A novel heterozygote mutation of SLC52A3 in a slowly progressive case of Brown-Vialetto-Van Laere syndrome

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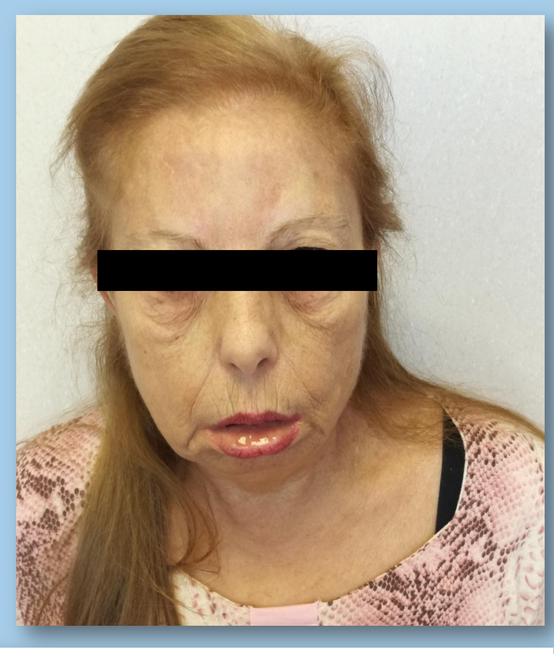
Background and Objectives

Brown-Vialetto-Van Laere syndrome (BVVLS) is a rare neurodegenerative disorder causing progressive ponto bulbar palsy due to lower motor neuron involvement and bilateral sensorineural deafness. Along with disease progression, signs of long tract involvement, cerebellar ataxia and cranial nerve palsies may occur. Homozygote and compound heterozygote mutations of SLC52A3 and SCL52A2 genes, encoding for Riboflavin Transporter type 2 and type 3, are traditionally considered as causative, determining impaired riboflavin metabolism [1]. Nevertheless, new heterozygote pathogenic mutations are emerging, suggesting the possibility of autosomal dominant inheritance as well, at least for clinically attenuated forms [2]. We describe a slowly progressive case of BVVLS associated with a novel heterozygote insertion in SLC52A3 gene.



Methods

A 73 year-old female patient presented since adolescence dysphonia, dysphagia and dysarthria with very slow progression, followed over time by increasing gait unsteadiness, severe bilateral deafness, facial diplegia and slight limbs weakness. Familial history was not contributing. Our latest neurological examination, after 30 years of follow-up, confirmed only moderate dysphagia, not requiring any supportive therapy, and independent walking, albeit with some difficulties, so that the patient was substantially autonomous in daily life. The extensive diagnostic protocol included laboratory assays, brain MRI, EMG, EEG, motor evoked potentials (MEPs), esophageal endoscopy, dynamic swallowing study, spirometry, tonal audiometry, cardiologic and ENT assessment. Molecular analysis of SLC52A3/hRFT2 and SLC52A2/hRFT3 genes was performed.

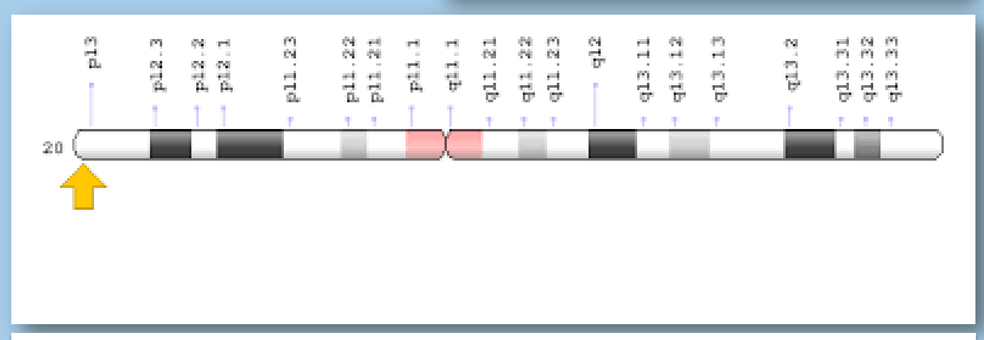


Fig 2: Figure showing cytogenetic location of SLC52A3/hRFT2 gene (Solute Carrier Family 52/ Riboflavin transporter 2) on chromosome 20.

Results

Blood tests and general examination were normal. MRI showed significant ponto bulbar atrophy in along with severe ischemic leukoencephalopathy. EMG revealed chronic neurogenic changes in muscular districts with pontobulbar innervation, where MEPs detected no signs of upper motor neuron involvement. Tonal audiometry confirmed severe bilateral sensorineural hearing loss, and mixed restrictive and obstructive lung disease of mild degree emerged at spirometry. Videofluoroscopy demonstrated impaired oropharyngeal dynamics without organic lesions. The diagnosis of BVVLS was hypothesized. Genetic analysis revealed the novel heterozygote variant c.481_484dupTCCG p.(Gly162ValfsTer11) in SLC52A3/hRFT2 gene.

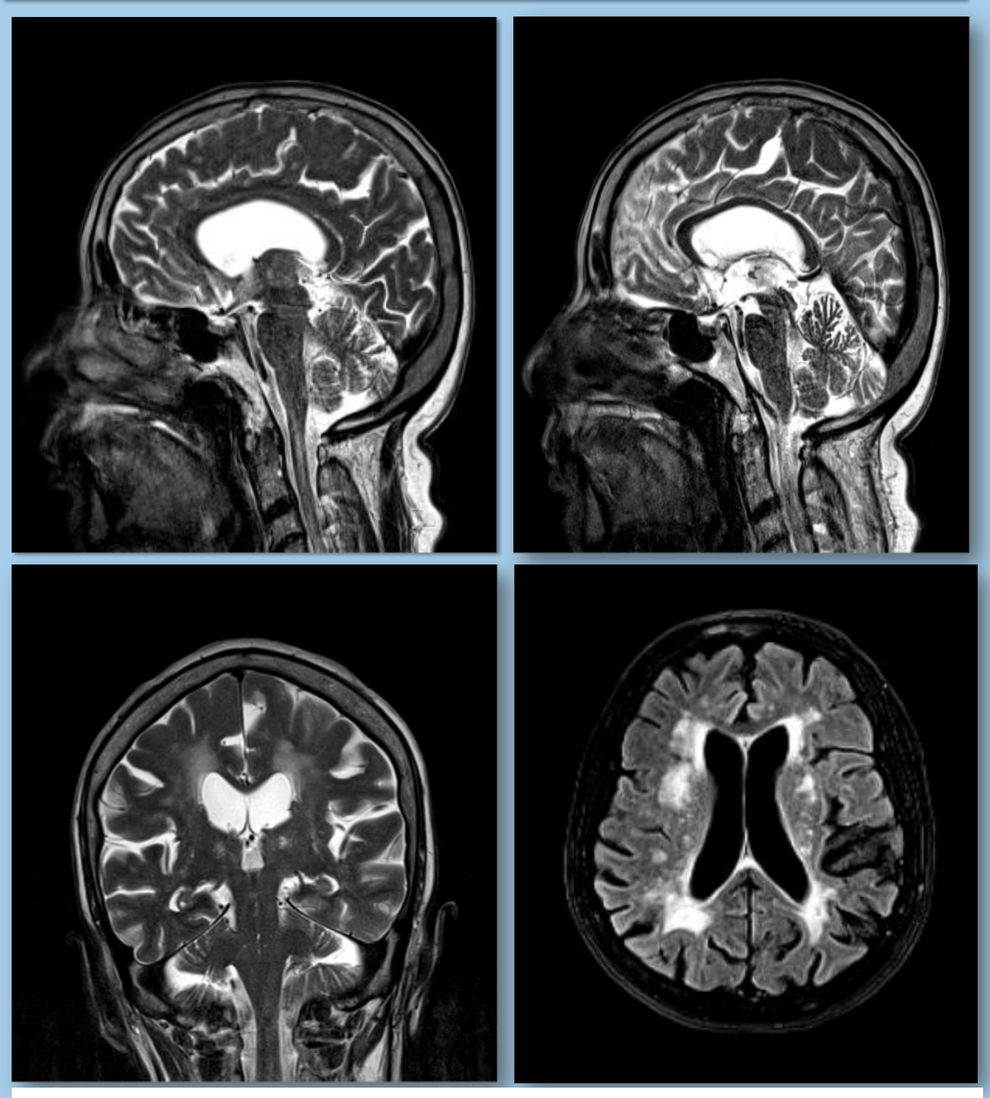


Fig 3: MRI of the patient, performed during our latest neurological examination, showing moderate ponto-bulbar and severe cerebellar atrophy, in along with significant multifocal leukoencefalophathy.

Discussion and conclusions

We reported an unusual sporadic case of BVVLS with very slow progression in a patient carrying a novel heterozygote mutation in *SLC52A3/hRFT2* gene. From a pivotal *in silico* analysis, this four-base insertion should add a new stop codon, thus resulting in truncated, non-functional protein. In accordance with emerging data upon heterozygous mutations, we speculate that the preservation of a residual functional activity due to the non-mutated allele should ensure at least a partial physiological metabolism of riboflavin, therefore justifying the relatively mild phenotype described in our patient.

Bibliografia

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[2] Dezfouli MA, Yadegari S, Nafissi S, Elahi E. Four novel C20orf54 mutations identified in Brown-Vialetto-Van Laere syndrome patients. J Hum Genet. 2012 Sep;57(9):613-7.