

Delineating *FOXP1* syndrome

From congenital microcephaly to hyperkinetic encephalopathy

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Abstract

Objective

To provide new insights into the *FOXP1*-related clinical and imaging phenotypes and refine the phenotype-genotype correlation in *FOXP1* syndrome.

Methods

We analyzed the clinical and imaging phenotypes of a cohort of 45 patients with a pathogenic or likely pathogenic *FOXP1* variant and performed phenotype-genotype correlations.

Results

A total of 37 *FOXP1* different heterozygous mutations were identified, of which 18 are novel. We described a broad spectrum of neurodevelopmental phenotypes, characterized by severe postnatal microcephaly and developmental delay accompanied by a hyperkinetic movement disorder, stereotypes and sleep disorders, and epileptic seizures. Our data highlighted 3 patterns of gyration, including frontal pachygyria in younger patients (26.7%), moderate simplified gyration (24.4%) and mildly simplified or normal gyration (48.9%), corpus callosum hypogenesis mostly in its frontal part, combined with moderate-to-severe myelination delay that improved and normalized with age. Frameshift and nonsense mutations in the N-terminus of *FOXP1*, which are the most common mutation types, show the most severe clinical features and MRI anomalies. However, patients with recurrent frameshift mutations c.460dupG and c.256dupC had variable clinical and imaging presentations.

Conclusions

These findings have implications for genetic counseling, providing evidence that N-terminal mutations and large deletions lead to more severe *FOXP1* syndrome, although genotype-phenotype correlations are not necessarily straightforward in recurrent mutations. Together, these analyses support the view that *FOXP1* syndrome is a specific disorder characterized by frontal pachygyria and delayed myelination in its most severe form and hypogenetic corpus callosum in its milder form.

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Glossary

FBD = forkhead binding domain.

Mutations in the *FOXG1* gene have been shown to cause a rare neurodevelopmental disorder. Initially described as a “congenital variant of Rett syndrome,”^{1,2} subsequent reports allowed delineation of the *FOXG1* syndrome, which is now considered a distinct clinical entity.^{3–7}

To date, more than 90 individuals with *FOXG1* mutations have been described, mostly within small case series.^{5,7} The disorder comprises a complex constellation of clinical features, including severe postnatal microcephaly, deficient social reciprocity, combined stereotypies and dyskinesias, epilepsy, poor sleep patterns, and unexplained episodes of crying.³ In parallel to these clinical criteria, the importance of brain MRI features has been emphasized.^{1,3,8} However, the spectrum of MRI features in *FOXG1* syndrome is yet to be fully defined.

FOXG1 encodes a transcription factor containing a highly conserved domain spanning from the forkhead binding domain (FBD) to the C-terminus and a variable N-terminus.⁹ *FOXG1* mutations include frameshifts, deletions, and point mutations.^{7,10} A recent study suggests that more severe phenotypes are associated with truncating *FOXG1* variants in the N-terminus and the FBD and milder phenotypes with missense variants in the FBD. The most significant differences were related to motor and speech development, while only borderline differences were found concerning corpus callosum anomalies, delayed myelination, and microcephaly.⁷

In light of these recent findings, the aim of this study was to provide a comprehensive overview of *FOXG1*-related clinical and imaging phenotypes by thorough analysis of a cohort of 45 clinically well-characterized patients with *FOXG1* mutation and refine the phenotype-genotype correlation in *FOXG1* syndrome.

Methods

We recruited patients with pathogenic or likely pathogenic *FOXG1* mutations from different cohorts through a large national and international network. Genetic testing was performed by array comparative genomic hybridization (CGH) (5/45), Sanger sequencing (31/45), targeted panel high-throughput sequencing (4/45), and whole-exome sequencing (4/45).

Standard protocol approvals, registrations, and patient consents

The study was approved by the ethics committee of the University Hospital of Necker Enfants Malades, Paris, France and the relevant local institutional review boards. Parental written informed consent was obtained for all affected patients.

All patients were personally known to at least 1 of the co-authors and were reexamined for the purpose of the study.

Five patients had been reported previously and were reassessed for the study.^{8,11,12} Standardized clinical information was recorded. Movement disorders were characterized in person by investigators and classified according to established criteria.¹³ Epileptic seizures were classified according to the recommendations of the Commission on Classification and Terminology of the International League Against Epilepsy.

In addition, for patients filmed, we obtained additional authorization for disclosure of any recognizable persons in videos.

The genetic testings were performed in accordance with the respective national ethics guidelines and approved by the local authorities in the participating study centers.

MRI studies

As the MRI studies were performed over a period of 10 years at many different imaging centers and on many different types of MR scanners, the imaging techniques that were used differed substantially, although a majority had at least axial and sagittal T1-weighted and axial T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. Imaging assessment was based on agreement between 2 investigators (N.B. and N.B.-B.) who reviewed the images. Each made initial evaluations independently, and any disagreements regarding the final conclusion were resolved by consensus.

Statistical analysis

All statistical analyses were performed in GraphPad Prism version 6.00. Data are described as mean \pm SEM. Differences were evaluated using the 2-way analysis of variance with multiple comparison tests.

The study was approved by the ethics committee of the University Hospital of Necker Enfants Malades, Paris, France and the relevant local institutional review boards. Parental written informed consent was obtained for all affected patients.

Results

Our cohort totaled 45 patients with *FOXG1* mutations, 22 males and 23 females ranging in age from 19 months to 42 years (median: 5.73 years) at the time of evaluation (table e-1 [links.lww.com/NXG/A97](https://www.lww.com/NXG/A97)).

A total of 37 *FOXG1* different heterozygous mutations were identified, of which 18 are novel. They comprised 32 small intragenic mutations and 5 large deletions of the whole *FOXG1* locus. All mutations were de novo, except 1 reported previously as a germinal mosaic.¹² Point mutations were mostly frameshifts (14/32; 43.75%) and missense mutations (12/32; 37.5%), with a small number of nonsense (4/32; 12.5%) and in-frame

mutations (2/32; 6.25%) (figure 1, A and B). Three recurrent mutations, c.460dupG, c.256dupC, and c.256delC, were identified.

Clinical presentation in patients with *FOXG1* mutations

Patients first came to medical attention at a median age of 3 months (birth to 20 months) because of developmental delay and microcephaly (15/45; 33.3%) or with lack of eye contact, or strabismus (16/45; 35.6%). Epileptic seizures or movement disorder were less common (4/45; <10%). In 5 cases (11.1%), brain anomalies were diagnosed prenatally.

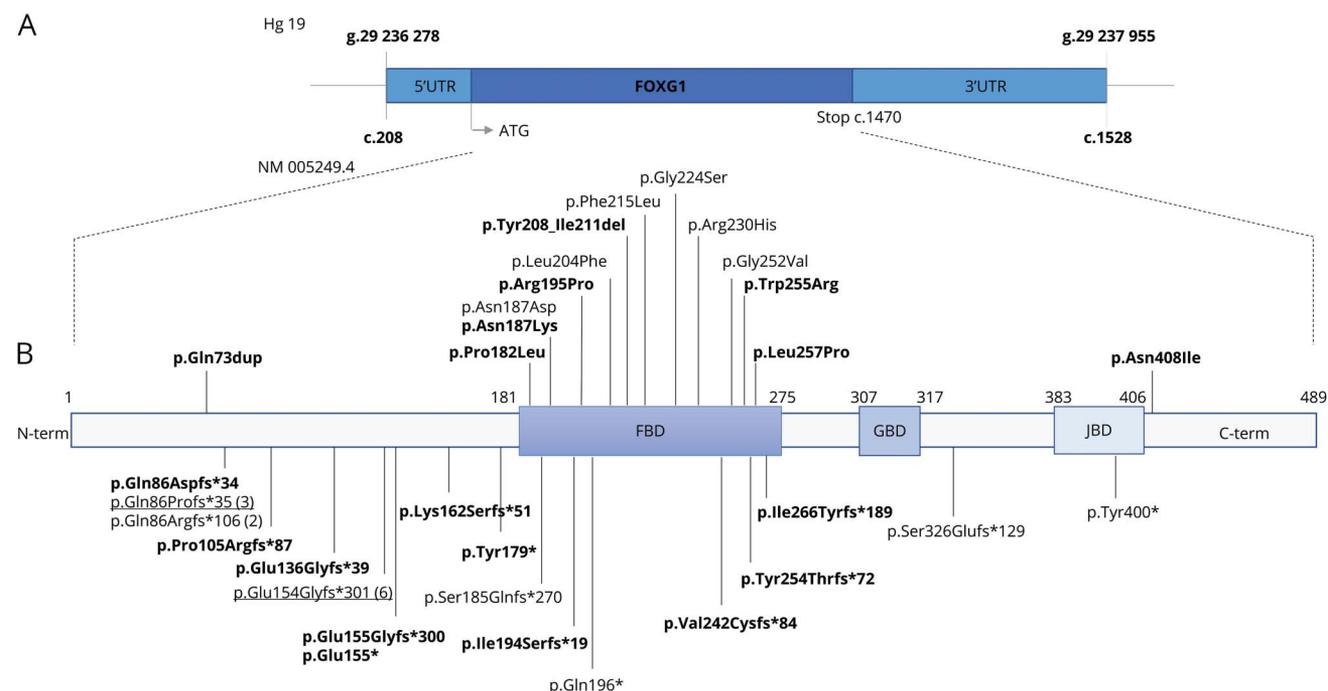
At birth, a majority of patients had normal body measurements and low normal birth head size (38/43; 88.4%). Severe postnatal microcephaly (−4 to −6 SD) became apparent after the age of 1 month.

At the age of the last evaluation (median: 5 years; 19 months to 42 years), all patients had profound developmental delay, with permanent esotropia (38/42; 90.7%) (video 1 links.lww.com/NXG/A99). Hand use was severely limited to involuntary gross manipulation (13/44; 29.5%) (video 2 links.lww.com/NXG/A100). On examination, a complex movement disorder was the most prominent feature characterized by generalized hyperkinetic and dyskinetic movements that was present at rest and

worsened with attempts to movement (videos 3 and 4 links.lww.com/NXG/A101 and links.lww.com/NXG/A102), with orolingual dyskinesias (12/33; 36.4%) (video 5 links.lww.com/NXG/A103); 34 of 43 patients (79.1%) also showed hand stereotypies, consisting of hand pressing/wringing or hand mouthing (videos 6 and 7 links.lww.com/NXG/A104, links.lww.com/NXG/A105), which are unusual in the context of dyskinetic movement disorders. Thirty-two of 44 patients (72.7%) had feeding difficulties associated with gastroesophageal reflux (videos 8 and 9 links.lww.com/NXG/A106 and links.lww.com/NXG/A107). Sleep problems were frequent (27/42; 64.3%) and included multiple nocturnal awakenings or difficulties in falling asleep with irritability and inconsolable crying or inappropriate laughing (25/40; 62.5%). Seizures were documented in 77.8% (35/45) of patients and occurred at a mean age of 2.5 years (range: 2 days to 12 years). Generalized tonic or tonic-clonic seizures were the most frequent seizure type (21/35; 60%). Of the 35 patients, 17 (48.6%) developed refractory epilepsy with multiple seizure types and 5 (14.3%) experienced at least 1 episode of status epilepticus (table 1).

Because, *FOXG1* mutations had been previously associated with congenital Rett variant, we examined the prevalence of congenital Rett-supportive manifestations. Overall, 2 of 21 females (9.5%) and 1 of 21 males (4.76%) fulfilled the diagnostic criteria for Rett syndrome¹⁴ (table e-2 links.lww.com/NXG/A98).

Figure 1 Schematic representation of *FOXG1* gene, protein domain structure, and positions of *FOXG1* mutations



(A) Schematic representation of *FOXG1* gene and (B) *FOXG1* protein domain structure and positions of the variations identified: N-terminal domain; FBD domain (forkhead DNA binding domain, amino acids 181–275), GBD domain (Groucho binding domain, amino acids 307–317), JBD domain (JARID1B binding domain, amino acids 383–406), and C-terminal domain are indicated. Mutations are located all along the *FOXG1* gene, within different protein domains. Missense mutations are predominantly located in the FBD (91.7%), whereas frameshift mutations are more prominent in the N-terminal domain (57.1%). The novel variants described in this article are highlighted in bold and the recurrent variants are underlined with the corresponding number of recurrences indicated in brackets. FBD = forkhead binding domain; GBD = Groucho binding domain; JBD = JARID1B binding domain.

Table 1 Individual data on epilepsy and MRI pattern on 45 patients with de novo *FOXG1* mutations/deletions

Patient/sex	Age at last follow-up	Mutation	Epilepsy	Age at seizure onset	Seizure history	Age at MRI	MRI Pattern
Tel02/M	4 y 6 mo	p.Gln73dup	Yes	1 y	Brief GTS (every 2 wk) under AED	2 y 8 mo	Moderate SIMP with cortical atrophy, severe myelination delay, hypoplastic CC, and normal cerebellum
Trs1/F	3 y 6 m	p.Gln86Profs*35	Yes	6 mo	IS then evolved to GTS (1 SE at 2 y 6 m) followed by GTCS, drug resistant	11 m	Mild SIMP gyral pattern, moderate myelination delay, hypogenesis of the CC affecting the rostrum, and normal cerebellum
Im11/F	1 y 7 mo	p.Gln86Profs*35	No	—	—	2 y 6 mo	Moderate SIMP, mild myelination delay, hypogenesis of the CC affecting the rostrum, and normal cerebellum
Im05/M	10 y 2 mo	p.Gln86Profs*35	Yes	5 mo	GTCS (1 each 6 mo) with LTG and CZP	2 y 8 mo	Moderate SIMP gyral with cortical atrophy, severe myelination delay, hypogenesis of the CC affecting the rostrum, and normal cerebellum
Nan02/F	3 y	p.Gln86Aspfs*34	Yes	1 y 6 mo	2 SE then GTS (1/m) with AED with LTG, VPA, CZP	3 y	Moderate SIMP with mild cortical atrophy, severe myelination delay, complete agenesis of the CC, and normal cerebellum
Bay01/F	7 y 5 mo	p.Gln86Argfs*106	No	—	—	3 y 2 mo	Normal gyral pattern, mild myelination delay, hypogenesis of the CC affecting the rostrum, and normal cerebellum
Mon01/M	10 y	p.Gln86Argfs*106	Yes	1 y	IS then myoclonic seizures with photosensitivity; seizure free from the age of 4	3 y 6 mo	Mild SIMP gyral pattern, severe cortical atrophy, mild myelination delay, complete CC agenesis, and normal cerebellum
Rou01/M	3 y	p.Glu136Glyfs*39	Yes	1 y 3 mo	GTS and IS; 1 SE, drug-resistant multifocal epilepsy with VGB and TPM	34 mo	Pachygyria, severe myelination delay, hypoplastic CC, and normal cerebellum
Ren01/M	12 y	p.Glu154Glyfs*301	Yes	6 y	1 episode of FS then seizure free	12 y 8 mo	Mild SIMP gyral pattern with mild cortical atrophy, normal myelination, hypogenesis of the CC affecting the rostrum, and cerebellar atrophy
Leu01/F	5 y	p.Glu154Glyfs*301	No	—	—	5 y	Normal gyral pattern, mild myelination delay, and normal CC and cerebellum
Thi01/F	9 y	p.Glu154Glyfs*301	Yes	2 y	GTS then seizure free	9 y 3 mo	Moderate SIMP with mild cortical atrophy, mild myelination delay, complete agenesis of the CC, and cerebellar atrophy
Im06/F	4 y 10 mo	p.Glu154Glyfs*301	No	—	—	1 y 11 mo	Pachygyria, severe myelination delay, hypogenesis of the CC with absence of rostrum, and mild cerebellar atrophy

Continued

Table 1 Individual data on epilepsy and MRI pattern on 45 patients with de novo *FOXG1* mutations/deletions (continued)

Patient/sex	Age at last follow-up	Mutation	Epilepsy	Age at seizure onset	Seizure history	Age at MRI	MRI Pattern
Im09/M	6 y	p.Glu154Glyfs*301	Yes	4 y	Occasional GTCS (1/y) with VPA (normal EEG)	3 y 3 mo	Mild SIMP, mild myelination delay, hypogenesis of the CC affecting the rostrum, and normal cerebellum
Ang02/M	2 y	p.Glu154Glyfs*301	Yes	3 mo	Focal motor seizures (4/mo)	1 y 3 mo	Mild SIMP gyral pattern with moderate cortical atrophy, severe myelination delay, hypogenesis of the CC affecting the rostrum, and normal cerebellum
Im04/F	11 y	p.Glu155Glyfs*300	Yes	4 mo	Myoclonic seizures treated with VPA, then seizure free from the age of 4 y	1 y 10 mo	Mild SIMP gyral pattern, severe myelination delay, hypogenesis of the CC affecting the rostrum, and normal cerebellum
Tou01/M	ND	p.Glu155*	Yes	10 mo	Drug-resistant multifocal epilepsy (Lennox Gastaut like)	2 y 6 mo	Pachygyria, severe myelination delay, hypoplastic CC, and normal cerebellum
Im10/M	4 y 12 mo	p.Lys162Serfs*51	Yes	2 y	Occasional GTCS with VPA	4 y	Moderate SIMP gyral pattern with cortical atrophy, severe myelination delay, partial agenesis of the CC, and normal cerebellum
Rdb02/M	6 y	p.Tyr179*	Yes	11 mo	Focal seizures, with secondary generalization refractory	2 y 3 mo	Pachygyria with moderate cortical atrophy, severe myelination delay, partial agenesis of the CC, and normal cerebellum
Im03/F	2 y 4 mo	p.Ser185Glnfs*270	Yes	1 y 5 mo	Focal seizures, with secondary generalization then seizure free with AED	2 y	Mild SIMP gyral pattern with mild cortical atrophy, moderate myelination delay, extremely hypoplastic CC, and normal cerebellum
Pit02/M	22 y	p.Ile194Serfs*19	Yes	1 y	GTS then seizure free	ND	Mild SIMP gyral pattern, myelination delay, hypoplastic CC with hypoplastic rostrum
Ren03/M	32 y	p.Gln196*	Yes	4 y	1 SE then occasional GTCS between 4 and 10 y then seizure free	7 mo	Partial agenesis of the CC and normal cerebellum
Ade01/M	7 y	p.Tyr208_Ile211del	Yes	1 y 8 mo	Recurrent seizures (3/d), then seizure free with AED	2 y 7 mo	Mild SIMP with mild cortical atrophy, absence of myelination delay, hypogenesis of the CC affecting the rostrum, and normal cerebellum
Str03/M	20 y	p.Val242Cysfs*84	Yes	6 mo	Myoclonic seizures and then GTCS	8 mo	Pachygyria, moderate myelination delay, hypoplastic CC, and normal cerebellum
Im01/F	10 y	p.Tyr254Thrfs*72	Yes	3 y	GTCS, FS, under 3 AED	7 y 4 mo	Moderate SIMP with cortical atrophy, mild myelination delay, hypoplastic CC affecting the rostrum, and normal cerebellum

Continued

Table 1 Individual data on epilepsy and MRI pattern on 45 patients with de novo *FOXG1* mutations/deletions (continued)

Patient/sex	Age at last follow-up	Mutation	Epilepsy	Age at seizure onset	Seizure history	Age at MRI	MRI Pattern
Tel01/M	3 y 6 mo	p.Ile266Tyrfs*189	No	—	FS once	11 mo	Moderate SIMP, mild myelination delay, hypoplastic CC, and normal cerebellum
Ren02/F	10 y	p.Pro182Leu	Yes	9 mo	Atypical absence, GTCS; drug resistant	1 y	Pachygyria, moderate myelination delay, hypoplastic CC affecting the rostrum, and normal cerebellum
Rdb01/M	8 y	p.Asn187Asp	Yes	1 y 6 mo	IS then multifocal drug-resistant epilepsy	18 mo	Pachygyria, severe myelination delay, hypoplastic CC affecting the rostrum, and normal cerebellum
Lau01/M	2 y	p.Asn187Lys	Yes	12 mo	IS then multifocal drug-resistant epilepsy	2 y 5 mo	Moderate SIMP with cortical atrophy, severe myelination delay, hypoplastic CC, and normal cerebellum
Im08/M	22 mo	p.Arg195Pro	Yes	8 mo	GTS (10/d every 6 mo) with VPA and CZP	2 y 2 mo	Moderate SIMP gyral pattern with moderate cortical atrophy, moderate myelination delay, hypoplastic CC, and normal cerebellum
Pit01/F	42 y	p.Leu204Phe	Yes	8 y	GTCS then seizure free	39 y	Mild SIMP with mild cortical atrophy, mild white matter loss, hypoplastic CC affecting the rostrum, and cerebellar atrophy
Mar01/F	4 y	p.Phe215Leu	Yes	10 y	GTCS, seizure free with VPA	3 y	Normal gyral pattern with mild cortical atrophy, moderate myelination delay, hypoplastic CC affecting the rostrum, and normal cerebellum
Im12/F	2 y 7 mo	p.Gly224Ser	Yes	6 mo	IS then seizure free under LTG, CZP from 2 y	2 y 6 mo	Normal gyral pattern, mild myelination delay, hypoplastic CC, and normal cerebellum
Ang01/M	2 y 4 mo	p.Arg230His	No	—	—	1 y 11 mo	Pachygyria, moderate myelination delay, hypoplastic CC affecting the rostrum and normal cerebellum
Str02/F	9 y	p.Gly252Val	No	—	—	19 mo	Pachygyria, severe myelination delay, hypoplastic CC, and normal cerebellum
Lyo01/M	4 y	p.Trp255Arg	Yes	1 y	ND	2 y 2 mo	Mild SIMP gyral pattern, mild myelination delay, CC hypogenesis, and normal cerebellum
Nan03/F	17 y	p.Leu257Pro	No	—	—	4 y	Normal cortex; anterior part CC nonmyelinated
Nan01/F	7 y 1 mo	p.Asn408Ile	Yes	9 y	Atypical absences with VPA	13 y	Normal

Continued

Table 1 Individual data on epilepsy and MRI pattern on 45 patients with de novo *FOXP1* mutations/deletions (continued)

Patient/sex	Age at last follow-up	Mutation	Epilepsy	Age at seizure onset	Seizure history	Age at MRI	MRI Pattern
Im02/M	4 y 9 mo	p.Ser326Glufs*129	Yes	1 y	IS treated with VGB and steroids, then seizure free	1 y 1 mo	Moderate SIMP with mild cortical atrophy, moderate myelination delay, hypogenesis of the CC affecting the rostrum, and normal cerebellum
Cle01/F	18 y	p.Tyr400*	No	—	—	7 y 11 mo	Normal
Dij01/F	18 y 2 mo	c.-715delinsTACAAAA	Yes	1 y 6 mo	GTCS then seizure free under VPA (3 ys); currently no treatment (11 y)	15 y 11 mo	Mild SIMP gyral pattern with mild cortical atrophy, absence of myelination delay, hypogenesis of the CC affecting the rostrum, and cerebellar atrophy
Lyo02/F	1 y 6 mo	del14q12 (29,222,002–29,258,618)	Yes	1 y 4 mo	IS, seizure free under VGB	8 mo	Mild SIMP gyral pattern, mild myelination delay, hypogenesis of the CC affecting the rostrum, and normal cerebellum
Lyo03/F	3 y 9 mo	del14q12 (26,415,516–29,677,148)	Yes	1 y 3 mo	GTS then seizure free during 2 mo, drug resistant (seizure frequency 1/w)	9 mo	Mild SIMP gyral pattern, moderate myelination delay, hypogenesis of the CC affecting the rostrum and the genu, and normal cerebellum
Im07/F	2 y	del14q12q13.1	No	—	—	5 mo	Moderate SIMP gyral pattern, moderate myelination delay, complete agenesis of the CC, and normal cerebellum
Aix01/M	7 y	del14q12 (18,798,641–19,484,013)	Yes	2 d of life	FS (<1/mo)	2 y	Mild SIMP gyral pattern with moderate cortical atrophy, moderate myelination delay, hypoplastic CC, and normal cerebellum

Abbreviations: AED = antiepileptic drugs; CBZ = carbamazepine, CC = corpus callosum; CZP = clonazepam; FS = focal seizures; GTCS = generalized tonic-clonic seizures; GTS: generalized tonic seizures; IS = infantile/epileptic spasms; LEV = levetiracetam; LTG = lamotrigine; SE = status epilepticus; SIMP = simplified gyration; TPM = topiramate; VGB = vigabatrin; VPA = valproic acid.

Brain images

Patients with *FOXG1* syndrome showed a variable degree of gyration, moderate-to-severe myelination delay or white matter loss (64.4%), and abnormal corpus callosum (95.6%). From our detailed review of these imaging studies, we were able to delineate 3 groups of severity of gyration defect that are most easily appreciated with multiple views in several planes, as shown in figures 2, A-L and 3, A-H.

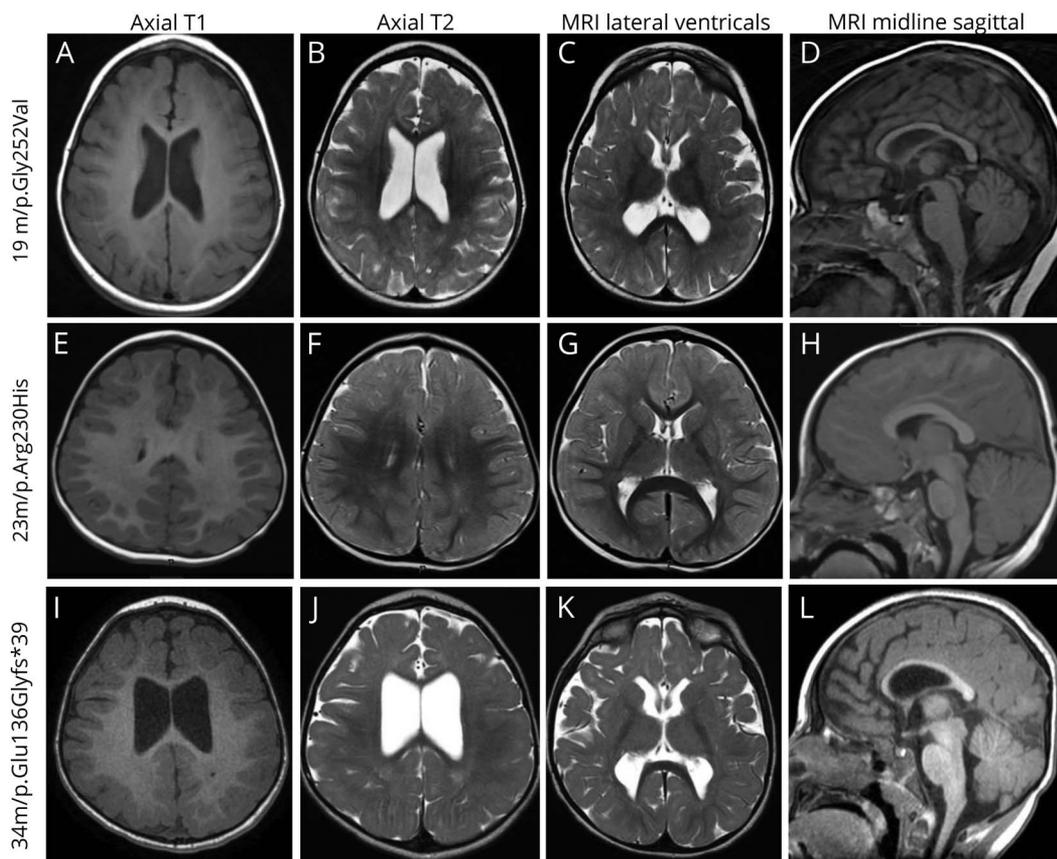
The first gyral pattern, the most severe, consisted of pachygyria, with thickened cortex with frontal lobe predominance (12/45; 26.7%). This pattern was seen in the youngest patients (mean age 1.8 years) and was accentuated by the underdevelopment of the frontal lobes and the reduced volume of the subcortical white matter. In this group, myelination delay was prominent, ranging from severe (7/11; 63.6%) to moderately delayed (4/11; 36.4%). The most common corpus callosum anomaly was anterior hypogenesis, mostly affecting the genu and the rostrum (6/11; 54.5%) (figure 2, A-L). Sequential MRI performed during the first years of life showed that this pachygyric appearance can be overestimated

between the ages of 12 and 24 months because of the immature myelination (figure 3, A-H). Delayed myelination improved with age, and no case of hypomyelination or dysmyelination was observed after the age of 5 years.

The second gyral pattern of intermediate severity met the subjective criteria of moderately simplified gyral pattern.¹⁵ This pattern was observed in 24.4% (11/45) of patients with mean age of 3.1 years. In this group, myelination was moderately to severely delayed. The corpus callosum showed a wide range of anomalies, including complete agenesis (5/11; 45.5%), global hypoplasia (3/11; 27.3%), and anterior hypogenesis (3/11; 27.3%).

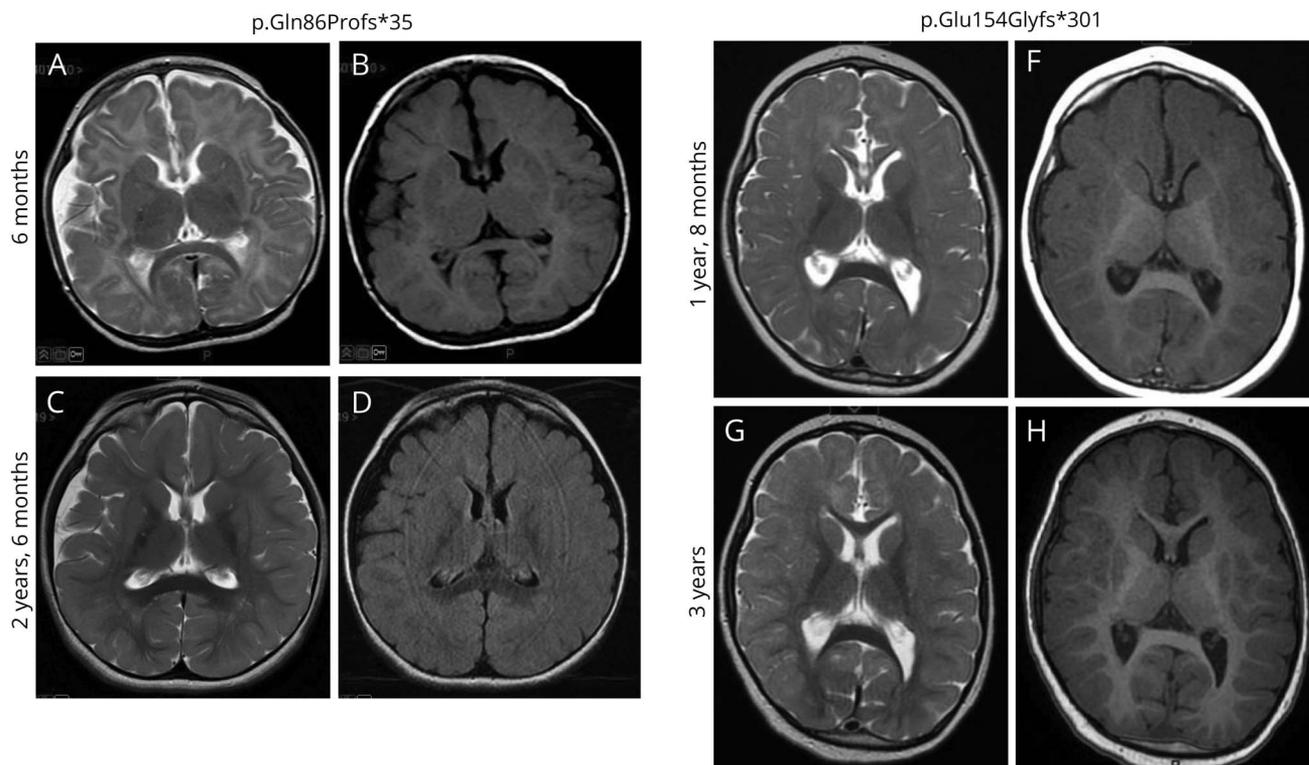
The third gyral pattern, the least severe, consisted of mildly simplified to normal gyral pattern. These patients (22/45; 48.9%) were older than the 2 previous groups (mean age 6.1 years). White matter anomalies were mostly mild or absent (14/22; 63.6%), and the corpus callosum was hypogenetic in its anterior part in the majority of cases (14/22; 63.6%) (figure e-1 links.lww.com/NXG/A91).

Figure 2 Representative MRI of pachygyric frontal cortex in *FOXG1* patients



Representative images at the level of centrum semiovale in axial T1-weighted (A, E, I) and T2-weighted (B, F, J) MRI, at the level of lateral ventricles (third column) and midline sagittal (right column). Each row shows images from the same patient respectively: (A–D) Str02 aged 19 months; (E–H) Ang01 aged 23 months; (I–L) Rou01, aged 34 months. The cortex appears mildly thick with a clear predominance in the frontal lobes. The appearance of pachygyria is accentuated by the underdevelopment of frontal lobes. T2-weighted (C, G, K) MRI at the level of the internal capsule showing associated myelination delay, with mature myelin only visible in both internal capsules (G and K). T1-weighted midline sagittal sections showing the wide range of appearance of the corpus callosum, from hypoplastic and thin (D, L) to thick with underdevelopment of the genu (H).

Figure 3 Changing appearance of the frontal cortex with age associated with increasing myelination



Representative images from 2 patients: Im11 p.Gln86Profs*35 (A–D) and Im09 p.Glu154Glyfs*301 (E–H). (A and B) Images obtained when the patient was 6 months old. T2-weighted image (A) shows normal thickness of both frontal lobes but delayed myelination. T1-weighted image (B) shows a pachygyric cortex in the same region. (C and D) Images obtained when the patient was 2 years 6 months. T2-weighted image (C) of the frontal lobe shows mildly thickened cortex, probably because of the poor myelination of the subcortical white matter. (E and F) Images obtained when the patient was 1 year 8 months. In the frontal lobe, T2-weighted (E) and T1-weighted (F) images show the same pattern of pachygyric cortex and severely delayed myelination (E). (G and H) At 3 years, the T2-weighted image (G) shows significant improvement of myelination, although still delayed in the frontal subcortical region: the T1-weighted image (H) shows mildly simplified gyral pattern, with no pachygyria.

Genotype-phenotype relationships

To assess genotype-phenotype associations in *FOXG1* syndrome, we investigated the correlation between the score of selected *FOXG1* criteria in the whole cohort and 5 genetic subgroups (e-results) (table 2).

Patients with N-terminal mutations and *FOXG1* deletions showed the highest global severity scores, while those with FBD frameshift and nonsense mutations showed the lowest global severity scores ($p < 0.05$). Patients with FBD missense and C-terminal domain mutations tended to have lower global severity scores, although the differences were not significant because of the small size of these groups (figure e-2A links.lww.com/NXG/A92).

When covariance analysis was performed in the whole cohort, we found significant positive covariance of gyral and myelination pattern scores, suggesting that whatever the type of *FOXG1* mutation, the most severe cortical anomaly (i.e., pachygyria) is correlated with the most severe myelination delay, further reinforcing the fact that this cortical anomaly may be overestimated because of the abnormal myelination of the subcortical fibers. Further analyses showed significant and distinct

covariance relationships in which the MRI pattern appeared the most relevant criteria in distinguishing the genetic groups (figures e-3 links.lww.com/NXG/A93 and e-4 links.lww.com/NXG/A94).

Interesting data also came from the analysis of patients with recurrent frameshift mutations c.460dupG and c.256dupC. Remarkably, among the patients with c.460dupG, we found significant differences in clinical and imaging presentations, demonstrating that genotype-phenotype correlation is not straightforward in *FOXG1* syndrome. On MRI, this mutation resulted in a spectrum of corpus callosum anomalies, from complete agenesis to global hypoplasia (figure e-5 links.lww.com/NXG/A96). By contrast, the 3 patients with the c.256dupC had a more consistent phenotype.

Discussion

Foxg1 is a transcription factor that plays nonredundant roles in brain development, such that loss of a single copy of the gene severely affects brain formation, and knock-out mice cannot survive after birth.^{9,16} Consequently, it is not surprising that all mutations identified in humans are heterozygous and result in

Table 2 Clinical and neuroimaging features related to the *FOXP1* genotype groups

	N-terminal domain variants		Forkhead domain frameshift and nonsense variants		Forkhead domain missense variants		C-terminal domain variants		Large deletions	
Cases number, n (%)	19	39.5%	6	13.3%	12	25.60%	3	7%	5	11.6%
Sex, M/F	10/9	52.6%/47.4%	4/2	66.7%/33.3%	6/6	50%/50%	1/2	33.3%/66.7%	1/4	20%/80%
Median age at last follow-up (y)	4.8		15		5.5		7.1		3.8	
Pregnancy and neonatal period										
Problems in pregnancy/scans	0/17	0%	2/4	50%	4/11	36.4%	0/3	0%	2/5	40%
Mean gestation at delivery (GW)/n	39.7	18	38.2	6	39.1	11	39.2	3	38.9	5
Neonatal issues	4/17	23.7%	1/4	25%	2/11	18.20%	1/3	33.3%	4/5	80%
Feeding difficulties at birth	3/17	17.6%	1/4	25%	1/11	9.1%	1/3	33.3%	2/5	40%
Body measurements at birth										
Length < -2SD	0/16	0%	0/5	0%	1/10	10%	0/3	0%	0/5	0%
Weight < -2SD	0/17	0%	0/5	0%	0/11	0%	0/3	0%	0/5	0%
HC < -2SD	1/18	5.6%	0/5	0%	3/12	25%	0/3	0%	0/5	0%
Body measurements at last evaluation										
Median age (y)/n	4.7	18	6.6	5	7.5	12	7.1	3	3.8	5
Height < -2SD	1/14	7.1%	1/3	33.3%	3/9	33.3%	0/2	0%	2/5	40%
Weight < -2SD	4/17	23.5%	1/3	33.3%	4/11	36.4%	1/3	33.3%	3/5	60%
HC < -2SD	18/19	94.7%	5/5	100%	8/10	80%	3/3	100%	5/5	100%
HC < -4SD	14/19	73.7%	3/5	60%	4/10	40%	1/3	33.3%	4/5	80%
Microcephaly score										
0 = Normal at birth and at last evaluation	1/18	5.6%	1/5	20%	2/11	18.2%	0/3	0%	0/5	0%
1 = Postnatal microcephaly	3/18	16.7%	1/5	20%	3/11	27.3%	2/3	66.7%	1/5	20%
2 = Severe postnatal microcephaly, -4 to -6 SD	13/18	72.2%	3/5	60%	3/11	27.3%	1/3	33.3%	4/5	80%
3 = Congenital and postnatal microcephaly	1/18	5.7%	0/5	0%	3/11	27.3%	0/3	0%	0/5	0%

Continued

Table 2 Clinical and neuroimaging features related to the *FOXP1* genotype groups (continued)

	N-terminal domain variants		Forkhead domain frameshift and nonsense variants		Forkhead domain missense variants		C-terminal domain variants		Large deletions	
Motor and speech development										
Social interactions (eye contact and smiling intentionally)	10/15	66.7%	3/3	100%	8/11	72.7%	3/3	100%	3/5	60%
Sit with support	6/19	31.6%	2/6	40%	7/12	58.3%	2/3	66.7%	1/5	20%
Walked independently	0/19	0%	0/6	0%	1/12	8.3%	2/3	66.7%	0/5	0%
Hand use	10/19	52.6%	3/5	60%	4/12	33.3%	1/3	33.3%	1/5	20%
Speech (at least bisyllabisms)	1/17	5.9%	0/6	0%	1/12	8.3%	1/3	33.3%	0/5	0%
Sleep and behavior disturbances										
Inappropriate laughing/crying/screaming spells	9/15	60%	3/5	60%	7/12	58.3%	3/3	100%	2/5	40%
Impaired sleep pattern	11/18	61.1%	4/5	80%	6/11	54.5%	2/3	66.7%	4/5	80%
Feeding difficulties	13/19	68.4%	3/6	50%	9/12	75%	2/3	66.7%	5/5	100%
First concern and disease course										
Median age at first concerns (mo)/n	3.7	18	3.5	6	3	11	6	3	0	5
What were the first concerns?										
Microcephaly	7/19	36.8%	1/6	50%	4/12	33.3%	1/3	33.3%	2/5	40%
Strabismus/poor eye contact/abnormal ocular pursuit	6/19	31.6%	2/6	33.3%	6/12	50%	0/3	0%	2/5	40%
Developmental Delay	8/19	42.1%	4/6	66.7%	4/12	33.3%	2/3	66.7%	1/5	20%
Corpus callosum abnormalities	0/18	0%	0/6	0%	1/12	8.3%	0/3	0%	2/5	40%
Seizures	2/19	10.5%	0/6	0%	2/12	16.7%	0/3	0%	0/5	0%
Movement disorders	2/19	10.5%	0/6	0%	2/12	16.7%	1/3	33.3%	1/5	20%
A period of regression	3/19	15.8%	2/5	40%	2/12	16.7%	2/3	66.7%	1/5	20%
Clinical examination										
Dysmorphic features	8/18	44.4%	2/5	40%	3/11	27.3%	1/3	33.3%	1/5	20%
Axial hypotonia	18/19	94.7%	5/6	83.3%	11/11	100%	3/3	100%	5/5	100%
Hypertonia/spasticity	13/19	68.4%	5/6	83.3%	8/12	66.7%	1/3	33.3%	3/5	60%

Continued

Table 2 Clinical and neuroimaging features related to the *FOXP1* genotype groups (continued)

	N-terminal domain variants		Forkhead domain frameshift and nonsense variants		Forkhead domain missense variants		C-terminal domain variants		Large deletions	
Movement disorders	19/19	100%	6/6	100%	12/12	100%	3/3	100%	5/5	100%
Stereotypic movements	15/19	78.9%	3/4	75%	8/12	63.6%	3/3	100%	5/5	100%
Strabismus	16/18	88.9%	4/4	100%	10/12	81.8%	3/3	100%	5/5	100%
Scoliosis	5/19	26.3%	1/5	20%	1/11	9.1%	1/3	33.3%	1/5	20%
Epilepsy										
Seizure occurrence	15/19	78.9%	5/6	80%	9/12	75%	2/3	66.7%	4/5	80%
Median age at seizure onset (y)	1		1.4		1		5		1.3	
Severity of epilepsy										
0 = No seizures	4/19	21%	1/6	16.7%	3/12	25%	1/3	33.3%	1/5	20%
1 = Seizure onset >2 y and seizure free after withdrawal AE	2/15	13.3%	1/5	16.7%	1/9	11.1%	0/2	0%	0/4	0%
2 = Seizure onset >2 y and seizure free with AE	2/15	13.3%	2/5	40%	2/9	22.2%	0/2	0%	1/4	25%
3 = Seizure onset <2 y and continuing seizures with AE	6/15	40%	2/5	40%	3/9	33.3%	1/2	50%	1/4	25%
4 = Severe infantile spasms or seizure onset <6 mo	5/15	33.3%	0/5	0%	3/9	33.3%	1/2	50%	2/4	50%
MRI pattern										
Median age at examination (y)	3.4		2.3		5.6		7.9		3.95	
Cortical anomalies										
Normal or mild SIMP gyral pattern	8/19	41.7%	2/5	40%	5/11	45.5%	2/3	66.7%	4/5	80%
Moderate SIMP gyral pattern	5/19	26.3%	2/5	40%	2/11	18.2%	1/3	33.3%	1/5	20%
Severe and pseudopachygyric cortex	6/19	31.6%	1/5	20%	4/11	36.4%	0/3	0%	0/5	0%
Cortical atrophy	12/19	63.2%	3/4	75%	7/11	63.6%	1/3	33.3%	2/5	20%
Myelination delay										
Absent to mild myelination delay	6/19	31.6%	2/4	50%	3/10	30%	2/3	66.7%	2/5	40%
Moderate myelination delay	2/19	10.5%	1/4	25%	5/10	50%	1/3	33.3%	3/5	60%
Severe myelination delay or white matter loss	11/19	57.9%	1/4	25%	2/10	20%	0/3	0%	0/5	0%

Continued

Table 2 Clinical and neuroimaging features related to the *FOXG1* genotype groups (continued)

Corpus callosum aspect	N-terminal domain variants	Forkhead domain frameshift and nonsense variants	Forkhead domain missense variants	C-terminal domain variants	Large deletions
Normal	1/19 5.3%	0/6 0%	0/11 0%	2/3 66.7%	0/5 0%
Hypoplastic but complete	3/19 15.8%	2/6 33.3%	3/11 27.30%	1/3 33.3%	3/5 60%
Hypogenetic with absent rostrum	10/19 52.6%	2/6 33.3%	6/11 54.5%	0/3 0%	1/5 20%
Partial or complete agenesis	5/19 26.3%	2/6 33.3%	2/11 18.2%	0/3 0%	1/5 20%
Cerebellar atrophy	3/19 15.8%	0/5 0%	1/11 9.1%	0/3 0%	1/5 20%

Abbreviations: AE = antiepileptic drug; CC = corpus callosum; SE = status epilepticus; SIMP = simplified gyration.

noticeable changes in brain size and mental development early in childhood. To date, *FOXG1* has been linked to a wide range of human congenital brain disorders.^{1-7,17-19} In this study, we describe detailed clinical and neuroradiological data on 45 patients with pathogenic single nucleotide variants and copy number variations affecting *FOXG1*. This is one of the largest cohort of patients with *FOXG1* syndrome and focuses on *FOXG1* point mutations, which affect both sexes equally. The aim of this study was to refine the phenotypic spectrum of *FOXG1* syndrome and its natural history and to further investigate genotype-phenotype correlations. In keeping with previously published *FOXG1*-associated clinical features, we found *FOXG1* syndrome to be associated with severe postnatal microcephaly (-4 to -6 SD), dyskinetic-hyperkinetic movement disorders, visual impairment, epilepsy, stereotypies, abnormal sleep patterns, and unexplained episodes of crying.^{1,3,5-8,18,20-23}

Our data clearly confirm that head circumference is usually normal to borderline small at birth and evolves during infancy to severe microcephaly below -3 SD, with normal somatic growth. Although no longitudinal data on head circumference are available from our series, it is interesting to note that microcephaly was the first concern in one-third of the cohort at the mean age of 3.47 months, suggesting that the slowdown in head growth occurs earlier than previously described. Of note, *FOXG1*-related postnatal microcephaly is characterized by underdevelopment of the frontal lobes, a unique pattern that does not occur in other causes of progressive microcephaly.²⁴ This underdevelopment of frontal lobes can be associated with a mildly to moderately simplified gyral pattern and reduced white matter or in the youngest patients with a pachygyric appearance. We observed this pattern on T2-weighted images in infants who showed mild gyral simplification later in childhood. The clue to the cause of the 2 patterns came from studying serial MRI of patients Im09 and Im11. Frontal pachygyria, which was observed at 6 months of age, changed into mild gyral simplification at 2.5 years of age. This finding suggested that the 2 cortical patterns did not represent differences of morphology but instead, differences in the maturity of the subcortical white matter. It is noteworthy that this changing appearance has been observed previously in polymicrogyria.^{25,26}

Another imaging hallmark of *FOXG1* disorder is the delayed myelination. While delayed myelination has a similar appearance to hypomyelination on a single MRI, especially if done at an early age, sequential studies can distinguish between them by demonstrating increasing myelin content in delayed myelination.²⁷ This evolution of delayed myelination toward normalization in childhood is not specific to *FOXG1* syndrome, as it has been observed in other developmental disorders, such as MCT8 deficiency and Xq28 duplication involving *MECP2* or *SPTAN1* encephalopathy.²⁷⁻²⁹

Taken together with the published literature, we suggest that *FOXG1* syndrome is a disorder in which hypogenetic corpus callosum is the most frequent finding. More specifically, corpus

callosum malformations in *FOXG1* syndrome are frontal predominant, similar to the gyral abnormality, suggesting that the same pathogenic mechanism operates for both the frontal cortical abnormalities and the callosal abnormalities. Complete agenesis occurs occasionally and is likely to represent the most severe end of the spectrum of pathogenic mechanisms underlying hypoplasia. This also illustrates that hypoplasia and agenesis are related to a similar mechanism and that genetic modifiers influence the severity of the callosal phenotype.³⁰ Of interest, the severity of corpus callosum anomaly does not correlate with the degree of microcephaly, the degree of myelination abnormality, or the degree of gyral abnormalities. This contrasts with data from congenital microcephaly that showed a correlation between the degree of microcephaly and the severity of the associated callosal anomaly.³¹

Hyperkinetic movement disorders have been recognized to be a key feature in *FOXG1* syndrome since its original description.^{6,18} Our data show that movement disorder is rarely the presenting feature of *FOXG1* syndrome; this has not been stressed previously. It is important that the combination of hand stereotypes, mostly hand to mouth, with generalized dyskinesia is one of the key characteristics of *FOXG1* syndrome that distinguishes it from other monogenic hyperkinetic movement disorders or neurodegenerative diseases.^{6,32} The hyperkinetic movement disorder, although affecting quality of life, was stable over time, never evolved into status dystonicus, and did not lead to any of the complications of severe dystonia that can be observed in other developmental or degenerative neurologic disorders.^{6,32}

A previous report suggested that *FOXG1* syndrome could be classified as an epileptic-dyskinetic encephalopathy¹⁸ like *ARX*- and *STXBPI*-related encephalopathies. Our data show that epilepsy is not a consistent feature, unlike dyskinetic-hyperkinetic movements. Although epilepsy affected 79% of patients reported here, which is within the range of previous reports (from 57%⁷ to 86%⁵), it did not show a particular seizure pattern that could help the clinician to define a specific epilepsy syndrome.

Since the first report that *FOXG1* mutations can be responsible for congenital Rett variant, a number of publications have emphasized the differences between these disorders.³³ Here, by applying the congenital Rett variant criteria,¹⁴ we confirm that the majority of patients with the *FOXG1* syndrome do not meet the criteria for congenital Rett variant. At all ages, *FOXG1* syndrome is more severe with respect to ambulation, reciprocity, and receptive language and has more disordered sleep, compared with Rett syndrome, as well as lacking the regression observed in Rett syndrome. These findings further reinforce that *FOXG1* disorder is clinically separable from Rett syndrome, with distinct clinical presentation and natural history. It is important that patients with *FOXG1* disorder receive appropriate counseling about medical comorbidities and natural history related to their disorder, avoiding the confusion with Rett syndrome.

The number of reported *FOXG1* mutations is now large enough to search for genotype-phenotype correlations in *FOXG1* syndrome. We observed that patients carrying mutations in the N-terminal domain and large deletion of *FOXG1*, which are the most common mutation types, show the most severe presentation and MRI anomalies, while those carrying mutations in the FBD or C-terminal domain were less severely affected. In previous series, a milder phenotype was observed in patients with missense variants in the FBD conserved site.⁷ However, the differences were found in items related to sitting, walking, and functional hand use, which are commonly severely impaired in all *FOXG1* mutation patients.⁷ Using covariance and cluster analyses, we highlighted relationships between gyral and myelination patterns in patients with *FOXG1* disorder. However, identical hotspot mutations c.256dupC and c.406dupG can be associated with highly variable features, such as variable epilepsy severity or degree of corpus callosum anomalies, underlining the importance of being cautious about predicting phenotype on the basis of genotype in the context of genetic counseling. This suggests that factors beyond the primary mutation can influence disease severity, including genetic modifiers and epigenetic and environmental factors.

The complexity and the poor reproducibility of genotype-phenotype relationships in *FOXG1* syndrome probably reflects the pleiotropic and nonredundant roles of *Foxg1* in vertebrate brain development.

This study, one of the largest to date, provides evidence that *FOXG1* mutations are responsible for a specific and recognizable neurodevelopmental disorder with a high degree of variability. We have expanded the phenotypic spectrum by defining 3 key brain imaging features of *FOXG1* syndrome, noting that the degree of cortical abnormality is not correlated with the severity of the corpus callosum malformation. Moreover, our data confirm that mutations leading to the loss of the FBD domain, lead to the most severe clinical presentation of *FOXG1* syndrome. The pathophysiology of such complex genotype-phenotype relationships reflects the pleiotropic and nonredundant roles of *Foxg1* during development.

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