Review of: "A recurrent, homozygous EMC10 frameshift variant is associated with a syndrome of developmental delay with variable seizures and dysmorphic features"

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Shao et al. reported 13 patients with a recurrent, homozygous EMC10 frameshift variant. The patients showed developmental delay, variable seizures, and dysmorphic features. EMC10 is one of ten subunits of the endoplasmic reticulum membrane complex (EMC) which is a highly conserved, multifuncitional complex. The authors experimentally confirmed that the variant caused significant reduction of EMC10 transcript, and unstable truncated EMC10 protein. They also uncovered that the variant arose on two founder haplotypes.

This is a nice paper showing the significance of EMC in human development especially in brain. Since another subunit, EMC1, has been identified as a causative gene for a human disorder including global developmental delay, cerebellar atrophy, seizure, microcephaly, and vision abnormalities, the identification of the pathogenic variant in EMC10 would highlight the significance of EMC in brain function.

I have following comments.

1. Since enrolled patients were of Middle East origin, I am wondering if two identified haplotypes are specific for Middle East.
2. What is the prevalence of heterozygous c.287delG in available database?
3. As the authors described in discussion, consequence of the dysfunction of EMC, such as change of membrane insertion rate of transmembrane proteins, is of most interest. It would be good if such functional assay is developed.