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Vanishing White Matter Disease Associated with a Novel Heterozygous EIF2B3 Variants using NGS

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Vanishing White Matter disease (VWM) is an autosomal recessive disorder caused by pathogenic mutations in any of the genes EIF2B1-5. These genes encode the 5 subunits of eukaryotic translation initiation factor 2B (eIF2Bα-ε), of which role is limiting global rates of protein synthesis from messenger RNA translation under stress condition. Therefore, any dysfunction of eIF2B, pathogenesis of VWM, results in stress-provoked episodic rapid neurological deterioration, followed by chronic progressive disease course. We describe a patient with infantile onset VWM of pre-described specific clinical course, subsequent neurologic aggravation induced by each viral infection and finally in a coma state without any response by external stimulus. Although the initial brain magnetic resonance imaging could not reveal specific pathognomonic sign of VWM to differentiate from many other demyelinating leukodystrophy, the next generation sequencing (NGS) study revealed heterozygous missense variants in EIF2B3, including a novel variant in exon 7 (C706G) as well as 0.008% frequency reported variant in exon 2 (T89C). Therefore, the unbiased genomic sequencing can have clinical impact in the patient care and decision making with the genetic disorders affecting white matter in pediatrics.

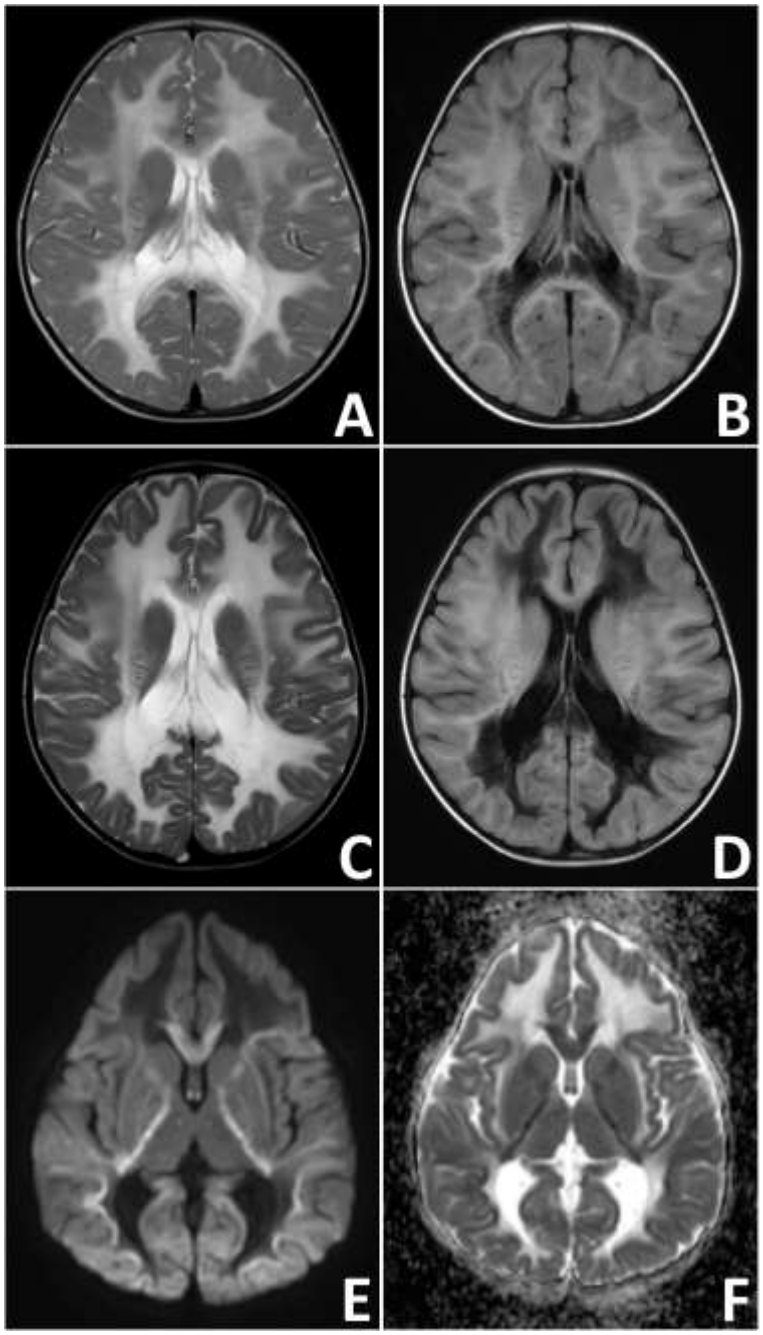

Fig 1. Magnetic resonance imaging of brain at the patient's 20 month old (A-B) and 28 month old (C-F). The T2-weighted image (A, C) shows the diffuse hyperintense abnormality of deep cerebral white matter spreading to whole white matter. The FLAIR image (B, D) shows that more parts of the abnormal white matter have a low signal intensity in D than B, similar to cerebrospinal fluid, indicative of progressive cystic degeneration. Within the abnormal white matter lesion, a pattern of radiating stripes is revealed suggestive of remaining tissue strands. The DWI (E) and ADC map (F) shows restricted diffusion around white matter lesion, indicative of ongoing spreading and active demyelinating process within the white matter.

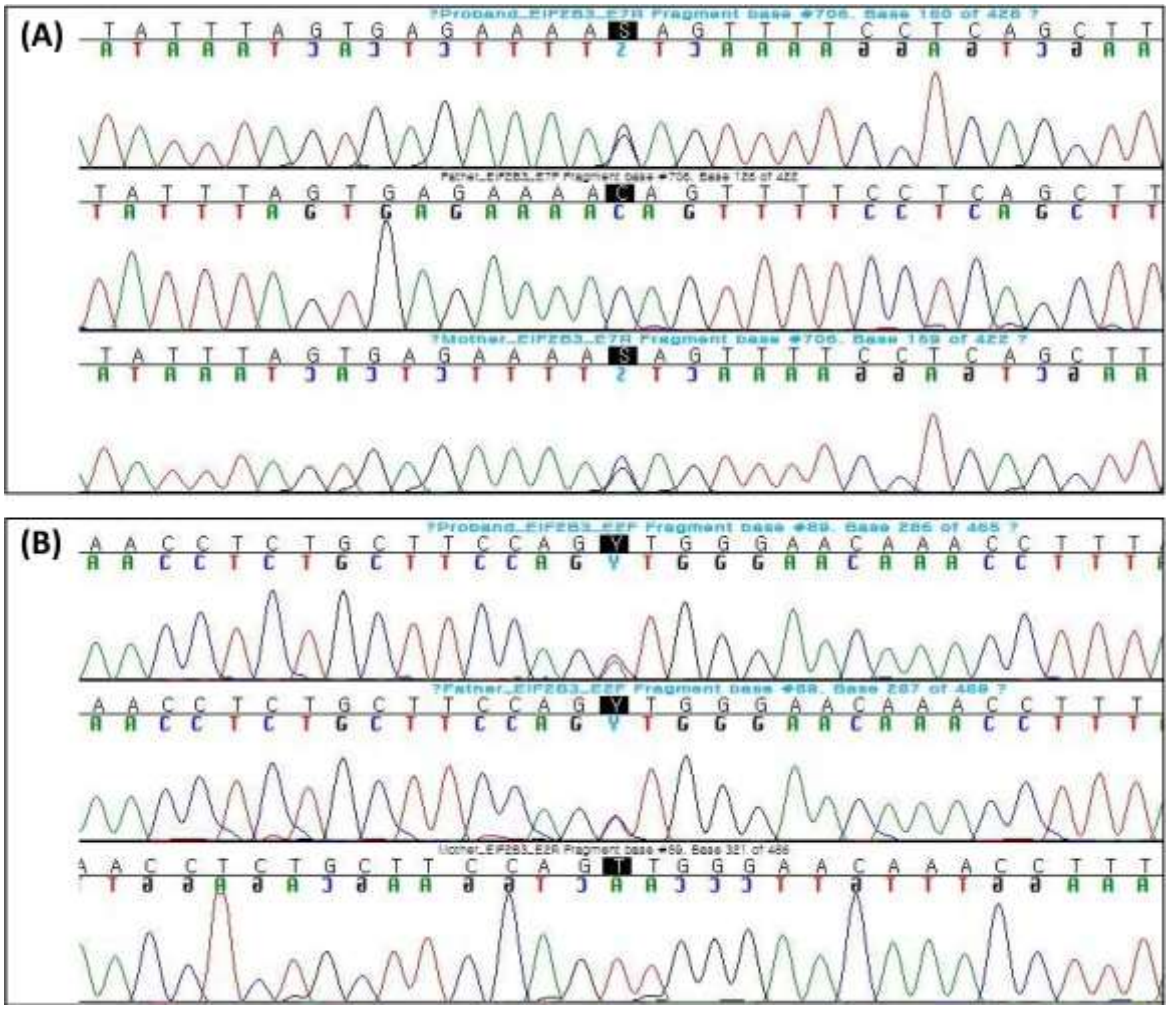

Fig 2. Variants in the eIF2B3 gene in the patient. (A) a novel variant c.706C > G/p.Gln236Glu (B) a rare variant c.89T > C/p.Val30Ala.