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Novel Bi-allelic *FRA10AC1* Variants in Neurodevelopmental Disorder: Implications for Growth Retardation, Dysmorphic Facies, and Corpus Callosum Abnormalities

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INTRODUCTION

The spliceosome mediates pre-mRNA splicing and it is essential for removing introns from the pre-mRNAs. More than 150 proteins participate in the splicing process and are organized in the spliceosomal A, B, and C complexes. The FRA10AC1 protein, part of the spliceosomal C complex, is crucial for recognizing and interacting with splice sites. Recently, *FRA10AC1* (MIM: #608866) bi-allelic variants were associated with neurodevelopmental disorder with growth retardation, dysmorphic facies, and corpus callosum abnormalities (NEDGFC)[1,2,3]. To date, only a limited number of cases have been reported, comprising 13 affected individuals from eight unrelated families, presenting with a broad clinical spectrum, ranging from severe neurological abnormalities with various organ malformations to mild intellectual disability. Here, we report five new cases from three unrelated consanguineous families, all exhibiting similar neurodevelopmental symptoms. Notably, in addition to the main clinical features, our patients also had turribrachycephaly, synpolydactyly, ocular issues, autistic features, and/or Hirschsprung disease.

METHODS

Biological samples were collected from three unrelated families after obtaining informed consent from the parents. The DNA extracted from the samples was subjected to whole genome sequencing (WGS) in family 1, and whole exome sequencing (WES) in family 2 and 3. Family 3 underwent a quadro-based analysis. Candidate variants were evaluated for pathogenicity using the American College of Medical Genetics (ACMG) guidelines recommendations. Segregation of *FRA10AC1* (NM_145246.5) variants in families 1 and 2 was assessed using Sanger sequencing.

RESULTS

Clinical assessment: All families reported consanguinity.

Family 1: Two siblings (III.2 and III.3) aged 9 and 15 years with muscle weakness, growth delay, gait imbalance, and language impairment.

Family 2: Two siblings (III.1 and III.3) with development and motor delay, intellectual disability, hypotonia, dysmorphism, rocker bottom feet, and brain abnormalities. The younger sibling also had autistic behavior and genital anomalies and passed away at age 1.5.

Family 3: One patient aged 13 years (deceased), with development and motor delay, intellectual disability, hypotonia, behavioral issues, dysmorphism, and skeletal, brain, cardiac, and ocular abnormalities.

Table 1. Clinical features of patients.

	F1, III.2	F1, III.3	F2, III.1	F2, III.3	F3
Gender	Female	Female	Male	Female	Male
Ethnic origin	Pakistan	Pakistan	Egypt	Egypt	Syria
Current age	15y 7m	9y 6m	1y 6m (deceased)	2y 5m	13y (deceased)
GDD	Yes	Yes	Yes	Yes	Yes
Motor delay	Yes	Yes	Yes	Yes	Yes
ID	N/A	N/A	Yes	Yes	Yes
Hypotonia	Yes		Yes	Yes	Yes
Seizures	N/A	N/A	No		No
Behavioral issues	N/A	N/A	autistic		lack of risk perception, no forward-thinking, self-injurious, aggressive
Brain abnormalities	N/A	N/A	mild cortical atrophy, thin corpus callosum, dilated ventricles	mild cortical changes, hypoplastic temporal lobe, dilated ventricles, thin corpus callosum	gliotic changes
Dysmorphism			nonspecific facies, long face, trichomegaly, low set ears	long face, trichomegaly, upturned nose, smooth long philtrum, full lips, macrostomia, low set ears	turribrachycephalus, microcephaly, short stature, transverse palmar crease, syndactyly, abnormalities of nose, eyes, mouth, ears
Skeletal abnormalities	N/A	N/A	Rocher bottom feet	Rocher bottom feet	hip dysplasia, pes planovalgus
Cardiac anomalies			congenital heart disease, severe aortic dilatation	congenital heart disease (large aortic aneurysm)	Fallot's tetralogy, pulmonary stenosis, aortopulmonary collaterals
Genital anomalies			small phallus, looks like enlarged clitoris, small testis, Hirschsprung	hypoplastic labia and clitoris	
Ocular issues					exotropia, myopia, astigmatism/early keratoconus

GDD: global development delay; ID: intellectual disability; N/A: not available

Genetic analysis

Family 1: Both affected siblings were found to be homozygous for a novel frameshift variant (c.464del; p.(Lys155fs*8)) in exon 7 of the *FRA10AC1* gene which was absent in gnomAD. Sanger analysis confirmed that both parents and unaffected brother are heterozygous for this variant (**Figure 2A, and B**). This variant was classified as likely pathogenic according to the ACMG guidelines (PVS1, PM2, PP1).

Family 2: Both affected siblings were found to carry a homozygous novel missense (c.550G>C; p.(Glu184Gln)) in exon 9 of *FRA10AC1*, with a minor allele frequency (MAF) of 0.0000106 in gnomAD. Parents are heterozygous for this variant. This variant was classified with uncertain significance according to the ACMG guidelines (PM2, PP1).

Family 3: Index was identified with a previously reported homozygous stop gain variant (c.481C>T; p.(Arg161*)) in exon 8 of *FRA10AC1*, with a MAF of 0.00006528 in gnomAD. This variant was classified as likely pathogenic according to ACMG guidelines (PVS1, PS4, PM2).

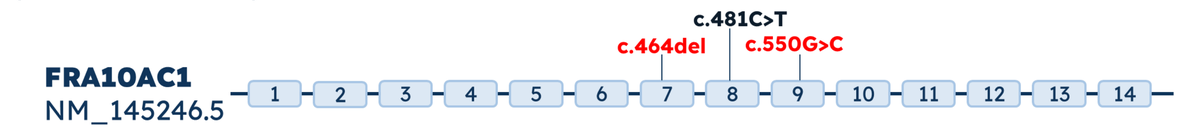

Figure 1. Schematic illustration of *FRA10AC1* and associated variants. Two novel and one previously reported variants identified in this study are indicated in red and black, respectively.

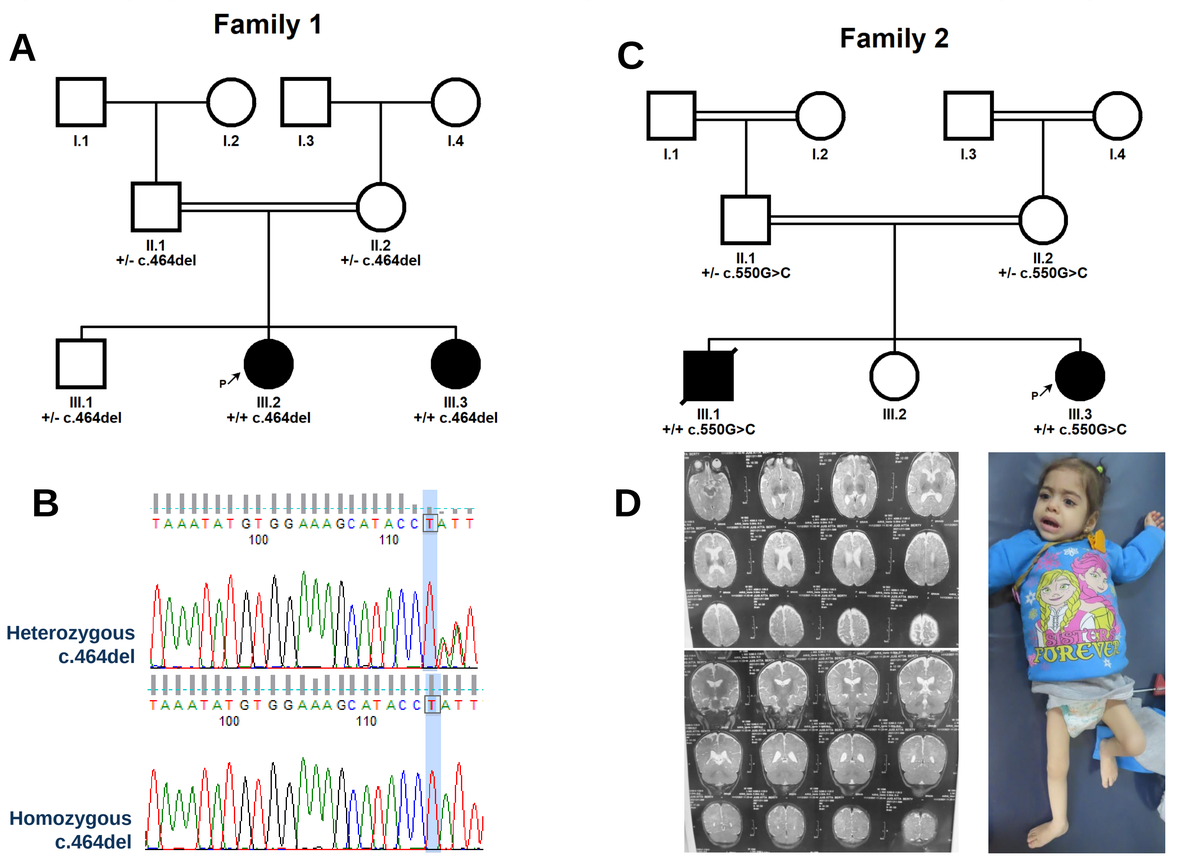

Figure 2. Family history and genetic analysis of patients.

Pedigrees for families 1 and 2 with indicated index harbouring homozygous *FRA10AC1* variants: c.464del (Family 1; A), c.550G>C (Family 2; C). Sanger results confirmed that the index and affected sister are homozygous for the c.464del variant, and that both parents and the unaffected brother are heterozygous in family 1 (B). MRI pictures showing dilated ventricles and hypoplastic temporal lobe, and clinical photographs from patient III.3 in family 2 (D).

CONCLUSION

We identified three rare homozygous *FRA10AC1* variants in the affected individuals: a novel frameshift variant (c.464del, p.(Lys155fs*8)) in Family 1, a novel missense variant (c.550G>C, p.(Glu184Gln)) in Family 2, and a previously reported stop gain variant (c.481C>T, p.(Arg161*)) in Family 3. Family data showed segregation of these variants with the disease.

Our study expands the phenotypic and genotypic spectrum associated with bi-allelic *FRA10AC1* variants, reinforcing its role in a clinically recognizable neurodevelopmental disorder. The affected individuals presented with global developmental delay, dysmorphic facial features, growth retardation, and corpus callosum abnormalities. These findings support *FRA10AC1* as a relevant gene for syndromic neurodevelopmental disorders and emphasize the importance of comprehensive genomic testing in patients with unexplained developmental phenotypes.

CONFLICT OF INTEREST: A. Simões, M. Ali and G. Oprea are current employees of Arcensus.

References: [1]Isaleh et al, Neurol Genet, 2022. [2]von Elsner et al , Brain, 2022. [3]Banka et al , Brain, 2022.

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