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Title:
Diagnostic Exome Sequencing Identifies a Novel Homozygous Alteration in *DEAF1* Further Delineating the Phenotypic Spectrum

Abstract:
In the last three years, three individuals from two families have been reported with a homozygous *DEAF1* mutation (c.676C>T) who all shared a phenotype characterized by microcephaly, brain abnormalities, and intellectual disability. The affected individuals also demonstrated a variety of other features including hypotonia, feeding difficulties, and behavioral abnormalities. Additionally, an intronic mutation causing exon skipping and which generated a premature stop codon in *DEAF1* was reported to cause disease in three siblings all affected by intellectual disability, autism, dyskinesia, abnormal cranial MRI and epilepsy. Here we report an additional patient with homozygous alterations in *DEAF1*. The patient is a 4 month old Afghani girl with developmental delay, delayed visual maturation, strabismus, hydronephrosis, vesicoureteral reflux and microcephaly as well as dysmorphic features including low posterior hairline, mild synophrys, thick and bushy eyebrows, long eyelashes, downslanting palpebral fissures, low set ears slightly posteriorly rotated with prominent antihelix bilaterally and Darwinian tubercle on the right, micrognathia, depressed nasal bridge, broad nasal tip, bilateral inverted nipples, and overlapping toes. Her head circumference was 38.1 cm (11th percentile). A MRI showed absence of splenium, hypoplastic putamina and other basal ganglia abnormalities, and wide and underdeveloped sylvian fissures. The family history is significant for multiple instances of consanguinity and an older brother who died at 6 months who had an abnormal CT of the brain. Family centered diagnostic exome sequencing (DES) on the proband and her healthy parents revealed a homozygous c.576C>A (p.Y192*) nonsense alteration in *DEAF1*. This alteration was not reported in healthy populations. This patient provides another example of a syndrome associated with homozygous mutations in *DEAF1*. While the patient's phenotype contains elements of previously reported patients, including developmental delay, relative microcephaly, truncal hypotonia, and brain malformations on MRI, the patient is notable for having a number of dysmorphic features not previously reported in homozygous *DEAF1* patients. This could represent an expansion of the phenotypic spectrum or could be the result of another cause such as the effect of an unidentified pathogenic alteration. This is not direct endorsement of Ambry Genetics by Kaiser Permanente or the Mid-Atlantic Permanente Medical Group.