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The hyperkinetic movement disorder of *FOXG1*-related epileptic–dyskinetic encephalopathy

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***FOXG1 Syndrome Study Group members are listed in Acknowledgements.**
This article is commented on by Parker on page 15 of this issue.

PUBLICATION DATA
Accepted for publication 12th June 2015.
Published online 6th September 2015.

ABBREVIATIONS
FOXG1 Forkhead Box G1

AIM Forkhead Box G1 (*FOXG1*) syndrome is a developmental encephalopathy characterized by postnatal microcephaly, structural brain abnormalities, facial dysmorphisms, severe delay with absent language, defective social interactions, and epilepsy. Abnormal movements in *FOXG1* syndrome have often been mentioned but not characterized.
METHOD We clinically assessed and analysed video recordings of eight patients with different mutations or copy number variations affecting the *FOXG1* gene and describe the peculiar pattern of the associated movement disorder.
RESULTS The age of the patients in the study ranged from 2 to 17 years old (six females, two males). They had severe epilepsy and exhibited a complex motor disorder including various combinations of dyskinetic and hyperkinetic movements featuring dystonia, chorea, and athetosis. The onset of the movement disorder was apparent within the first year of life, reached its maximum expression within months, and then remained stable.
INTERPRETATION A hyperkinetic–dyskinetic movement disorder emerges as a distinctive feature of the *FOXG1*-related phenotype. *FOXG1* syndrome is as an epileptic–dyskinetic encephalopathy whose clinical presentation bears similarities with *ARX*- and *STXBP1*-gene related encephalopathies.

Forkhead Box G1 (*FOXG1*), an evolutionarily conserved winged-helix transcriptional repressor, plays an important role in telencephalon development[1] and is a crucial component of the transcription regulatory network that controls proliferation, differentiation, neurogenesis, and neurite outgrowth.[2,3]

The core phenotype of the *FOXG1* syndrome includes postnatal microcephaly, severe developmental delay with defective social interactions, and absence of language. Additional manifestations include behavioural disturbances, stereotypies, dyskinesia, and epilepsy.[4–6] Agenesis of corpus callosum, simplified gyral pattern, and cortical thickening of the frontal lobes are commonly observed on brain magnetic resonance imaging.[4] Characteristic facial dysmorphisms, including round face, flat midface and forehead, epicanthal folds, depressed nasal bridge, upturned nose, and abnormally formed ears have also been described, most often in patients with large 14q12 deletions.

Abnormal movements in *FOXG1* syndrome have been frequently mentioned,[4,7,8] but a systematic description is lacking. We describe eight patients with different mutations or copy number variations affecting the *FOXG1* gene and characterize the associated peculiar pattern of movement disorder.

CASE REPORT

We obtained clinical data and brain magnetic resonance imaging findings from eight Italian patients (six females, two males) with *FOXG1*-related encephalopathy as diagnosed by clinical and genetic criteria. We also assessed all the patients with repeated video recordings in order to characterize their abnormal motor pattern. We followed them up with serial clinical evaluations in order to appreciate the movement disorder progression and any relevant clinical changes. We obtained blood or DNA samples from patients and their parents after written informed consent. Parents gave their consent to publish the results. The study was approved by the Institutional Review Board of the Tuscany Region, Italy.

Neurological examination revealed typical clinical and behavioural features of the *FOXG1* syndrome (Table I)

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including postnatal microcephaly (7/8 patients), facial dysmorphisms (8/8), axial hypotonia (6/8), absence of language (8/8), severe developmental delay (8/8), poor sleep pattern (6/8), hyperactivity (6/8), and crying or inappropriate laughing (5/8) (Table I). Brain magnetic resonance imaging revealed corpus callosum dysgenesis (6/8 patients) and a simplified gyral pattern in some patients (3/8) (Fig. 1). Most patients exhibited focal seizures (5/8), which had appeared from age 5 months to 6 years, often in association with epileptic spasms and requiring multiple antiepileptic medications. No significant period of remission of seizures was observed. Electroencephalography showed slow background, multifocal spikes, and sharp waves. Five patients exhibited a severe movement disorder (Patients 1, 2, 3, 5, and 7), manifested as continuous dyskinesia with a mixture of hyperkinetic, dystonic, choreic, and athetoid movements mainly involving the four limbs and face, and stereotypic movements that largely impaired normal hand use and fine motor skills. Dyskinesia of the mouth–tongue area was a prominent feature and was associated with hand-mouthing and sialorrhoea. There was, however, no evidence of dysphagia or swallowing difficulties. These patients had not reached independent walking and were overall severely disabled by the movement disorder. Two patients (Patients 6 and 8) exhibited only mild distal dyskinetic movements involving the arms and were able to walk with support. One patient (Patient 4), carrying a 14q12 duplication, had a distinctively less severe phenotype featuring mild hyperkinetic and perseverative stereotyped hand–mouth movements. Abnormal movements disappeared during sleep. The abnormal movements were first noticed between the fifth and twelfth month of life and had not changed in severity and semiology at last follow-up, between age 2 years and 17 years, as documented by video recordings (see Videos S1–S4, online supporting information).

Three patients were treated with antidyskinetic drugs (Patients 1, 5, and 7) (Table I). Limited benefit was obtained using pimozide in two patients (Patients 1 and 7).

Genetic analysis through multiplex ligation-dependent probe amplification (SALSA P075 version A1, MRC-Holland, Amsterdam, the Netherlands) revealed two de novo deletions of the *FOXG1* gene in Patients 1 and 3. Array comparative genomic hybridization confirmed a 2.5Mb deletion in Patient 1 (between nucleotides 27 154 000 and 29 743 000) and a 9.1Mb deletion in Patient 3. This is the largest deletion reported so far at chromosome 14q12 (between nucleotides 25 168 212 and 34 247 857), which includes the *FOXG1* and flanking genes. In Patient 2, array comparative genomic hybridization revealed a de novo 14q12 deletion of 2.8Mb (minimal deleted interval 27 265 913–30 511 768). In Patient 4, multiplex ligation-dependent probe amplification identified a de novo duplication involving *FOXG1*, which was confirmed by array comparative genomic hybridization to be 7.3Mb in length (minimal deleted interval 24 453 489–31 784 795) (Table I). Array comparative genomic hybridization was performed using the whole genome 180K Agilent platform (Agilent Technologies, Santa Clara, CA, USA). Physical positions correspond to the UCSC genome browser (genome assembly Feb 2009, hg19, http://genome.ucsc.edu).

Sanger sequencing detected four heterozygous *FOXG1* intragenic point mutations, including a novel frameshift mutation c.298delC (p.Gln100Serfs*92) in Patient 5, a nonsense mutation c.136C>T (p.Q46X) in Patient 6, a recurrent frameshift mutation c.460dupG (p.Glu154Glyfs*301) in patient 7, and a frameshift mutation c.256delC (p.Gln86Argfs*106) in Patient 8 (*FOXG1* Genbank Accession Number NM_005249).

All four point mutations were de novo and caused loss of all three downstream functional critical domains of the gene: the forkhead domain (FHD), which allows the binding to DNA, and the Groucho binding domain (GBD) and the JARID1B binding domain (JBD), which recruit transcriptional corepressor proteins. All mutations are predicted to cause haploinsufficiency.

What this paper adds

- Assessment of movement disorder in patients with *FOXG1* mutations or copy number variations.
- *FOXG1* syndrome can be defined as an epileptic–dyskinetic encephalopathy.

DISCUSSION

Eighty-eight mutations involving the *FOXG1* gene have been described in more than 90 patients and include 36 intragenic sequence changes (missense, nonsense, and frameshift), 27 deletions, 17 duplications, and 8 complex rearrangements.[9]

Despite the relatively large number of identified mutations and reported patients, genotype–phenotype correlations are emerging slowly. Initial descriptions had ostensibly labelled *FOXG1*-related phenotypes as a 'congenital variant' of Rett syndrome.[10] Only the subsequent identification of additional patients with *FOXG1* mutations, having different ages and exhibiting sufficiently distinctive clinical features, suggested the '*FOXG1* syndrome' to be a specific 'developmental encephalopathy'.[4] As is often the case with newly identified clinical entities, after the core phenotypic features have initially been characterized and a causative gene found, collection of a larger number of observations, including less typical cases, allows a proper characterization of the whole clinical spectrum.[5]

In our series, all the patients exhibited the common clinical symptoms previously associated with *FOXG1* syndrome.[4,6,8] Almost all patients also exhibited a prominent movement disorder of variable severity. Five patients (1, 2, 3, 5, and 7) harbouring deletions or mutations exhibited a complex and more severe movement disorder initially noticed within first year of life and featuring hyperkinetic, dystonic, choreic, and athetoid movements, mainly involving the orobuccal area and extremities, with upper limb predominance severely interfering with voluntary movement (Video S1–S4). Two patients with truncating mutations exhibited only distal dyskinetic movements of the upper extremities (Patients 6 and 8), which in this series

Table I: Clinical features and therapy of patients with *FOXG1* mutations

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Sex	F	M	F	F	F	F	M	F
Age (y:mo)	9:0	3:6	2:0	10:0	10:0	17:0	2:6	13:0
FOXG1 mutation/ CNV (Mb)	Del (2.5Mb) on 14q12, involved genes: *FOXG1, C14orf23, PKRD1* (de novo)	Del (2.8Mb) on 14q12, involved genes: *FOXG1, C14orf23, PKRD1, SCFD1, G2E3, SCFD1, COCH, STRN3* (de novo)	Del (9.1Mb) on 14q12, involved genes: *STXBP6, NOVA1, FOXG1, C14orf23, PKRD1, SCFD1, G2E3, COCH, STRN3, AP4S1, HECTD1, DTD2, NUBPL, ARHGAP5, AKAP, NPAS3* (de novo)	Dup (7.3Mb) on 14q12, involving *FOXG1* and additional 50 genes (de novo)	c.298delC; p.Gln100Serfs*92 (de novo)	c.136C>T, p.Q46X (de novo)	c.460dupG p.Glu154Glyfs*301 (de novo)	c.256delC p.Gln86Argfs*106 (de novo)
Possible effect of the *FOXG1* mutation/CNV	Haploinsufficiency	Haploinsufficiency	Haploinsufficiency	Gene dosage effect	Loss of all the *FOXG*1 functional domains	Loss of all the *FOXG*1 functional domains	Loss of all the *FOXG*1 functional domains	Loss of all the *FOXG*1 functional domains
Phenotype								
Microcephaly (SD; age, y:mo)	Postnatal (−4.5; 0:3)	Postnatal (−3.5; 0:3)	Postnatal (−4.0; 0:8)	− (−2 at birth; −1; 3:0)	Postnatal (−2.5; 0:5)	Postnatal (−2.8; 0:4)	Postnatal (−4.0; 1:2)	Postnatal (−3.5; 1:6)
Developmental delay	+	+	+	+	+	+	+	+
Intellectual disability	+	+	+	+	+	+	+	+
Language development	−	−	−	−	−	−	−	−
Walking	−	−	−	+	−	+	−	−
Hypotonia	+	+	+	+	−	−	+	+
Behaviour								
Social Interactions	−	+/−	−	+	+/−	−	−	+
Sleep disturbances	+	+	+	+	−	+	+	−
Irritability	+	+	+	+	+	−	+	−
Hyperactivity	+	+	−	+	+	−	+	+
Crying	+	+	−	+	+	−	+	−
Laughing (Inappropriate)	+	+	−	−	+	−	+	−
Facial dysmorphisms	Flat forehead and midface, bilateral epicanthal folds, thin upper lip, large abnormally formed ears	Midface hypoplasia, thin upper lip, bulbous nasal tip, anteverted nares	Flat forehead, long eyelashes, tented upper lip, bulbous nasal tip	Round face, exotropia, small nose, simple shaped ears	Flat forehead and midface, bilateral epicanthal folds, thin upper lip, bulbous nasal tip, anteverted nares, diastasis of teeth, thick and everted lower lip	Midface hypoplasia, slight upslanting palpebral fissures, bulbous nasal tip and anteverted nares, prognathism, diastasis of teeth, thick and everted lower lip	Flat forehead, bulbous nasal tip and anteverted nares, everted lower lip	Flat forehead, thick eyebrows with mild synophris, long eyelashes, tented upper lip, prominent incisors
Epilepsy								
Age at seizure onset (y:mo)	1:6	0:11	0:8	0:7	6:0	0:5	0:11	1:4
Seizure types	Tonic, spasms	Focal	Spasms	Focal, spasms	Focal	Focal, spasms	Focal	Tonic, spasms
Interictal EEG	Slow background activity, multifocal spikes	Slow background activity, multifocal spikes	Slow background activity	Slow background activity, multifocal spikes	Slow background activity, multifocal spikes	Slow background activity, multifocal spikes	Slow background activity, multifocal spikes	Slow background activity, diffuse theta activity

Table I: Continued

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Motor disturbances								
Age at onset (y:mo)	1:0	1:0	0:6	0:7	1:0	0:5	1:0	0:6
Stereotypies	+	–	+	+	+	+	+	+
Dyskinesia	+	+	+	+	+	+	+	+
Antiepileptic drugs[a]	CBZ, RUF, LEV, PB	VPA	VGB	VPA, CLB, LTG, VGB, ACTH, vitamin B6	VPA, CLB	PB, VGB, CBZ, ESM	VPA, CBZ, CLN, PB	CLB, VPA vitamin B6
Antidyskinetic drugs[a]	PMZ, BPR	–	–	–	TRB	–	TRIH, PMZ, CLN, TRB	–
Brain MRI abnormalities								
Corpus callosum hypoplasia	+	+	+	–	+	–	+	+
Simplified gyral pattern of frontal lobes	+	–	+	–	+	–	–	–
Delayed myelination/white matter reduction	–	–	+	+	+	–	+	+

[a]Drugs are listed according to the sequence they were used. F, female; M, male; y, years; mo, months; del, deletion; dup, duplication; EEG, electroencephalogram; CBZ, carbamazepine; RUF, rufinamide; LEV, levetiracetam; PB, phenobarbital; VPA, valproate; VGB, vigabatrin; CLB, clobazam; LTG, lamotrigine; ACTH, adrenocorticotropic hormone; ESM, ethosuximide; CLN, clonazepam; PMZ, pimozide; BPR, biperiden; TRB, tetrabenazine; TRIH, trihexyphenidyl hydrochloride; MRI, magnetic resonance imaging; +/–, mildly impaired.

Figure 1: Representative brain magnetic resonance imaging showing the main anatomic abnormalities in two patients in comparison to a normal brain. (a), (c), and (e) sagittal sections passing through the midline and showing the corpus callosum and midline strictures. (b), (d), and (f) axial sections passing through the Sylvian fissures and the lateral ventricles. (a) and (e) T1-weighted images; (b), (c), (d), and (f) T2-weighted images. (c) and (e) demonstrate corpus callosum hypoplasia (arrows). (d) and (f) show a simplified gyral pattern in the frontal lobes (arrows) which also appear considerably reduced in volume. (f) there is also marked enlargement of the lateral ventricles (asterisk), with the basal ganglia and thalami protruding into the ventricular lumen.

represents the mild end of the movement disorder spectrum. No significant worsening or attenuation of the abnormal movements was apparent in any of the patients over time.

Assessment of our patients and the review of previous reports in which the movement disorder was mentioned, suggest its presence in most cases, with a variable combination of dyskinetic and hyperkinetic movements and, with few exceptions,[7] an age at onset within the first years of life.

We could not find a genotype–phenotype correlation between the type of genetic defect affecting *FOXG1* and the severity of the movement disorder since all the truncating mutations and deletions we observed (Patients 1–3, 5–8) were predicted to cause haploinsufficiency. The duplica-

tion at 14q12 in Patient 4 was associated with hand–mouth stereotypies and less prominent hyperkinetic movements. Clinical features in patients with 14q12 duplications have been consistently reported to differ from those observed in association with deletions and inactivating mutations, suggesting that the phenotype is markedly influenced by *FOXG1* gene dosage.

Overall, the severe movement disorder observed in most patients in this series is also remarkably different from that described in Rett syndrome, in which hyperkinetic choreoathetoid movements are unusual and not as prominent.[11]

Unfortunately, no effective antidyskinetic treatment for these patients has been reported to date and our experience does not allow us to draw any conclusion with respect to treatment issues. However, we noticed that among the three patients who performed antidyskinetic therapy (Table I), the two who were treated with pimozide, exhibited some improvement (Patients 1 and 7). This preliminary observation might encourage further therapeutic trials against the hyperkinetic–dyskinetic movements. We did not observe any (beneficial or worsening) effect of the different antiepileptic medications on the movement disorder either.

The *FOXG1*-related phenotype can be classified as an epileptic–dyskinetic encephalopathy as are *ARX*-[12–14] and *STXBP1*-related[15] encephalopathies. We recommend the consideration of *FOXG1* mutational analysis in the diagnostic assessment of patients with developmental delay, epilepsy, and prominent dyskinetic movements.

ACKNOWLEDGEMENTS

This work was supported by funding from the European Union Seventh Framework Programme FP7/2007–2013 under the project DESIRE (grant agreement n°602531) (to RG). The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

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SUPPORTING INFORMATION

The following additional material may be found online:

Video S1: *Patient 1*: Severe hyperkinetic–dyskinetic movement disorder affecting all four limbs, with prominent hand–mouth–tongue movements. This patient is severely affected, has a very poor control of her posture, and is non-ambulatory.

Video S2: *Patient 5*: Hyperkinetic–dyskinetic movements affecting the upper limbs. Finalized hand movements are impaired. This patient is severely affected, has a very poor control of her posture, and is non-ambulatory.

Video S3: *Patient 7*: Severe generalized hyperkinetic–dyskinetic movement disorder affecting the four limbs and the face, markedly impairing fine motor skills. The male's motor development is severely delayed.

Video S4: *Patient 8*: Mild dyskinetic movements involving the upper extremities. There are no dyskinetic movements in the lower extremities. This female is able to walk with support.

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