Heterozygous mutations of HTRA1 gene in patients with familial cerebral ischemic small vessel disease

Di Donato I[1], Bianchi S[1], Gallus GN[1], Malentacchi G[2], Zini A[3], Nannucci S[4], Valenti R[4], Pescini F[4], Inzitari D[4], Pantoni L[4], Federico A[1], Dotti MT[1].

[1] Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy.

[2] Azienda Ospedaliera S. Carlo, Potenza, Italy.

[3] Stroke Unit, Department of Neuroscience, "S. Agostino Estense" Hospital; Modena, Italy.

[4] Neuroscience Section, NEUROFARBA Department, University of Florence, Florence, Italy.

INTRODUCTION

Homozygous or compound heterozygous mutations of HTRA1 gene are causative of CARASIL (Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, OMIM 600142), an autosomal recessive cause of early-onset (usually <40 years) small vessel disease (SVD). The disease is characterized by leukoencephalopathy, which is clinically expressed with neurological (motor impairment, cognitive decline, mood disorders, stroke-like episodes) and extraneurological (scalp alopecia, spondilosis and disk degeneration) features. HTRA1 codes for a serin-protease highly conserved both in prokaryotes and eukaryotes, which is involved in the regulation of TGF-β signaling.

OBJECTIVE

We aimed to screen for HTRA1 mutations in patients with NOTCH3-negative CADASIL-like phenotype.

PATIENTS AND METHODS

We selected 137 patients with cerebral ischemic SVD. The inclusion criteria were marked leukoaraiosis, recurrent strokes and/or cognitive impairment, a family history of stroke or dementia with a Mendelian pattern of inheritance and negative screening for NOTCH3 gene. In all patients total genomic DNA was extracted from whole blood. Then the entire coding regions and adjacent intronic regions of HTRA1 were amplified by PCR and directly sequenced.

RESULTS

We identified 8 unrelated index carriers of different single heterozygous HTRA1 gene variants (Fig. 1). All but one mutation were previously unreported and fallen within the functional domains of the protein. For most of them, mutation-prediction software analyses indicated a high potential for being cause of disease. None of the allelic variants we found were present in 320 chromosomes of neurologically healthy controls. In all patients the age at onset ranged from 40 to 65 years. Of particular interest was a family where the proband resulted heterozygous for the c.883G>A mutation which segregated with clinical phenotype (white matter signal abnormalities and neurological manifestations) in some first-degree relatives (Fig.2).

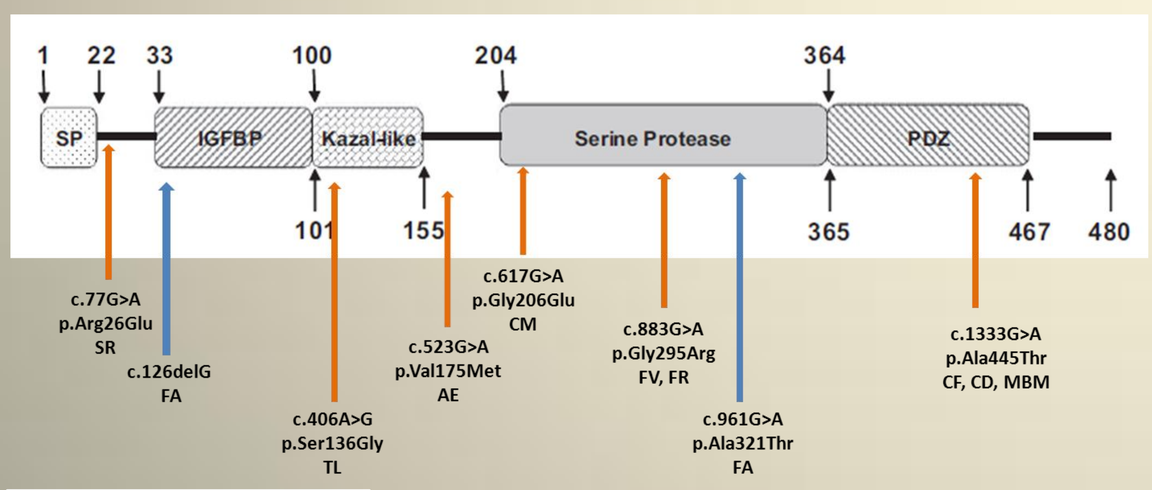

Fig.1: Genetic results.

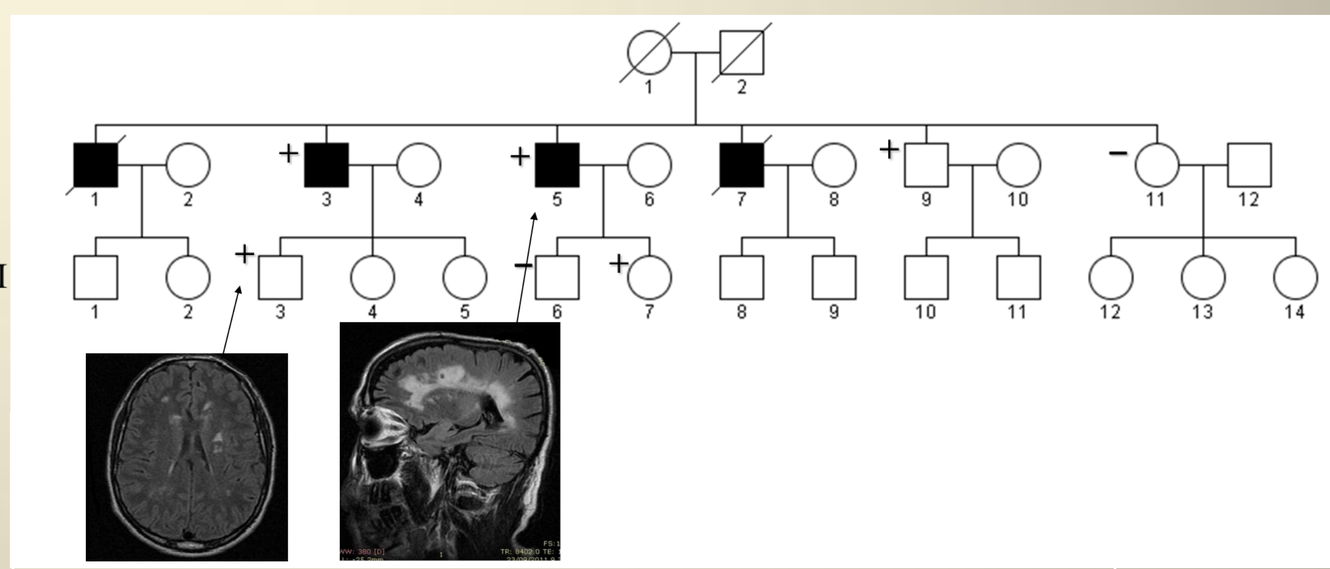

Fig.2: Family tree of our family**. Legend: +**: carriers of the mutation
-: no mutations of gene.

DISCUSSION

The role of single heterozygous mutations in putative recessive genes in the development of specific clinical phenotypes (e.g. PNK1 in Parkinson Disease, MFN2 in Charcot-Marie Tooth type2) is still poorly understood and a matter of debate. Our findings of HTRA1 heterozygous mutations in patients with familial SVD provide novel evidence that these mutations may act as a susceptibility genetic factor of developing vascular leukoencephalopathy. We suggest that the presence of heterozygous mutations in HTRA1 gene can reduce the protein functionality, leading to an attenuated form of the disease with a later onset with respect to the classical CARASIL phenotype.

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