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Familial Recurrences of *FOXG1*-Related Disorder: Evidence for Mosaicism

Kelly Q. McMahon^{1,*}, Apostolos Papandreou^{2,3,4}, Mandy Ma⁵, Brenda J. Barry⁶, Ghayda M. Mirzaa⁷, William B. Dobyns⁷, Richard H. Scott^{4,8}, Natalie Trump⁸, Manju A. Kurian^{2,3}, and Alex R. Paciorkowski^{1,9}

¹Department of Neurology, University of Rochester Medical Center, Rochester, New York

²Developmental Neurosciences, UCL-Institute of Child Health, London, United Kingdom

³Department of Neurology, Great Ormond Street Hospital, London, United Kingdom

⁴Genetics and Genomics Medicine, UCL-Institute of Child Health, London, United Kingdom

⁵University of Buffalo School of Medicine, Buffalo, New York

⁶Children's Hospital Boston, Boston, Massachusetts

⁷Department of Pediatrics, Division of Genetic Medicine, University of Washington, Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, Washington

⁸North East Thames Regional Genetics Service, Great Ormond Street Hospital, London, United Kingdom

⁹Departments of Pediatrics and Biomedical Genetics, Center for Neural Development and Disease, University of Rochester Medical Center, Rochester, New York

Abstract

FOXG1-related disorders are caused by heterozygous mutations in *FOXG1* and result in a spectrum of neurodevelopmental phenotypes including postnatal microcephaly, intellectual disability with absent speech, epilepsy, chorea, and corpus callosum abnormalities. The recurrence risk for de novo mutations in *FOXG1*-related disorders is assumed to be low. Here, we describe three unrelated sets of full siblings with mutations in *FOXG1* (c.515_577del63, c.460dupG, and c.572T>G), representing familial recurrence of the disorder. In one family, we have documented maternal somatic mosaicism for the *FOXG1* mutation, and all of the families presumably represent parental gonadal (or germline) mosaicism. To our knowledge, mosaicism has not been previously reported in *FOXG1*-related disorders. Therefore, this report provides evidence that germline mosaicism for *FOXG1* mutations is a likely explanation for familial recurrence and should be considered during recurrence risk counseling for families of children with *FOXG1*-related disorders.

*Correspondence to: Kelly Q. McMahon, MS, CGC, University of Rochester Medical Center, Department of Neurology, 601 Elmwood Ave, Rochester, NY 14642. KellyQ_McMahon@urmc.rochester.edu.

Keywords

FOXG1; 14q12; gonadal mosaicism; familial recurrence

INTRODUCTION

The *FOXG1* gene, on chromosome 14q12, encodes the transcription factor forkhead box G1 that is expressed in the fetal and adult brain. *FOXG1* is critically important in the regulation of neurogenesis in the telencephalon [Martynoga et al., 2005]. *FOXG1*-related disorders are a spectrum of neurodevelopmental phenotypes [Papa et al., 2008; Jacob et al., 2009; Florian et al., 2012], caused by de novo heterozygous abnormalities in *FOXG1*. Intragenic mutations of *FOXG1* and deletions of 14q12 encompassing *FOXG1* result in postnatal microcephaly, intellectual disability with absent speech, variable epilepsy, corpus callosum abnormalities, generalized hypotonia, and choreiform movements [Bisgaard et al., 2006; Ariani et al., 2008; Papa et al., 2008; Jacob et al., 2009; Bahi-Buisson et al., 2010; Mencarelli et al., 2010; Philippe et al., 2010; Kortüm et al., 2011; Le Guen et al., 2011; Seltzer et al., 2014]. Additionally, larger deletions of 14q12 involving *FOXG1* have been associated with dysmorphic facial features [Bisgaard et al., 2006; Papa et al., 2008; Jacob et al., 2009]. Duplications of 14q12 involving *FOXG1*, on the other hand, result in developmental delay/intellectual disability with absent speech, infantile spasms, and an autism phenotype [Yeung et al., 2009; Brunetti-Pierri et al., 2011; Paciorkowski et al., 2011; Striano et al., 2011; Tohyama et al., 2011; Bertossi et al., 2013; Seltzer et al., 2014].

Mosaicism is described as more than one genetically or cytogenetically discrete cell lines within an organism [Youssoufian and Pyeritz, 2002]. Mosaicism can be present either in the somatic cells and gonadal cells, giving an offspring recurrence risk of up to 50% or confined to the gonadal cells (or germline), in which case it typically involves a subset of the gonadal cells depending on the gonadal generation in which the mutation occurred [van der Meulen et al., 1995]. Individuals with somatic mosaicism may be unaffected or mildly affected, depending on the tissue distribution and burden of mutation in a given tissue, while individuals with gonadal mosaicism are generally unaffected [Hall, 1988]. Familial recurrence of a presumed de novo mutation in a child [Wijsman, 1991] has been reported in several conditions in which gonadal mosaicism has been well described, including Duchenne muscular dystrophy [Bakker et al., 1987], osteogenesis imperfecta type II [Byers et al., 1988], and neurofibromatosis type I [Lázaro et al., 1994].

Here, we describe three unrelated sets of full siblings with recurrence of *FOXG1* mutation. In one family, with three affected children, the *FOXG1* mutation was documented in maternal DNA from blood, skin, and saliva implicating germline mosaicism as the likely disease mechanism. The recurrence in the other two families also likely resulted from parental germline mosaicism, although somatic mosaicism was not evident on parental testing. Two of the sibling pairs were published previously [Seltzer et al., 2014], and now we discuss the implications for genetic counseling. To our knowledge, gonadal mosaicism has not previously been reported in *FOXG1*-related disorders.

METHODS

Patients

Patients were ascertained through the Genetic Studies of Developmental Brain Disorders research program (Rochester) and the Study of Inherited Metabolic Diseases program (London, UK). Informed consent was obtained with approval of the University of Rochester Research Studies Review Board and the National Research Ethics Service (NRES) in the UK (NRES Committee: London – Bloomsbury, REC reference: 13/LO/0168, IRAS project ID: 95005). Retrospective clinical records and brain MRI scans were reviewed by the investigators.

FOXG1 Sequencing

Targeted single gene *FOXG1* sequencing (NM_005249) was performed on families DB12-017 and DB13-029 as part of their routine clinical evaluations. Skin, saliva, and blood DNA samples were obtained from family DBL01-010 and *FOXG1* sequencing was performed at the Great Ormond Street Hospital Genetics laboratory using the diagnostic multiple gene panel test targeted for disorders causing early infantile epilepsy and developmental delay.

RESULTS

Clinical Report

Family 1—DB12-017a1, a female (Fig. 1A), was the first child born to healthy, non-consanguineous parents with an unremarkable family history. Pregnancy was uncomplicated and she was delivered by cesarean section due to failure to progress. Birth weight was 3.3 kg with no postnatal complications. At age 9 years, head circumference was -4 SD. She could crawl and sit with assistance but was not able to walk independently. She had constipation, gastroesophageal reflux, pain insensitivity, and sensitivity to heat. She had strabismus surgically corrected and required G-tube placement for feeding. She had limited purposeful hand movements and was nonverbal. She was diagnosed with complex partial seizures at 18 months and was on one anti-seizure medication.

DB12-017a2, a female (Fig. 1B), was the second child born to the same parents. Pregnancy was uncomplicated. She was born full term by scheduled repeat cesarean section. She weighed 3.8 kg at birth and had jaundice requiring phototherapy. At age 6 years, head circumference was -4 SD; she could roll, scoot, and walk with assistance. She was nonverbal but could use pictures for communication. She had constipation, pain insensitivity, and strabismus. She could feed herself by mouth with assistance and did not require a G-tube for feeding. She had limited purposeful hand movements. Unlike her sibling, DB12-017a1, she has never had seizures. The *FOXG1* mutation c.515_577del63/p.Gly172_Met192del was identified in both siblings in this family by clinical testing.

Family 2—DB13-029a1, a female (Fig. 1C), was the first child born to healthy, consanguineous parents with an unremarkable family history. Pregnancy was uncomplicated. She was born at full-term by spontaneous vaginal delivery and weighed 3.4

kg. She remained in the neonatal intensive care unit (NICU) for difficulty eating and failure to thrive. A patent ductus arteriosus (PDA) was subsequently identified and closed on its own without surgical intervention. At age 25 years, she was in an adult day care program. She could not walk independently and had limited purposeful hand movements. She had constipation, gastroesophageal reflux, scoliosis, strabismus, and cold extremities. She could eat pureed food by mouth with assistance but primarily required a G-tube for feeding. She was nonverbal and laughed and smiled inappropriately. She was diagnosed with generalized tonic-clonic seizures at 2 years old, was treated with valproic acid, had her last seizure at 15 years of age, and no longer required anti-seizure drugs.

DB13-029a2, a male (Fig. 1D), was the third child born to the same parents. There is one unaffected sibling between DB13-029a1 and DB13-029a2. Pregnancy was uncomplicated. He was born full-term by spontaneous vaginal delivery and weighted 4.1 kg with no postnatal complications. At age 22 years, he cannot walk independently. He had constipation, gastroesophageal reflux, strabismus, and scoliosis. He required a G-tube for feeding. He was nonverbal, had limited purposeful hand movements, and laughed and smiled inappropriately. He was diagnosed with generalized tonic-clonic seizures at 2 years old and continued to require two anti-seizure drugs. The *FOXG1* mutation c.460dupG p.Glu154GlyfsX301 was identified in both siblings in this family by clinical testing.

Family 3—Subject DBL01-010a1, a female, was born at term by spontaneous vaginal delivery. Pregnancy was unremarkable. She had low muscle tone as an infant and febrile convulsions at 4 months of age, followed by absence seizures at 3 years. She is currently 18 years old and on lamotrigine monotherapy for seizures (facial grimacing and perioral cyanosis followed by limb jerking) occurring infrequently, every few months. There have been no hospitalizations for complications of epilepsy. She sat at 18 months and walked independently at 2 years of age. She can speak in sentences and is in a special needs school. She is able to feed and dress herself, can play basic games, but has limited eye contact and a high pain threshold. Head circumference is currently 57.5 cm (91st–98th centile).

Subject DBL01-010a2, a female and the second child born to the same parents, was born at 42 weeks gestation through spontaneous vaginal delivery following an uncomplicated pregnancy. The neonatal and early infantile period was unremarkable. During childhood, she showed delay in achieving milestones, sitting at 1 year and walking at 2 years of age. She had three episodes of absence seizures associated with fever (two in early childhood and one at 11 years of age) but was never diagnosed with epilepsy and at 13 years of age is not on anti-seizure medication. Head circumference is 56 cm (between the 75th and 91st centile). She has better language skills than her other affected siblings and is in a mainstream classroom with educational support. She is able to perform activities of daily living with minimum assistance.

Subject DBL01-010a3, a male, is the youngest of the three siblings. He was born at term by normal vaginal delivery following an uncomplicated pregnancy. He developed seizures at 4 years of age, which are primarily absences in semiology. At the age of 11 years, he is currently well-controlled on valproic acid, and his last seizure was over 2 years ago. Head circumference is 55 cm (just above 50th centile). He walked at 3.5 years of age, has around

20 words that are used consistently, but his receptive language skills are described as better than his expressive language skills. He requires help with dressing and other fine motor tasks. The *FOXG1* mutation c.572T > G/p.Met191Arg was identified in all three siblings in this family. Additionally, parental studies revealed the same mutation in maternal DNA extracted from blood, skin, and saliva. The chromatographic tracing of the variant allele in all maternal samples was consistently lower than expected for a heterozygote and in keeping with somatic mosaicism.

Brain Imaging

Brain MRI scans performed clinically were reviewed for subjects DB12-017a1, DB12-017a2, DB13-029a2, DBL01-010a1, DBL01-010a2, and DBL01-010a3. Hypoplasia of the genu of the corpus callosum was seen in subjects DB12-017a1, DB12-017a2, and DB13-029a2, along with mild underdevelopment of the frontal lobes (Fig. 2A–C). Subjects DBL01-010a1 and DBL01-010a2 had normal callosal and frontotemporal structure appearances but mild prominence of the cerebellar fissures. Subject DBL01-010a3 had mild hypoplasia in the posterior part of the corpus callosum associated with parietal underdevelopment, as well as a greater degree of cerebellar hypoplasia which was more pronounced in the cerebellar vermis. DB13-029a1 did not have scans available for review. The genotypes and phenotypes of subjects in this report are summarized in Table I.

DISCUSSION

FOXG1 Familial Occurrence

In males, spermatogenesis begins at puberty and continues throughout adult life. In contrast, oogenesis in females begins during embryogenesis during which oogonia differentiate into primary oocytes, which then enter and arrest in prophase of Meiosis I until ovulation [Chandley, 1991]. It is estimated that the number of gonadal generations is approximately 23 in females and 30 in males followed by an additional 23 divisions per year following puberty in males [Wijsman, 1991]. The distinction between gonadal and somatic mosaicism is difficult [Youssoufian and Pyeritz, 2002] because mosaicism in tissues is random and the tissues sampled by any given method or study may not be mosaic. The parents of all siblings we report here were clinically unaffected. Somatic mosaicism in the parents of the DB12-017 and DB13-029 families was not detected by Sanger sequencing of both blood and saliva-derived DNA. We did find the *FOXG1* mutation present in the mother of the DBL01-010 family, indicating both gonadal and somatic mosaicism. Somatic mosaicism has not been described in *FOXG1*-related disorders before.

The recurrence risk for a single occurrence of a heterozygous de novo mutation, with unaffected parents, is generally assumed to be low [Emery, 1986]. However, as more evidence emerges that gonadal mosaicism is not as uncommon as once thought, recurrence risks should be adjusted [Hall, 1988]. While the number of gonadal cells containing a mutation depends on the stage at which the mutation occurred [Zlotogora, 1998], this cannot be accurately predicted. Recurrence risks for unaffected couples with disorders can be calculated and are dependent on parental age, sex, and number of unaffected offspring [Campbell et al., 2014; Hartl, 1971; van der Meulen et al., 1995]. In practice, these factors

are difficult to model for individual genes and empiric data are generalizations at best. Additional factors influence recurrence risk, such as parental origin of mutation, particularly if the condition is known to have a strong paternal age effect [Wijsman, 1991; Campbell et al., 2014], and evidence of reduced penetrance [Emery, 1986]. Reduced penetrance and paternal age effect have not been demonstrated in *FOXG1* mutations.

Siblings DB12-017a1 and DB12-017a2 were the only children born to their unaffected parents. Using the empiric recurrence risks for gonadal mosaics available, it can be predicted that recurrence risk for an additional child is approximately 33% [van der Meulen et al., 1995]. Siblings DB13-029a1 and DB13-029a2 have one unaffected sibling. Recurrence risks with two affected children and one unaffected children, without known parental origin, are approximately 28% (van der Meulen et al., 1995). Siblings DBL01-010a1, DBL01-010a2, DBL01-010a3 were the only children born to this family, and given the documented maternal mosaicism, the recurrence risk could be as high as 50%.

It is also remarkable that the three siblings in family DBL01-010 have the most mild neurocognitive phenotypes described to date in *FOXG1*-related disorder. All three were able to walk independently. Two of the three had epilepsy, with seizures well-controlled on monotherapy in both cases. All three had verbal language, although dysarthria and speech delay was more prominent in the youngest. Interestingly, head circumferences were within normal limits and MRI brain findings were also mild in comparison to those with classical *FOXG1* syndrome.

In conclusion, we describe here three families with recurrence of intragenic *FOXG1* mutations out of 38 families with related phenotypes reported to date. This is evidence that germline mosaicism for *FOXG1* mutations is a likely explanation for familial recurrence in a child with clinically unaffected parents, and, therefore, has implications for recurrence risk counseling. The overall prevalence of *FOXG1*-related disorders is unknown, and, therefore, we cannot predict how common or uncommon this event may be. Given the number of cases reported to date, our data suggest gonadal mosaicism is present in 8% (3/38) of families currently reported. Most children with a *FOXG1* mutation and unaffected parents will be a result of a de novo mutation; however, parental mosaicism should be kept in mind during counseling for recurrence risks of *FOXG1*-related disorders.

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FIG. 1.
Subject DB12-017a1 at 9 years of age (A) and sibling DB12-017a2 at 6 years of age (B).
Subject DB13-029a1 at 25 years of age (C) and sibling DB13-029a2 at 21 years of age (D).

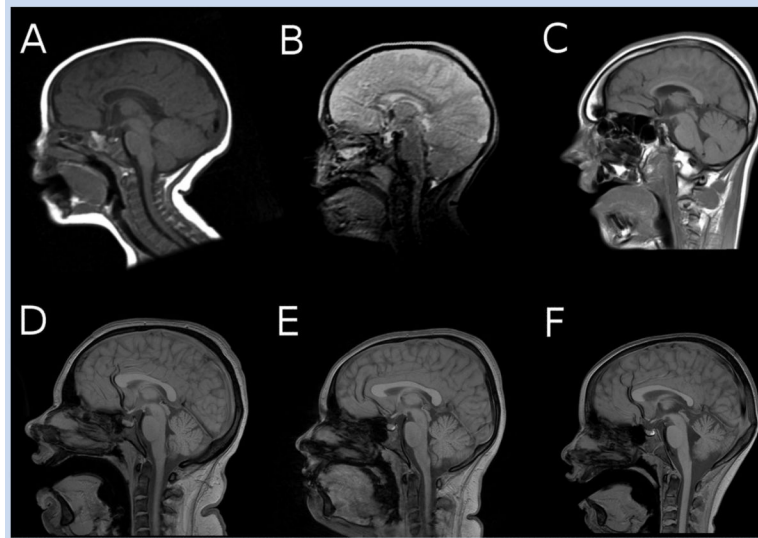


FIG. 2. Brain MRI of subjects DB12-017a1 (A), DB12-017a2 (B), and DB13-029a2 (C) demonstrating hypoplasia of genu of the corpus callosum. MRI scan of subjects DBL01-010a1 (D) and DBL01-010a2 (E) show mild prominence of the cerebellar fissures, whereas in DBL01-010a3 (F) mild hypoplasia of the splenium of the corpus callosum, along with a greater degree of cerebellar hypoplasia, are seen. All subjects in family DBL01-010 had normal anterior corpus callosum morphology.

TABLE I
Genomic and Clinical Features of Subjects With Familial Recurrences of *FOXP1*-Related Disorder

Subject	FOXP1 genotype	Sex	Age at time of study	Epilepsy	ID	Walking	Movements
DB12-017a1	c.515_577del63/p.Gly172_Met192del	Female	9 years 8 months	Complex partial	Yes	No	Hyperkinesia, with choreiform movements
DB12-017a2	c.515_577del63/p.Gly172_Met192del	Female	6 years 19 months	None	Yes	No	Hyperkinesia, with choreiform movements
DB13-029a1	c.460dupG p.Glu154GlyfsX301	Female	25 years 10 months	Generalized tonic-clonic	Yes	No	Hypokinetic, with hand stereotypies and increased tone.
DB13-029a2	c.460dupG p.Glu154GlyfsX301	Male	22 years	Generalized tonic-clonic	Yes	No	Hypokinetic, with hand stereotypies and increased tone.
DBL01-010a1	c.572T > G p.Met191Arg	Female	18 years	Absence	Yes	Yes	Hyperkinesia, with choreiform movements, dystonia
DBL01-010a2	c.572T > G p.Met191Arg	Female	13 years	None	Mild	Yes	Hyperkinesia, with choreiform movements, dystonia
DBL01-010a3	c.572T > G p.Met191Arg	Male	11 years	Absence	Yes	Yes	Hyperkinesia, with choreiform movements dystonia, orofacial dyskinesia