supplementary table 1.

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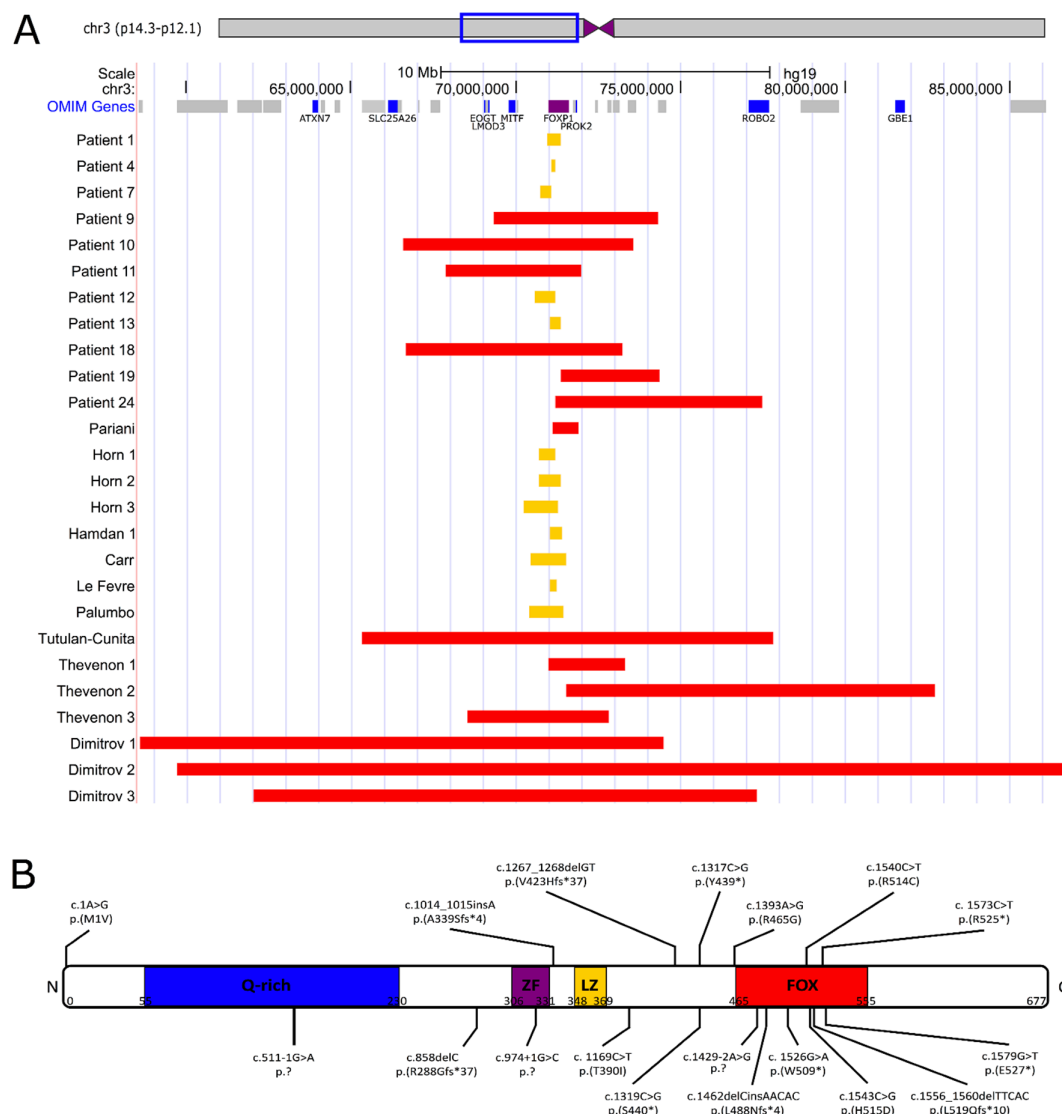
J Med Genet 2018;**55**:72. doi:10.1136/jmedgenet-2017-104579corr1



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Correction to: *Correction: FOXP1-related intellectual disability syndrome: a recognisable entity*

The text of the *erratum* article (jmedgenet-2017-104579corr1¹) is correct, but unfortunately we included the wrong figure. The correct figure is the following:



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J Med Genet 2018;**55**:214. doi:10.1136/jmedgenet-2017-104579corr2



REFERENCE

1. Correction: FOXP1-related intellectual disability syndrome: a recognisable entity. *J Med Genet* 2018;**55**:72–3.