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Abstract Title:- Further evidence of biallelic variants in FTO as a cause of growth retardation, developmental delay, and facial dysmorphism

Presenting author name & institute:- Gopika K N, Department of Medical Genetics, IQRAA International Hospital & Research Centre

Co-authors name:- Dhanya Lakshmi Narayanan, Anju Shukla, Periyasamy Radhakrishnan

Co-authors institute:-Department of Medical Genetics, IQRAA International Hospital & Research Centre, and Department of Medical Genetics, Kasturba Medical College, Manipal

Aims:-To delineate the clinical and genetic diagnosis of two siblings with growth retardation, developmental delay, and facial dysmorphism

Methods:- Detailed clinical history and examinations of the patients were done. Clinical exome sequencing was performed in proband following the informed consent. Segregation analysis of the variant was done by Sanger sequencing.

Results:- The proband (P1) is a female child born at 35 weeks of gestation. Her developmental milestones regressed after 6 months of age. Clinical examination at 11 years revealed a head circumference of 48 cm (-3.7 SD), height to be 106 cm (-5.3 SD), and weight to be 15.5 kg (-4 SD). She had coarse facial features with bitemporal narrowing, low set ears, open mouth, retrognathia, short neck, and bilateral fifth finger clinodactyly. She had a fair complexion with hypopigmented skin patches on the back and hyperpigmented macules of bilateral upper and lower limbs. The tone was normal and deep tendon reflexes were not elicitable. MRI brain at 1 year was suggestive of hypoxic-ischemic insult with gliosis. A repeat MRI brain at 4 years showed pachygyria with thickened gyri. The second pregnancy of the couple was terminated at 23 weeks of gestation given intrauterine growth retardation in the fetus. Third pregnancy, the mother delivered a male child (P2), currently a four-year-old presented with similar clinical presentations as P1. A male child (P3) was born in the fourth pregnancy and succumbed at 3 months of age due to cholestatic jaundice and acute liver failure.

Clinical exome sequencing was performed in P1 and revealed a homozygous variant c.608T>C, p.(Leu203Ser) in FTO (NM_001080432.3). Her sibling P2 carries the variant in a homozygous state. Her parents were heterozygous carriers for the variant. Prenatal testing in the fourth pregnancy showed the fetus was a heterozygous carrier for the variant. Postnatal examination of the child revealed cholestatic jaundice and acute liver failure in the child. Exome sequencing was performed to ascertain the cause and it was non-diagnostic.

Conclusions:- Genomic variants in FTO are associated with growth retardation, developmental delay, and facial dysmorphism (MIM#612938). To date, 12 patients from four families have been reported with variants in FTO. Here, we report a novel variant in FTO in two siblings with phenotypes comparable with previous reports. Additionally, P1 and P2 had repetitive hand movements and fair complexion with hyperpigmented, and hypopigmented patches. Neither sibling had any structural cardiac anomalies as seen in the previous patients. With these findings, we further confirm and expand the phenotypic spectrum of FTO variants.

Keywords:- FTO, fair complexion, growth retardation