# Clinical phenotype of FOXP1 syndrome: parent-reported medical signs and symptoms in 40 individuals

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Original research

# Clinical phenotype of FOXP1 syndrome: parent-reported medical signs and symptoms in 40 individuals

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## ABSTRACT

**Background** The first studies on patients with forkhead-box protein P1 (FOXP1) syndrome reported associated global neurodevelopmental delay, autism symptomatology, dysmorphic features and cardiac and urogenital malformations. The aim of this study was to assess the prevalence of congenital abnormalities in an unbiased cohort of patients with FOXP1 syndrome and to document rare complications.

**Methods** Patients with FOXP1 syndrome were included, mostly diagnosed via whole-exome sequencing for neurodevelopmental delay. A parent-report questionnaire was used to assess medical signs and symptoms, including questions about features rated as most burdensome by patients and their family.

**Results** Forty individuals were included, 20 females and 20 males. The mean age at assessment was 13.2 years (median 8.5 years; range 2–54 years; ≥18 years n = 7). Seven adults were included. All patients had developmental problems, including cognitive, communication, social-emotional and motor delays. The most prevalent medical signs and symptoms include delayed bladder control, sleeping problems, hypermetropia, strabismus, sacral dimple, undescended testes, abnormal muscle tone and airway infections. The most burdensome complaints for patients with FOXP1 syndrome, as perceived by parents, include intellectual disability, impaired communication, behaviour problems, lack of age-appropriate self-reliance, attention problems and anxiety. According to parents, patients have quite similar reported symptoms, although incontinence, obsessions and a complex sensory profile have a higher ranking.

**Conclusion** The results of this study may be used to further guide medical management and identify patient priorities for future research targeted on those features of FOXP1 syndrome that most impair quality of life of patients and their families.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Forkhead-box protein P1 (FOXP1) syndrome is associated with neurodevelopmental delay, autism, dysmorphic features and cardiac and urogenital malformations.

### WHAT THIS STUDY ADDS

⇒ This study uses parent-report questionnaires for detailed phenotyping, including the assessment of most burdensome symptoms to parents and patients. We found a high prevalence of behaviour problems, delayed bladder control, sleeping problems, hypermetropia, strabismus, sacral dimple, undescended testes and abnormal muscle tone.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study identified the characteristics of patients with FOXP1 syndrome that are most bothersome to parents and patients, which should be used to guide future research and medical management.

## INTRODUCTION

After the first description of a multigenic deletion including *FOXP1* in a person with speech delay and dysmorphic features in 2009,[1] many children and adults have been diagnosed with FOXP1 syndrome.[2–7] The forkhead-box protein P1 (*FOXP1*) gene encodes for the transcription factor FOXP1, which is critical in neurogenesis.[8 9] In a large nationwide (United Kingdom) exome sequencing study, pathogenic variants in *FOXP1* were among the 15 most commonly found causes of intellectual disability.[10]

*FOXP1*-related neurodevelopmental disorder (FOXP1 syndrome) was initially associated with neurodevelopmental delay, autism, dysmorphic features and cardiac and urogenital malformations.[2–7] Later, in-depth studies showed a complex neurobehavioural phenotype[4 5] with a marked speech disorder, largely characterised as dysarthria, alongside receptive and expressive language impairment.[6] In most cases, FOXP1 syndrome will be diagnosed on broad genetic analysis (eg, whole-exome sequencing) for non-specific neurodevelopmental delay since the phenotype is too non-specific for an a priori clinical diagnosis. A group of physicians from the Icahn School of Medicine at Mount Sinai in New York City proposed a guideline for medical assessment and monitoring,[11] based on the patients reported in the literature until 2020.



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Since it is expected that the number of congenital abnormalities associated with rare syndromic neurodevelopmental disorders is actually lower than reported in the first studies and that rarer complications of the syndrome can only be identified in larger cohorts,[12] we sought to include a more unselected group of patients, who were mostly diagnosed on whole-exome sequencing for neurodevelopmental delay. The classic phenotyping studies in clinical genetics ask clinicians to rate the presence or absences of a list of symptoms. This is time consuming for clinicians, especially given the level of detail that was aimed at in this study. Earlier, it was reported that parent-reported phenotype data show high consistency with medical files and have proven of high value in capturing the full phenotypic spectrum of rare disease.[13]

A detailed, online questionnaire containing medical, functional and neurobehavioural questions was designed in close collaboration with parents and a multidisciplinary team of international FOXP1 experts (including the authors of this manuscript). This parent-report questionnaire was used to describe the medical signs and symptoms associated with FOXP1 syndrome, as well as the complaints rated as most burdensome by patients and their families. Moreover, parent-reported data provide unique insights into the clinically relevant features of a syndrome from the families' lived experience of the condition.

By asking parents to report on the most burdensome complaints, we gain unique insight into FOXP1 syndrome and families' experiences. The results of this study may be used to further guide medical management and identify themes for future research targeting the characteristics of FOXP1 syndrome that have the largest impact on quality of life.

## METHODS

The questionnaire was developed based on the results of previous studies,[3–6] in close dialogue with patients (KindBeter Foundation) and (inter)national experts in Psychiatry (MPT), Speech and Language pathology (AM, RB), Clinical Genetics (SK), Paediatrics (FGR) and Paediatric Immunology (DB).

Patients of all ages, with a (likely) pathogenic variant in *FOXP1* or a deletion of *FOXP1* were eligible for inclusion. Patients with a larger deletion (ie, including more genes than only *FOXP1*) were excluded from this study.

Parents were recruited through (1) the physician of their child (the Netherlands), (2) the KindBeter Foundation, (3) the Dutch and International FOXP1 Facebook group, (4) the International FOXP1 Foundation and (5) during an online patient-conference hosted by the Seaver Institute (New York, USA). Finally participants who had participated of a previous study focused on Speech and Language were recontacted.[6] After informed consent, the genetic report of the patient was reviewed to confirm eligibility. Parents subsequently received a link to the online questionnaire based in CastorEDC (https://www.castoredc.com and online supplemental file 1). Parents were asked to collect the information from the letters they had received from their clinicians. The questionnaire was available in English, Dutch and German. Previous diagnostic/(para-)medical information (IQ test, speech therapy, treating physician, ultrasound, MRI) could be uploaded when available, complying with data safety regulations.

Biometric data were compared with the Dutch standards (TNO Groeicalculator; https://www.tno.nl/nl/gezond/werk-jeugd-gezondheid/jeugd/eerste-1000-dagen-kind/groeidiagrammen-groeicalculators/). Target height (TH) was calculated using 47.1+0.334×height father+0.364×height mother (males) and 32.8+0.389×height father+0.410×height mother (females). Short stature was defined as a growth below the −2 Standard Deviation Score (SDS).

The medical ethical committee of Leiden-Den Haag-Delft, the Netherlands, has reviewed and approved this study protocol (N21.085). Data analysis was performed in SPSS (IBM SPSS Statistics for Windows, V.25.0. Armonk, New York, USA). The difference between the group of missense variant and non-sense variants was calculated with the independent samples Mann-Whitney test (continuous data) and the $\chi^2$ test (proportions). Bonferroni correction was applied to correct for multiple testing.

## RESULTS

Forty individuals were included in the analysis (n=20 females; 50%). The mean age at assessment was 13.2 years (median 8.5 years; range 2–54 years). Seven adults were included. Thirty-four participants were from Europe (26 Dutch-speaking, 4 German-speaking, 4 English-speaking); six individuals were from Northern America. The questionnaire was filled out by the mother in 24 cases, by both parents in 14 cases and in 2 cases by father or sister and mother, respectively.

### Genetic diagnosis

Most individuals were referred for genetic evaluation because of neurodevelopmental conditions including global developmental delay (n=31) sometimes in combination with congenital abnormalities (n=6), motor and language delay (n=1), isolated motor delay (n=2) or difference in foot size (n=1). The mean age at genetic diagnosis was 9.8 years (range 0–54 years). The (likely) pathogenic variants in *FOXP1* included 17 truncating variants, 8 splice variants, 2 deletions (encompassing part of the FOXP1 protein) and 13 missense variants (see figure 1). Eleven missense variants were present in the DNA-binding domain, of which three were recurrent in 10 patients. The three missense variants that were not recurrent were de novo variants in amino acids in which a (likely) pathogenic variant was described in ClinVar. One of the splice variants was mosaic in blood (reported to be present in 25% of reads).

## MEDICAL PROBLEMS

A list of medical signs and symptoms and their prevalence reported by parents in our cohort and in literature[5 11 14–16] is presented in online supplemental table 1.

### Pregnancy

Pregnancy was uncomplicated in all but one case, in which impending premature birth required maternal intervention at 23 weeks gestational age. In five cases, the prenatal ultrasound was abnormal, showing intrauterine growth retardation (n=2), large head circumference (n=1), hyperechogenic spots on the liver (n=1) and suspicion for clubfeet (n=1).

### Neonatal period

One child was born with a congenital malformation (cleft lip, not detected by prenatal ultrasound). Fifteen (38%) children were hospitalised in the first days after birth for different reasons: suspicion of infection (n=3), low Apgar Score (n=3), late preterm birth (n=2), hyperbilirubinaemia (n=2), polycythaemia (n=2), breathing problems (n=2) and cleft lip (n=1; mentioned above). Postpartum evaluation by a paediatrician was performed in five cases: for non-descended

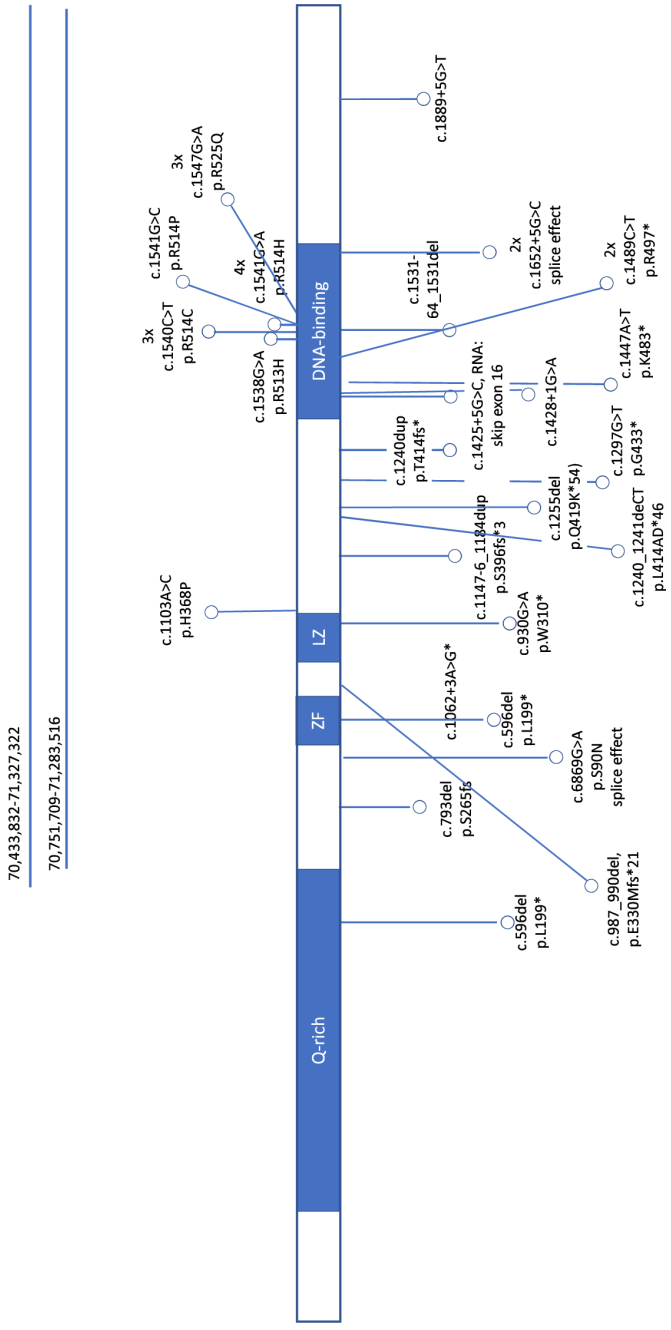


**Figure 1** Distribution of forkhead-box protein P1 (*FOXP1*) variants in this cohort Q-rich, glycine-rich domain; ZF, zinc finger domain; LZ, leucine zipper domain; DNA-binding, DNA-binding forkhead box domain. Lines above represent deletions; variants above the schematic representation of the gene: missense variants; below: nonsense variants.

testes, for a sacral dimple, for pre-auricular tag and/or for dysmorphic features.

Three children were hospitalised in their first month of life: one because of pneumococcal infection, two because of breathing problems. Ten individuals (27%) were reported to be floppy after birth; nine (26%) had a high muscle tone. Twenty children (51%) were reported to have feeding difficulties; one of them was tube-fed. Reported feeding problems include: problems latching the nipple (n=5), slow drinking, swallowing problems, choking (n=4), bringing up milk (n=3), sucking difficulties (n=2) and messy drinking (n=1).

## Biometric information

Of the included adults, only one female was reported to have a short stature (1.52 cm; −3.0 SDS). Mean height of the females was 160 cm (−1.7 SDS; range 152–169 cm); whereas the mean TH was 171 cm (0.0 SDS). Two adult males were reported to have normal height (170 and 182 cm). Apart from a mid-teens girl with a height of 146 cm (−3.2 SDS; TH 169 cm; −0.3 SDS), no children with short or tall stature were reported (n=15). Mean body mass index (BMI) was 25.2 kg/m$^2$ in six adults (range 21.7–28.7 kg/m$^2$); four had a BMI above 25 kg/m$^2$.

Two boys, two men and one girl were reported to have a head circumference >2 SDS (range +2 to +3.2).

## Development

All individuals were reported to have neurodevelopmental problems. Ninety-seven per cent show a communication impairment, 95% have a cognitive delay, 79% have a motor impairment and 95% have a delay in social and emotional development. IQ scores were only reported in 17 individuals: median total IQ is 56 (range 51–93); median performance IQ is 64 (range 55–95; n=13); median verbal IQ is 55 (range 50–92; n=12) and median processing speed is 60 (range 50–103; n=9).

Loss of previously acquired skills was reported in a female in her mid-50s (not specified) after an episode of psychosis in her mid-30s and in a female in her mid-40s (ie, bladder control, intelligibility).

## Neurology

Epilepsy was present in three individuals; one adult female had generalised seizures (probably focal to bilateral tonic-clonic seizures) from the age of 11 to 28 years and now has frequent, focal impaired awareness seizures which have less impact on her quality of life. Another female has about 10 generalised seizures a year; a pubertal female experienced 2 (non-specified) seizures, that were controlled after initiation of antiepileptic medication (clobazam). One of these three patients had an MRI on which no abnormalities were seen.

A brain scan (non-specified) was performed in 25 individuals; abnormalities were reported in 16, including ventriculomegaly (n=3), periventricular white matter abnormalities (n=2), mega cisterna magna, Chiari I malformation, thick corpus callosum and vermis hypoplasia, delayed myelination, cerebellar microbleeds, abnormal vasculature (not further specified), and parental description of a cyst and 'a developmental problem of the frontal lobe' (all n=1).

Muscle tone abnormality was reported, denoted as high in 34% (n=12) and low in 18% (n=5). Muscle weakness was reported by five parents. Coordination problems were reported by 23 parents (43%); an abnormal walking pattern was reported in 40%. Parents report toe walking (n=7), gait instability (n=6), equinus foot deformity (n=4), stiffness (n=2) and long strides (n=1).

## Ophthalmology

Visual problems were reported in 72% of patients, of which 64% wear glasses. Hypermetropy (mean +4.9; range +0.5 to +10.25) was reported in all cases where the strength of glasses was known. Cerebral visual impairment was reported in three individuals.

Strabismus was reported in 23 patients (62%), mostly inward (n=14) or outwards (n=4), and variable in some cases (n=5). Ptosis was reported in two patients.

### Hearing

Hearing loss was reported in two individuals, of which one individual is reported to have 28 dB loss (no details reported; no report of the other individual is available).

### Cardiology

Twenty-two individuals had a cardiac ultrasound examination. An atrial septal defect was present in three children. In a school age girl, a significant atrial septal defect type II, requiring surgical closure, was detected at screening . A mild aortic stenosis was present in another patient.

### Urogenital

A renal ultrasound was performed in 22 individuals, in which a duplex collecting system and a detrusor hypoactivity with bilateral hydronephrosis without vesicoureteral reflux in another case. At least two individuals experienced glomerulonephritis.

Undescended testes (cryptorchidism) at birth were present in 12 boys (67%); hypospadias was not reported.

Daytime urinary incontinence was present in 15 individuals above the age of 4 (45%; range 5–43 years; mean age of achieving daytime bladder control: 12 years; median age 5.5 years). Of the patients who acquire bladder control, the mean age at which daytime bladder control was reached was 7 years (range 2.5–18 years; n=16).

Three patients use medication for an overactive bladder.

### Gastroenterology

Seven individuals were reported to currently have feeding problems, including difficulties with textures of food and limited food variety (n=2) and poor oral motor abilities and stuffing (n=1). Swallowing problems were reported in five individuals; constipation in two patients, diarrhoea in one individual and gastro-oesophageal reflux in three individuals.

### Infections

Parents report more than two infections in the past year in 30% of individuals (median and mean 8; range 4–20). These infections include mainly upper airway infections (n=13), ear infections (n=7), urinary tract infections (n=4), skin infections (n=3) and shingles (n=2). Of these, serious infections (ie, requiring hospitalisation or intravenous antibiotics) were reported in 10 patients (45%; 10/22); including two postoperative infections requiring intravenous antibiotics in one patient and Whipple's disease in one individual each.

Nine parents (23%) considered the frequent infections an important problem for their child, and parents of one participant in her mid-40s noted this is still a major complaint. Three parents mentioned that the infections stopped being a major complaint by the time their children reached school age.

### Mental health problems

Fifteen out of 17 patients (88%) in which IQ was reported have a total IQ below 70. Eighty-one per cent (n=31) of parents reported that their child had behavioural problems of some kind. Nineteen individuals carried a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5[17]) classification of autism spectrum disorder (ASD; 54%), with four other individuals presenting with features of ASD without formal diagnosis. Sleeping problems were reported in 45%; melatonin is used by three individuals. Finally, a diagnosis of attention-deficit/hyperactivity disorder (ADHD) was present in 10 individuals (40%).

### Miscellaneous

A sacral dimple was present in 16 individuals (47%), tethered cord was reported in 1 individual. Camptodactyly was present in two children. No scoliosis was reported; the oldest individual has spondylosis. Congenital hip dysplasia was present in one case. In one case a non-ossifying fibroma was present, leading to a bone fracture.

Autoimmune problems were reported in three adults: one female was suffering from leukocytoclastic vasculitis, one female was diagnosed with psoriasis and a male with psoriatic arthritis. The female with psoriasis also had hypothyroidism. Pain was reported in the female with leukocytoclastic vasculitis and the male patient with psoriatic arthritis; for both patients, pain is a one of their major complaints. One previously reported child[18] has neuroendocrine hyperplasia of infancy.

### Genotype–phenotype correlation

When comparing individuals with non-sense variants to individuals with missense variants, no significant differences in age of diagnosis, number of infections, IQ (total and subscales), presence of ASD or other behavioural problems were observed (p=0.09–0.7).

Notably, the participant with a mosaic missense variant, diagnosed at the age of 16 months of age, carries a diagnosis of ASD and ADHD.

### Most burdensome consequences of FOXP1 syndrome

Thirty-one parents provided data on the, to their opinion, most burdensome complaints of the children and also their perception of the most burdensome complaints from their child's perspective. The complaints with the highest burden for parents included impaired/delayed cognition, communication impairments, behavioural difficulties and problems with attention and independence. The most burdensome complaints for FOXP1 patients, as perceived by parents, were impaired communication, lack of age-appropriate self-reliance, intellectual disability, impaired social interaction, incontinence, obsessions, a complex sensory profile and impaired motor skills (online supplemental table 2 ; n=31).

## DISCUSSION

In this study, we describe the parent-reported clinical phenotype of FOXP1 syndrome in 40 patients, including 7 adults. The most prevalent neurodevelopmental symptoms in our cohort were intellectual disability, impaired speech and language development, behavioural problems, features of ASD and ADHD, incontinence and sleeping problems. Other medical signs and symptoms included hypermetropia, strabismus, sacral dimple, undescended testes, abnormal muscle tone, infections and short stature after puberty. Possible rarer complications were autoimmune disorders, reported at adult age only. Cognition, communication, lack of age-appropriate independence and behaviour were among the most-mentioned domains that parents would like to change for their child. We found no clear genotype–phenotype correlation, as was observed previously.[3]

Most signs and symptoms in this study were previously identified[3 4 7] and are also present in other genetic forms of intellectual disability. Although we doubt that FOXP1 syndrome is a clinically recognisable entity,[3] more specific signs of FOXP1

syndrome seem to be strabismus, hypermetropia, and sleeping problems in combination with the previously described dysmorphic features.[3]

Not much is known about the clinical manifestations of FOXP1 syndrome in adulthood. Three out of six adult patients included in our study have autoimmune conditions. Given the role of FOXP1 interaction partner FOXP3[19] in the immune system[20] this may be related to the FOXP1 haploinsufficiency. Studies to unravel the pathophysiology and possible treatment options of these autoimmune conditions have been initiated.

Previously reported features such as neuroendocrine hyperplasia of infancy, skeletal disorder, relapsing-remitting fevers, diaphragmatic hernia, iron deficiency anaemia, or childhood-onset hypothyroidism and diabetes mellitus type 2[3 4 18] were not reproduced in our cohort. Larger studies are needed to differentiate whether these, and the less common signs and symptoms reported in this study, are indeed rare complications of FOXP1 syndrome or just co-incidental findings in these patients.

The study provides unique insight into the consequences of FOXP1 syndrome with most impact from the perspective of the family. In general, it is important to ask families and patients about their most burdensome complaints, since these symptoms should guide future research of interventions and outcome measures that matter to parents and patients.[21] Engwerda previously showed that parent-reported data may give new insight into clinically relevant symptoms not previously detected.[13] Although we cannot be sure that the symptoms rated by parents as most burdensome represent the perspective of the patient, they will provide the most representative and useful source of information, as recognised within the field of paediatrics.

Unexpectedly, we observed incontinence to be one of the more burdensome complaints in a subset of patients. Although incontinence after the age of 4 years is present in 45% of individuals in this study and the difficulty attaining bladder control was already reported in 2017,[4] this is the first study recognising the importance of this symptom to patients and their parents. More knowledge on the pathophysiology and natural course of the incontinence in FOXP1 syndrome is needed to counsel parents and guide bladder control training.

Previously, a guideline on the management and follow-up of individuals with FOXP1 syndrome recommended referral to a neurologist and/or a developmental paediatrician and special attention for hearing and visual analysis, imaging of the brain and heart in all newly diagnosed individuals and imaging of the kidneys on indication.[11] In our cohort, consisting of mainly individuals not previously described, only mildly dilated lateral ventricles were reported in more than one individual. Although these results should be interpreted cautiously since brain abnormalities seem to be under-reported by parents,[13] mildly dilated lateral ventricles were reported before,[4] as were other non-specific and non-significant abnormalities without implication for management or prognosis.[5] Lozano *et al* recommend brain imaging in all newly diagnosed individuals with FOXP1 syndrome. In our opinion, the potential adverse effects of anaesthesia and burden of examination for the family/child should be weighed against the possibly low probability of detecting an abnormality with implications for management in patients with a pathogenic variant in the *FOXP1* gene with a stable neurodevelopmental disorder and neurological features typical for FOXP1 syndrome.

Cardiac screening, performed because of increase prevalence of congenital heart defects in FOXP1 syndrome and the clear role of FOXP1 in cardiac morphogenesis,[19] detected a haemodynamically significant atrial septal defect II requiring surgical closure in an asymptomatic school age girl, who also had a fixed splitting of the second heart sound on auscultation. We therefore endorse the recommendation to perform an cardiac ultrasound in all newly diagnosed individuals with FOXP1 syndrome.

In our cohort, one patient had bilateral hydronephrosis without vesicoureteral reflux, detected after a glomerulonephritis. Previously described urogenital malformations include a duplicated left-sided renal collecting duct system,[4] horseshoe kidney and unilateral renal agenesis.[22] As always, we recommend excluding anatomical anomalies by an ultrasound investigation before starting intensive toilet training.

Given the clear role of FOXP1 in cardiac and urogenital morphogenesis,[22 23] it is plausible that congenital abnormalities of the heart and genitourinary system are part of FOXP1 syndrome. Now that whole-exome sequencing is increasingly performed in the prenatal setting—and FOXP1 syndrome can therefore be diagnosed prenatally—a better picture of the clinical, functional and behavioural phenotype is warranted to inform expecting parents.

In this study, parents report on the medical phenotype of their child. The high motivation for parents to participate in research led to a more detailed picture of the clinically relevant features of the patient.[24] Although high consistency between parent-reported characteristics and medical files was reported previously,[13 25] only 18% of parents in this study report their child to have hypotonia, whereas prospective studies report much higher percentages.[5 11] Undescended testes, strabismus, gait abnormalities and sacral dimples were reported in much higher rates than reported in literature. The inconsistencies may not only be explained by incompleteness of information from both parents and medical professionals, but also by difference in timing and formulation of the question, expansion of the phenotypic spectrum and the increasing availability of whole exome sequencing for unselected cases with neurodevelopmental delay including milder cases, leading to a better delineation of the milder part of the FOXP1 spectrum.

Since the aim of phenotyping in rare syndromes is to gain knowledge about the spectrum of the full phenotype and not to determine the exact prevalence of a symptom in a cohort,[24] parent-reported studies are a relatively quick way to gain detailed information about the clinically relevant and less prevalent features of the syndrome. Another major advantage is that the data reflect the perspective of the parents and thereby gives insight into the major challenges of patients and their families, which should be the starting point for developing care and therapy.

## CONCLUSION

Using a parent-reported questionnaire, we identified the most burdensome consequences of FOXP1 syndrome, which should be used to guide future studies. By continually adding patients to our cohort, we will be able to refine our recommendations for baseline investigations and management, which should be aimed at improving patient outcome and providing prognostic information.

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**Competing interests** None declared.

**Patient consent for publication** Consent obtained from parent(s)/guardian(s).

**Ethics approval** The ethical committee of Leiden-Den Haag-Delft, the Netherlands, has exempted this study because only parents were interrogated by the questionnaire and patients were not involved themselves (N21.085). Participants gave informed consent to participate in the study before taking part.

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