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A Biallelic Variant in *FRA10AC1* Is Associated With Neurodevelopmental Disorder and Growth Retardation

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Abstract

Objectives

Our objective was to identify the genetic cause in a family with a remarkable history of neurodevelopmental disease and growth retardation.

Methods

A neurologic evaluation was performed, and DNA samples were obtained from the affected siblings and parents to perform whole-exome sequencing (WES).

Results

Both siblings presented with dysmorphic features, failure to thrive, global developmental delay, generalized hypotonia, feeding problems, and congenital heart disease. WES revealed a homozygous nonsense variant in the *FRA10AC1* gene in both siblings.

Discussion

A recent study has reported the first association of biallelic variants in the spliceosomal C complex gene, *FRA10AC1*, with syndromic neurodevelopmental disease and growth retardation in 5 patients from 3 consanguineous families complex. In this study, we provide the first confirmation of the reported *FRA10AC1*-related neurologic syndrome in an additional family.

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Glossary

CES = clinical exome sequencing; **LOF** = loss of function; **WES** = whole-exome sequencing.

A recent study confirmed the association of biallelic inactivation of the spliceosomal C complex gene, *FRA10AC1*, with a syndromic neurodevelopmental disease and growth retardation in 5 patients from 3 consanguineous families.[1] The reported variants have an overall loss of function (LOF) effect following an autosomal recessive mode of inheritance. In this study, we report a consanguineous family with 2 affected children with a similar phenotype. Both patients were found to carry a homozygous LOF variant (nonsense) in *FRA10AC1*. Our study provides the first independent confirmation of the recently reported *FRA10AC1*-related neurodevelopmental disorder and growth retardation.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Whole-exome sequencing (WES) studies were indicated based on the phenotype and family history. Informed and disclosure consents were obtained from all participants as per an approved institutional review board protocol (TU MLT-2019-07).

Whole-Exome Sequencing

WES was performed and analyzed as previously described.[2] In brief, DNA was extracted from whole blood samples collected in EDTA tubes. The DNA libraries were prepared and sequenced using the SureSelect Kit (Agilent, Santa Clara, CA) and Hiseq2000 platform (Illumina, San Diego, CA), respectively. The Genome Analysis Toolkit was used for variant calling. Variants in known and candidate genes were classified as per the ACMG guidelines.[3]

Data Availability

All data are available from the corresponding author upon reasonable request.

Results

Case Presentation

Case 1 (IV: 1)

The proband was the first born of a consanguineous couple and a product of uneventful pregnancy and full-term, spontaneous vaginal delivery (Figure, A). The family history was remarkable for 3 cousins with a similar disease and other 3 cousins with confirmed genetic diagnosis of mucopolysaccharidosis type IVA (Figure, A). She was small for gestational age, with low birth weight of 1.9 kg (z score = −2) and no NICU admission. According to the family, she was fine until the age of 5 months when she was admitted with chest infection, followed by 2 more admissions for the same reason at the age of 6 and 9 months. At 9 months, she was noted to have failure to thrive, central hypotonia, protruding tongue, brachycephaly, microcephaly, global developmental delay, poor vision, strabismus, and dysmorphic features.

A full workup was performed, and she was found to have a right lower pulmonary vein stenosis. At the age of 3 years, she was diagnosed with severe oropharyngeal dysphagia and subsequently started on nasogastric tube feeding. She further developed a movement disorder and spasticity.

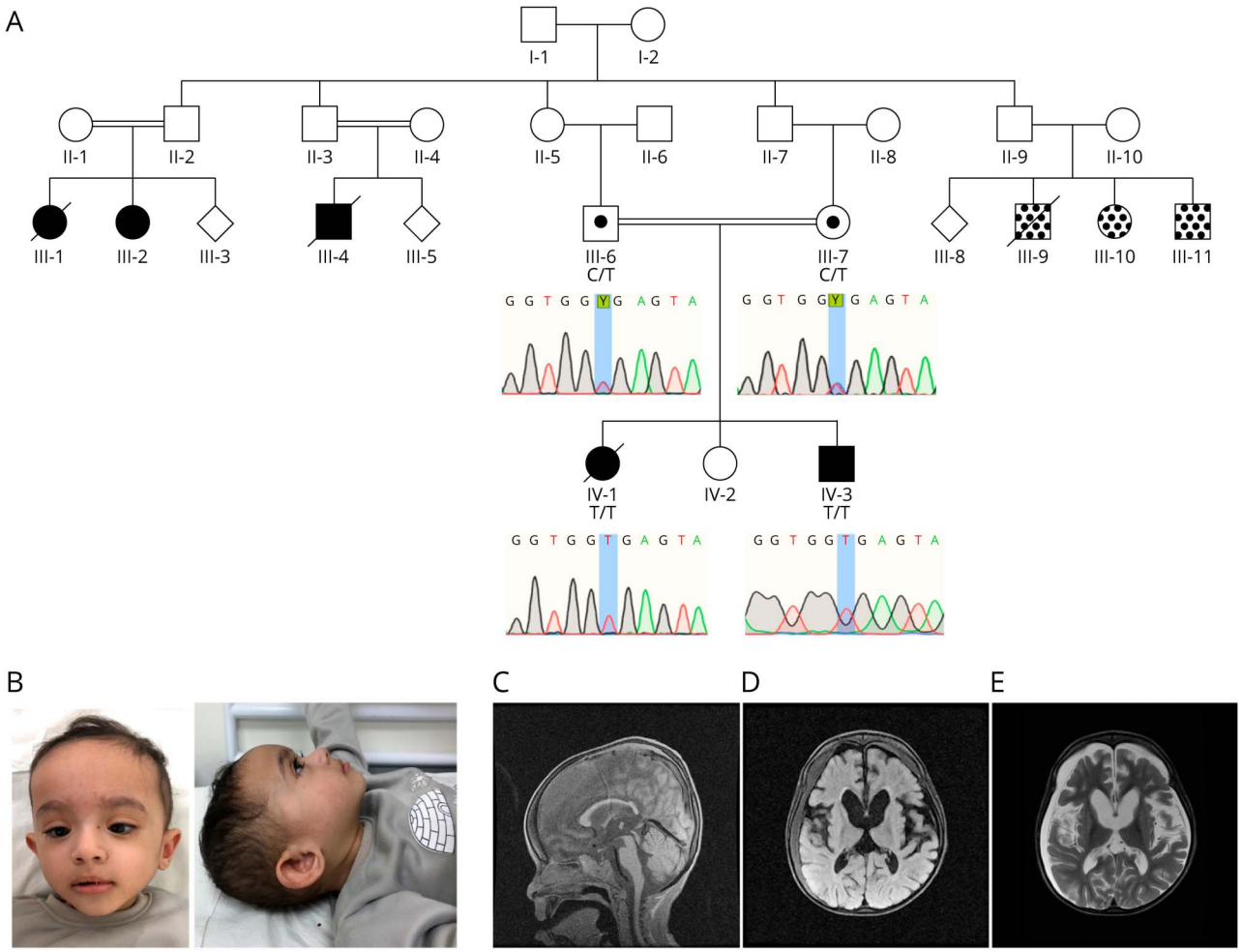
Visual evoked potential and electroretinogram were unremarkable. A brain MRI finding at the age of 3.6 years showed a thinning of the corpus callosum, mainly the posterior body and splenium, with diffuse brain atrophic changes with consequent prominence of lateral ventricles and sulci in addition to the extra axial CSF spaces (Figures, C–E). There were bilateral subdural fluid collections larger on the right side. MRI spectroscopy at the left basal ganglia showed mildly reduced N-acetylaspartate and elevated level of choline with no lactate peak.

Tandem mass spectrometry and urine gas chromatography-mass spectrometry studies were unremarkable. Her lactate levels were initially normal; however, with every hospitalization and illness, it increased and sometimes reached as high as 6.3 mmol/L (reference: <1.4 mmol/L). Ammonia levels were unremarkable except 1 occasion where she was very sick with an ammonia level of >200 umol/L (reference: < 50 μmol/L) and along with high lactate of 6.3 mmol/L, which was possibly due to liver dysfunction and sepsis. However, total homocysteine, carbohydrate-deficient transferrin, very long-chain fatty acids, serum amino acids, urinary mucopolysaccharides, and oligosaccharides were all unremarkable. Her coagulation profile (PT/PTT and INR) tended to be high during periods of illness, where the highest was PT 32.1 seconds (reference: 11.5–14.5)/PTT 42 seconds (reference: 30–41) and INR 3 seconds (reference: 09–1.3), when she was hospitalized with septic shock and she was on inotropes and mechanical ventilation.

Chromosomal microarray revealed no clinically significant copy number variants. However, several large regions of homozygosity (3 megabases or larger) were detected, encompassing at least 10% of the genome, consistent with the degree of consanguinity. In 2016, the clinical exome sequencing (CES) including mitochondrial genome performed by a commercial laboratory showed negative results.

She died of septic and hypovolemic shock at the age of 6 years. Then, her weight was 6 kg (z score = −6.23), height

Figure Pedigree, Facial Images, and MRI Findings of the Patient With *FRA10AC1* Variant



(A) Family pedigree showing multiple affected members in different related families. Patients IV: 1 and IV: 3 segregate the homozygous *FRA10AC1* variant, which was detected by whole-exome sequencing and confirmed by Sanger sequencing. Patients III-1, III-2, and III-4 reported to have a history of ID, GDD, and brain atrophy. Patient III-4 has bilateral perisylvian syndrome, congenital post parietal disc microgyria, and seizure disorder. Patients III-9, III-10, and III-11 are genetically confirmed cases of mucopolysaccharidosis type IV (MPS IV). (B) Dysmorphic facial features of case 2 (at the age of 15 months) include deformational plagiocephaly, frontal bossing, high forehead, medial flaring of eyebrows, inverted epicanthus, strabismus, anteverted nares, pointed chin, and prominent ears with simple antihelix. Brain MRI at the age of 3.6 years: sagittal T1 WI module (C) in case 1 revealed thinning of the corpus callosum, mainly the posterior body and splenium, with diffuse brain atrophic changes with subsequent prominence of lateral ventricles and sulci, as well as the extra-axial CSF spaces. There is abnormal relatively high signal intensity in the T1 WI module along the lower aspect of the pituitary stalk likely representing ectopic posterior pituitary gland. (D) and (E) Both axial T2 WI modules show predominantly white matter paucity with atrophy of the basal ganglia and faint T2 high signal of bilateral caudate and putamina. There were bilateral subdural fluid collections larger on the right side. GDD = global developmental delay; ID = intellectual disability; rev = reverse primer.

83 cm (z score = −6.47), and head circumference 45.5 cm (z score = −3.92).

Case 2 (IV: 3)

Case 2 is the younger brother of the proband (Figure, A). The pregnancy was uncomplicated, and he was born via normal spontaneous delivery at term. His newborn examination was notable for a murmur that necessitated a stay for 3 days in the nursery where he was diagnosed with a mild aortic coarctation and atrial septal defect (ASD II). After he was circumcised, he was noted to experience a mild glanular hypospadia. At 4 months of age, he developed a left inguinal hernia necessitating a surgical repair. At 6 months of age, he was noted to experience gross motor delay, and, given the positive family history, further workup was initiated including referral to neurology.

Currently, he is aged 15 months and globally delayed; he rolled over at 12 months and is still unable to sit without support. He only babbles but cannot specifically say dada or mama. He responds when called by his name; he can also follow, track, turn, and laugh when played with. He has feeding difficulties. A neurologic evaluation revealed generalized hypotonia, nystagmus, and strabismus.

On physical examination, his weight was 8.5 kg (z score = −2.36), length 84 cm (z score = +1.6), and head circumference 47.5 cm (z score = −0.08). He experienced deformational plagiocephaly, frontal bossing, high forehead, medial flaring of eyebrows, inverted epicanthus, strabismus, nystagmus, anteverted nares, pointed chin, prominent ears with simple antihelix, generalized hypotonia, mild hypospadias, one

Table Molecular and Clinical Characteristics of Reported Patients With Biallelic *FRA10AC1* Variants

Family/Patient	1/1	2/2	3/3-1	3/3-2	3/3-3	4/4–1 (case 1)	4/4–2 (case 2)
Sex	Female	Female	Male	Male	Male	Female	Male
Consanguinity	+	+	+	+	+	+	+
Ethnicity	Arabic	Arabic	Arabic	Arabic	Arabic	Arabic	Arabic
Variant (NM_145246.5)	NG_016832.1: g.4656_7575del p.?	c.561_562insTTTA p.(Ser188Phefs*6)	c.494_496del p.(Glu165del)	c.494_496del p.(Glu165del)	c.494_496del p.(Glu165del)	c.481C>T p.(Arg161*)	c.481C>T p.(Arg161*)
Last examination							
Age (Y, M)	3.1	9	15	10	7	6	1.3
Height in cm (*z* score)	85 (−2.8)	109 (−4.3)	134 (−4.8)	113.5 (−4.2)	109 (−2.9)	83 (−6.47)	84 (+1.6)
Weight in kg (*z* score)	9.4 (−3.4)	15 (−5.3)	32 (−3.9)	20.5 (−3.6)	19 (−1.8)	6 (−6.23)	8.5 (−2.36)
OFC in cm (z score)	45 (−4.1)	47 (−4.8)	50.3 (−3.8)	49.4 (−3.1)	50 (−2.0)	45.5 (- 3.92)	47.5 (−0.08)
Development							
Motor delay	+ (Severe, non-ambulatory)	+ (Moderate)	–	+	–	+ (Severe, nonambulatory)	+ (Moderate)
Intellectual disability	+ (Profound)	+ (Profound)	+ (Mild)	+ (Borderline)	+ (Borderline)	+ (Profound)	+ (Mild)
Neurologic and psychiatric features							
Muscular hypotonia	+ (Severe)	+	+	+	+	+	+
Seizures	+	–	–	–	–	–	–
Behavioral problems	–	+	–	–	–	–	–
Brain abnormalities	+ (Corpus callosum agenesis, mild hydrocephalus internus)	+ (Partial agenesis of the corpus callosum, colpocephaly, unilateral retro-orbital cyst)	+ (Thin stretched corpus callosum)	+ (Thin stretched corpus callosum)	+ (Thin stretched corpus callosum)	+ (Thinning of the corpus callosum, mainly the posterior body and splenium, with diffuse brain atrophic changes)	ND
Dysmorphism	+	+	+	+	+	+	+
Skeletal abnormalities	+ (Bilateral 5th finger clinodactyly)	+ (Bilateral 5th finger clinodactyly)	+ (Clinodactyly of the 4th and 5th toes)	+ (Clinodactyly of the 4th and 5th toes)	+ (Clinodactyly of the 4th and 5th toes)	–	–
Additional features	+ (Feeding problems, recurrent airway infection, congenital heart disease)	+ (Feeding problems, recurrent airway infection)	+ (Growth hormone deficiency)	+ (Growth hormone deficiency)	–	+ (CHD, movement disorder, poor vision, strabismus)	+ (CHD, glanular hypospadias, inguinal hernia, nystagmus, strabismus)
Reference	von Elsner et al._2021	von Elsner et al._2021	von Elsner et al._2021	von Elsner et al._2021	von Elsner et al._2021	This report	This report

Abbreviations: CHD = congenital heart disease; ND = not determined; OFC = occipital frontal circumference.

large hyperpigmented lesion in the lower back, and atopic dermatitis (Figure, B).

Metabolic screening including plasma amino acids, plasma acylcarnitines, and electrolytes were unremarkable. He has a mildly but persistently elevated PT (15.5 and 15.3).

WES, on a research basis, was performed and analyzed for him and his parents as previously described.[2] Consistent with the results of CES for his deceased sibling, no variants were detected in clinically relevant and established genes. However, when analyzed to search for candidate novel genes, a homozygous LOF (nonsense) variant in

FRA10AC1: Chr10(GRCh38): g.93687434G>A: NM_145246.5: c.481C>T, p.(Arg161*) was identified in this patient, while parents were heterozygous. The variant was confirmed by Sanger sequencing (Figure, A). This variant was found as heterozygous in gnomAD (v2.1.1) in 10/242634 (0.004%) chromosomes and not found as homozygous in the gnomAD or a local database of 2,379 ethnically matched exomes. It introduced a premature stop codon in exon 8 and, therefore, predicted to undergo nonsense-mediated decay and results in LOF. Based on this evidence of pathogenicity and clinical correlation with the recently published cases, the CES of the deceased sister was reanalyzed, and she was confirmed to be homozygous for the same *FRA10AC1* variant (Figure, A).

Discussion

Recently reported cases presented with phenotypes similar to those in our patients.[1] They all had failure to thrive, microcephaly, global developmental delay, generalized hypotonia, feeding problems, brain anomalies (abnormal corpus callosum), and dysmorphic features with or without congenital heart disease (Table).

In this study, over time, case 1 experienced severe delay with severe failure to thrive, growth retardation, and secondary microcephaly. Her brain imaging showed thinning of the corpus callosum with diffuse brain atrophy. As for the younger brother, it is possible that he may develop a secondary microcephaly later because the youngest reported case with microcephaly was aged 3 years. However, we do not have a brain MRI for him yet. His height and head circumference are still within the normal limits compared with his weight (z score = −2), which is most likely due to his feeding difficulties. None of our cases had seizures or obvious skeletal abnormalities, as reported in the other cases. Case 2 has genitourinary abnormalities in the form of glanular hypospadias and inguinal hernia. Both cases had vision problems including nystagmus in case 2 and strabismus in both cases, which were not reported in the published cases.

There is a positive family history of 3 cousins with intellectual disability, global developmental delay, brain malformation and atrophy, and seizure disorder, which might be due to the same variant but with a phenotypic expansion. However, the bilateral perisylvian syndrome and congenital postparietal disc microgyria have not yet been reported in individuals with biallelic *FRA10AC1* variants. Thus, the phenotype of individuals III: 1, III: 2, and III: 4 is possibly due to another gene variant that is different from or in addition (dual molecular diagnosis) to that identified in cases 1 and 2 (Figure, A). Unfortunately, those patients are either not available for testing or died before completing their workup.

In conclusion, our study provides an independent corroboration of the recently reported autosomal recessive *FRA10AC1*-associated syndromic neurodevelopmental disease and growth retardation.[1] This syndrome is characterized by failure to thrive, microcephaly, global developmental delay, generalized hypotonia, feeding problems, agenesis of corpus callosum, and dysmorphic features with or without congenital heart disease.

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Disclosure

The authors declare that they have no conflict of interest. Go to Neurology.org/NG for full disclosures.

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Amal Alhashem, MD	Prince Sultan Military Medical City, Riyadh, Saudi Arabia	Clinical evaluation and reviewed the manuscript
Brahim Tabarki, MD	Prince Sultan Military Medical City, Riyadh, Saudi Arabia	Clinical evaluation and reviewed the manuscript
Sarar Mohamed, MD	Prince Sultan Military Medical City, Riyadh, Saudi Arabia	Clinical evaluation and reviewed the manuscript
Essa Alharby, MSc	Taibah University, Medina, Saudi Arabia	WES data interpretation and Sanger confirmation
Fowzan S. Alkuraya, MD	King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia	Clinical evaluation and reviewed the manuscript
Naif A.M. Almontashiri, PhD	Taibah University, Medina, Saudi Arabia	Funded the project, supervised and managed the study, interpreted the data, and drafted the manuscript

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