Identification of a novel variant of the CDKL5 gene associated with atypical Rett Syndrome

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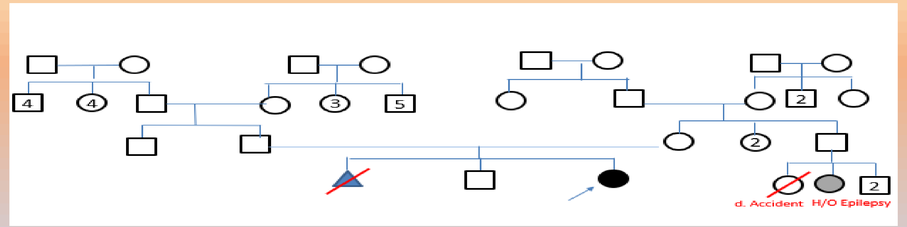
Clinical Summary

- We present a 4 months old female child, presented with recurrent seizures, staring, jerks, clonic stiffening and posturing.
- Onset of symptoms were at 1.5 months post vaccination
- Anthropometric evaluation and dysmorphology : Child has broad prominent forehead , antiverted nares, large appearing eyes, fuller lips and generalized hypotonia
- Child was delivered via LUCS , at term, BW=3.2 kgs, CIAB, was able to suck and swallow
- Developmental milestones
  HH= partial , Social smile present, fleeting eye contact

Investigation

- MRI (B) was normal
- TMS/GCMS was normal
- Whole exome sequencing with mitochondrial genome analysis indicated a heterozygous VOUS in CDKL5 gene at exon5, c.272A>C and homoplasmy for c.674A>G at MT –ATP6

Family H/O



GENOTYPE PHENOTYPE CORRELATION

Developmental and epileptic encephalopathy-2 (DEE2) is an X-linked dominant severe neurologic disorder characterized by onset of seizures in the first months of life and severe global developmental delay resulting in impaired intellectual development and poor motor control. Other features include lack of speech development, subtle dysmorphic facial features, sleep disturbances, gastrointestinal problems, and stereotypic hand movements. There is some phenotypic overlap with Rett syndrome (312750), but DEE2 is considered to be a distinct entity (summary by Fehr et al., 2013).

In Silico variant analysis

- Variant is novel and not present in 1000 genomas and genom AD
- Damaging by in silico analysis , by polyphen , SIFT and Mutataster
- Conserved by consurf analysis

Segregation study

Variant not identified in mother as determined by Sanger seq
Mother also had similar homoplasmy in MT-ATP6 and was asymptomatic

Conclusion

Based on the above finding

- A diagnosis for DEE2 is suggested for the manifestation can be due to the heterozygous missense
- Variant of uncertain significance (c.272A>C) in exon 5 of the CDKL5 gene. **There is a large physicochemical difference between Tyrosine and Serine, which is likely to impact secondary protein structure as these residues differ in polarity, charge, size and/or other properties**. The observed variant is not present in both the 1000 Genomes and gnomAD databases. The reference base is conserved across the species and in-silico predictions by Polyphen and SIFT are damaging.
- As this is a X-linked dominant inheritance mother was screened by sanger sequencing . This mutation in the child is a spontaneous mutation, and hence chances of recurrence if the parents plan another child is extremely low. However, there is a chance of gonandal mosaicism
- Based on the above information an ACMG variant classification of likely pathogenic can be established.
- **Hence we report a novel variant with overlapping features of Rett syndrome. Atypical Rett syndrome should be investigated in such cases and just investigating for MECP2 is not enough. Pre clinical trial for CDKL5 Deficiency Disorder (CDD) are available , and thus frequency of different mutation types and genotype-phenotype correlations in CDKL5 Deficiency Disorder (CDD) are of utmost important.**