A novel heterozygous mutation in HTRA1 gene

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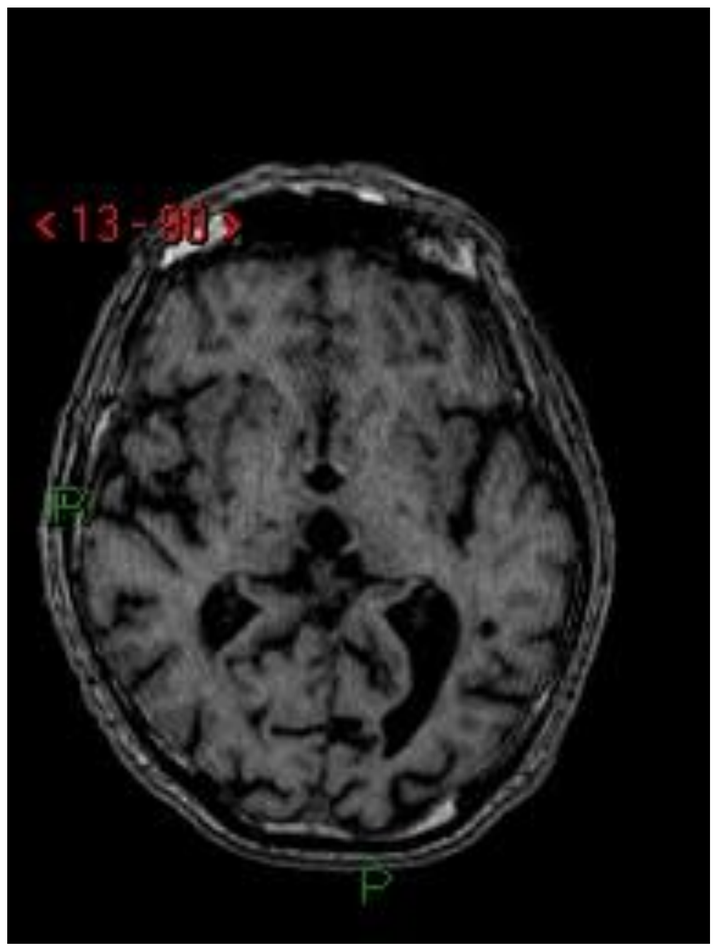
Background

HTRA1 is a gene located on chromosome 10q encoding Htra1 protein, which normally represses transforming growth factor-β (TGF-β) signaling. It is the only gene causing CARASIL, an inherited autosomal recessive cerebral small vessel disease characterized by early-onset leukoencephalopathy, ischemic strokes, cognitive dysfunction, gait disturbance, spondylosis and alopecia

Case report

•A 60 year-old man with progressive gait disturbance since one year, speech disorder since some months and widespread leukoencephalopathy
•His mother and his maternal uncle showed the same clinical phenotype since the age of 70 years
•No vascular risk factors
•Neurological examination: ataxic gait, mutism, slowed saccades, dysphagia, dysarthria, minimal dysmetria, mild spasticity, increased deep-tendon reflexes at limbs
•Neuropsychological tests: relevant cognitive impairment
•Neurophysiological exam: axonal motor and sensitive polyneuropathy
•Brain MRI: leukoencephalopathy, paraventricular white matter hyperintensity, brainstem lesions and microbleeds
•Amyloid angiopathy, frontotemporal dementia, vasculitis, CADASIL and leukoencephalopathy with axonal spheroids were excluded

→ **a novel heterozygous missense variant p.Gln151Lys (c.451C>A) in exon 1 in HTRA1 (High temperature requirement protein A1) gene, related to CARASIL**



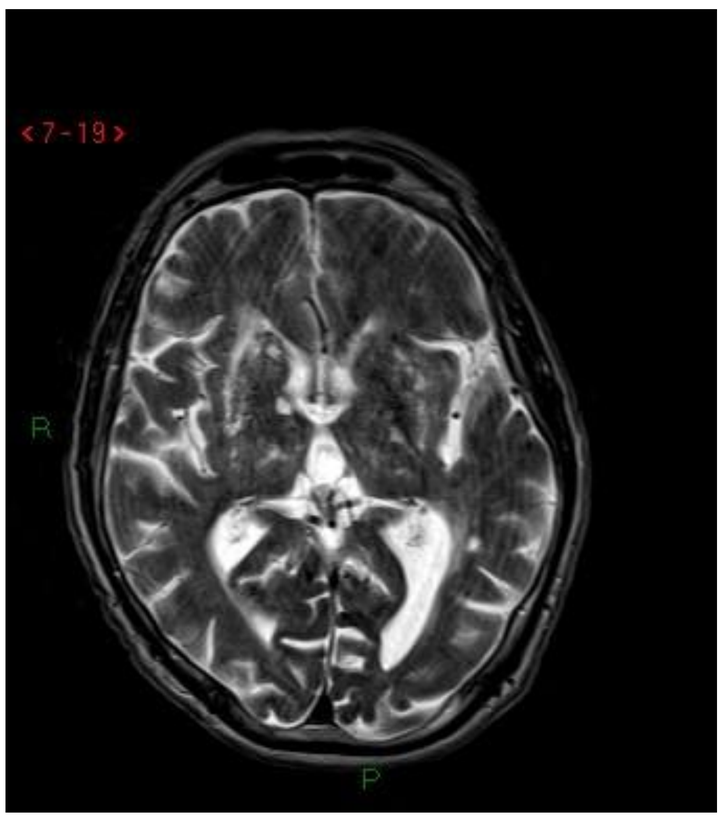


Fig. T1, T2 brain RMI: leukoencephalopathy, paraventricular white matter hyperintensity, brainstem lesions and microbleeds

Conclusion

In our patient the presence of a heterozygous variant in a gene usually related to a recessive disease raises the question of the expression of clinical phenotype in the carriers of heterozygous mutations. A recent study described thirteen heterozygous HTRA1 variants, eleven of which considered deleterious and two benign, confirming that heterozygous variant in HTRA1 gene can induce cognitive impairment associated with leukoencephalopathy, in absence of alopecia and spondylosis, which are specific extra-neurological signs of CARASIL disease, representing the pattern of a familial SVD with a dominant inheritance transmission. Further similar evidences have been reported also by our group. The differences between CARASIL and autosomal dominant SVD are the older age of onset, the absence of alopecia and spondylosis and a typical status cribrosum at brain RM in SVD. For the presence of all these aspects in our patient we, confirming the previously reported data, concluded that heterozygous variant in HTRA1 can be associated to the clinical phenotype of autosomal dominant SVD.

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