Clinical exome sequencing identifies a novel gene, LINS, associated with intellectual disability, failure to thrive, seizures, dysmorphology, and language regression.

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ABSTRACT:

Clinical Whole Exome Sequence analysis of an 8 year-old Caucasian female affected with intellectual disability (ID), failure to thrive, myopia, microcephaly, seizures, dysmorphic features, and language regression with aphonia identified two compound heterozygous alterations in LINS, the human homolog of the Drosophila segmentation lins protein, which is involved in the Wnt signaling pathway. The paternally-inherited c.2020dupA frameshift alteration and maternally-inherited c.1394+1G>T splice site alteration are both expected to result in a deleterious effect on the LINS gene. The patient evaded diagnosis through clinical evaluation and extensive genetic testing over many years including negative chromosome analysis, FISH for Smith Magenis syndrome, CGH/SNP microarray, Angelman syndrome methylation analysis, *MECP2* and *CDKL5* analysis for Rett syndrome, mitochondrial DNA array and gene sequencing panel, as well as uninformative biochemical results. The two *LINS* gene alterations we identified are likely to provide an explanation for the patient's symptoms and no other likely candidate gene alterations were identified to explain the patient's phenotype. LINS is a newly characterized gene involved in human cognition and brain development. Mutations in LINS have been described in only two cases of autosomal recessive ID and microcephaly. In one previously reported case, a homozygous frameshift mutation was identified in an Iranian family with four children affected with moderate ID and microcephaly. In a separate case, a 5-nucleotide homozygous deletion affecting a donor splice site was identified in a Yemeni male and female sibship affected with early onset ID, developmental delay and head nodding behavior. Consanguinity was present in both of the previously reported cases. Phenotypic overlap with the current case include microcephaly and intellectual disability; however, there appears to be a spectrum of clinical symptoms associated with LINS mutations. Diagnostic exome sequence analysis is an effective method for contributing to the mutational and phenotypic spectrum of LINS-related diseases.