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Comment on "Retinitis Pigmentosa and Molar Tooth Sign Caused by Novel AHI1 Compound Heterozygote Pathogenic Variants: A Case Report"

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Joubert syndrome (JS) is a rare congenital neurodevelopmental disease which is basically a primary Ciliopathy. It's characteristic manifestation on imaging is so called 'molar tooth sign' in the brainstem and cerebellum. JS can involve multiple organs, mainly including retina, kidney, bone and liver. Clinical signs of early onset JS include hypotonia, developmental delay, breathing abnormalities, and ocular motor apraxia. Late onset patients usually develop ataxia, intellectual impairment, and variable organ involvement, which are easily misdiagnosed [1]. There have been more than 40 genes reported contributing to the pathogenesis of JS. The clinical property and genotype phenotype correlations has been recently reviewed [2]. Such as JS patients carrying pathogenic variants in TMEM67 have a higher risk of liver fibrosis, while those in NPHP1, RPGRIP1L, and TMEM237 are frequently involved to with renal problems. These evidences directed us to monitor liver and renal functions for earlier diagnosis and protection [3]. Some "mild molar tooth sign (MTS)" including vermis hypoplasia, superior cerebellar folial dysplasia, and subtle-to-mild abnormalities of the superior cerebellar peduncles due to AHI1 or CEP290 gene are occasionally reported [1,4]. Several gene mutations (AHI1, INPP5E, ARL13B and CC2D2A) that occur almost exclusively in Joubert syndrome with retinal disease [2].

Chen et al. have reported a novel variant at c.1330A>T (p.I444F) of the Abelson helper integration site 1 (AHI1) gene, which added new mutation cite to the Human Genome Database. The new gene mutation originated from a young man with mild MTS has been identified by members of Professor Du Ailian's research group in the Department of Neurology, Shanghai Tongren Hospital. The patient has had vision loss for nearly 29 years and has been walking unsteadily for 2 years. The ophthalmological examination found many problems, such as vision loss, tubular visual field, as well as retina pigmentation. Neurological examination showed slight nystagmus on bilateral gaze, slight intention tremor on finger—nose pointing, unstable at toe heel walking and straight walking. Other organs, including heart, liver, kidneys, lungs, etc. were normal. The patient was intellectually normal and working in a bank currently. Obvious molar tooth sign on MRI suggests JS and subsequent genetic testing further confirms the diagnosis. They found two compound heterozygous variants at NM_017651.4: c.2105C>T (p.T702M) and c.1330A>T (p.I444F) in the AHI1 gene. The T702M variant has been previously reported, while p.I444F is a novel mutation.

Another contribution from the Prof. Du's research group was the 3D structure homology modeling and visualization of Jouberin protein resulted from the mutation. Two mutations in AH1 gene were confirmed to be missense mutations which resulted in amino acid changes. Mutation of c.2105C>T (p.T702M) will cause the replacement of a hydroxylic polarly amino acid threonine by a sulfuric non-polarly methionine. The difference will result in local 3D structure from β-sheet to D-loop. Similarly, the mutation c.1330A>T (p.I444F) will change the 3D structure from α-helix to D-loop. Both of these mutations will decrease the protein stability. We are looking forward to Prof. Du's research group carrying out more related research on these two AH1 gene mutations in the future, to provide more clues for the pathogenesis of JS.

The third contribution is about treatment. This patient is

currently treated with regular dose of vitamin B12, vitamin B1, and vitamin B6. And he is satisfied with the current status of his health. JS has obvious genetic and clinical phenotype correlation, so gene-targeted precision treatment is future direction of JS therapy. In 2017 Russell et al. has improved visual function in specific types of retinal dystrophies by injecting expression vectors directly into the human retina using gene therapy [5]. Besides, CEP290 gene, a major cause of Leber congenital amaurosis and JS, is already under study [6,7]. Gene therapies have been used for other diseases in humans, such as spinal muscular atrophy [8]. Although gene therapy for JS is still in infancy, future research on targeting AH1 gene therapy will benefit a large number of similar JS patients. And maybe they could continue to follow up this patient to see related changes of the ophthalmology and neurology.

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