Novel heterozygous c.298_299insG variant in the *HTRA1* gene in a patient with leukoencephalopathy and stroke recurrence: a case description.

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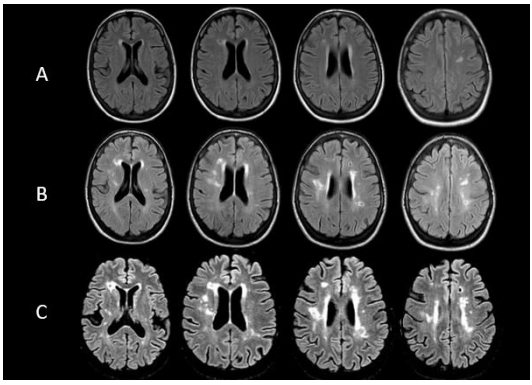
Case description

A 55-year-old Caucasian woman presented to the Emergency Department with acute left-hand weakness and dysarthria. Head CT revealed diffuse subcortical hypodensities as expression of chronic vascular damage, and CT-angiography excluded large vessel occlusion. Aspirin was started, and she was admitted to the Stroke Unit. Brain MRI showed an **acute ischemic lesion** in the right centrum semiovale, extensive bilateral white matter hyperintensities, and lacunar lesions (Figure 1B). Compared to a previous MRI performed two years earlier for **headache** (Figure 1A), white matter changes and brain atrophy had progressed. No embolic source was found, so a loop recorder was implanted.

One year later, another transient episode of dysarthria occurred. The loop recorder excluded arrhythmias. Brain MRI (Figure 1C) demonstrated further **leukoencephalopathy** progression and cortical atrophy, without evidence of new ischemic lesions. Given the patient's young age, progressive vasculopathy, and recurrent ischemic events of undetermined origin, genetic testing for vascular leukoencephalopathies (n=35 genes) was performed using Next Generation Sequencing. A *novel heterozygous HTRA1 variant* (c.298_299insG, p.Thr200Serfs*69) was identified, causing frameshift and truncation of the protein, and classified as likely pathogenic (ACMG class 4). Clinical and radiological findings were consistent with HTRA1-related CSVD.



Conclusions

Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL MIM#600142) is a rare form of Cerebral Small Vessel Disease (CSVD) caused by biallelic loss-of-function mutations in the *HTRA1* gene, leading to aberrant upregulation of transforming growth factor β1 (TGF-β1) signaling pathways (Uemura M, 2020). Recent findings (Li YM, 2023; Zhuo ZL 2020; Coste T, 2021) showed that heterozygous mutations in the HTRA1 gene can also result in a milder form of CSVD. We identified a novel heterozygous mutation of HTRA1 gene (c.298_299insG) in a patient with history of two acute cerebrovascular events of undetermined etiology, lacunar lesions, biemispheric leukoaraiosis and progressive brain atrophy. This specific mutation results in a truncated protein with a possibly haploinsufficient mechanism. The reported variant has never been reported in the general population, and it can be classified as presumably pathogenic.

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