Impaired riboflavin transport due to missense mutations in SLC52A2 causes Brown-Vialetto-Van Laere syndrome.

Brown-Vialetto-Van Laere syndrome (BVVLS [MIM 211530]) is a rare neurological disorder characterized by infancy onset sensorineural deafness and ponto-bulbar palsy. Mutations in SLC52A3 (formerly C20orf54), coding for riboflavin transporter 2 (hRFT2), have been identified as the molecular genetic correlate in several individuals with BVVLS. Exome sequencing of just one single case revealed that compound heterozygosity for two pathogenic mutations in the SLC52A2 gene coding for riboflavin transporter 3 (hRFT3), another member of the riboflavin transporter family, is also associated with BVVLS. Overexpression studies confirmed that the gene products of both mutant alleles have reduced riboflavin transport activities. While mutations in SLC52A3 cause decreased plasma riboflavin levels, concordant with a role of SLC52A3 in riboflavin uptake from food, the SLC52A2-mutant individual had normal plasma riboflavin concentrations, a finding in line with a postulated function of SLC52A2 in riboflavin uptake from blood into target cells. Our results contribute to the understanding of human riboflavin metabolism and underscore its role in the pathogenesis of BVVLS, thereby providing a rational basis for a high-dose riboflavin treatment.