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COMMENTARY

A Commentary on 'Four novel C20ORF54 mutations identified in Brown–Vialetto–Van Laere syndrome patients.'

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Brown–Vialetto–Van Laere Syndrome (BVVL) is a rare childhood neurological disorder characterized by progressive ponto-bulbar palsy associated with sensorineural deafness and respiratory difficulties. The syndrome was first described by Charles Brown[1] in 1894 in a 15-year-old German boy, and then further reported by Vialetto[2] in 1936 and Van Laere[3] in 1966. The majority of cases are apparently sporadic in nature, consistent with the autosomal recessive mode of inheritance noted in several families, although autosomal dominant inheritance has been observed in one kindred.[4] Patients with BVVL have overlapping clinical features with other childhood motor neuron disorders such as Madras Motor Neuron Disease, Boltshauser syndrome, Nathalie syndrome and Fazio–Londe syndrome. It is very likely that these disorders are allelic with the disease genes associated with BVVL.[4]

Mutations in the *C20ORF54* gene that encodes a riboflavin transporter protein have been identified as a cause of BVVL in a number of families and sporadic cases.[5,6] In humans there are three members of the riboflavin transporter gene family, recently mutations in a second transporter, *SLC52A2* or *GPR172A* gene was identified in BVVL families from Lebanon and England with a similar clinical phenotype but a slightly later age at onset.[7] The identification of mutations in BVVL have been important in the diagnosis of patients, but of far greater importance has been the treatment of BVVL patients with riboflavin supplements, which has shown clinical benefit in children with *C20ORF54* and *SLC52A2* genetic defects.[7]

Here, Mitra Ansari Dezfouli and colleagues[8] report the identification of four novel mutations in the *C20ORF54* gene in three unrelated Iranian BVVL patients. This expands the geographical distribution and mutation spectrum of *C20ORF54* defects in BVVL. Two of the families with mutations presented with a phenotype most similar to Fazio–Londe syndrome and then 7 years later developed hearing loss and the overall phenotype consistent with BVVL. Two of the mutations identified were acting in a compound heterozygous fashion and in two other BVVL kindreds, single heterozygous mutations were found that are highly likely to be pathogenic on one allele, but suggest that occult heterozygous copy number defects exist on the other. The authors speculate that single heterozygous *C20ORF54* mutations may be associated with BVVL, which is possible as the families reported have an atypically late age of onset in the second decade, but unlikely as the parents are clinically unaffected. Overall, this study highlights the extreme importance of screening the riboflavin receptor genes in children and young adults who present with features of motor neuron disease, even if the phenotype is not fully compatible with BVVL. The *C20ORF54* and *SLC52A2* genes should be considered in all populations and before the identification of mutations riboflavin supplements should be instigated as a therapy shown to improve symptoms and signs.

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