A New Chinese Family of Autosomal Dominantly inherited Cerebral Small Vessel Disease Related to A Heterozygous HTRA1 Mutation

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Letter

Keywords:

Posted Date: July 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-656926/v1

Abstract

none

Main Text

Cerebral small vessel diseases (CSVDs) represent a group of clinically and genetically heterogeneous disorders which is the leading cause of vascular dementia(1). The typical neurological features include diffuse white matter lesions, lacunar infarcts, and microbleeds(1). Although most cases of CSVDs are sporadic, several genes have been identified to be associated with familial CSVD, including *NOTCH3*, *HTRA1*, *CTSA, GLA*, *COL4A1/A2*, *TREX1*, and *CSF1R*(2). Here, we reported a new autosomal dominant hereditary Chinese CSVD pedigree carrying a *HTRA1* heterozygous mutation previously reported in Italian, Spanish, Greek and Chinese families(3-6).

A 62-year-old man presented to our department with progressive changes of behavior and personality for 5 years. Initial symptoms of the patient included irritability, indifference to his surroundings, disinhibition and forced behaviors. He was misdiagnosed with mental illness and sent to psychiatric hospital. One year later, he developed a progressive decline in cognitive function.

He was a former cigarette smoker with a history of ischemic stroke, hypertension, diabetes and hyperlipidemia. There was no evidence of baldness or receding hairline, nor history of back pain. His mother had died of cerebral hemorrhage at the age of 78, his maternal uncle had a history of mental illness. His older brother had a history of alopecia, and presented personality changes at the age of 56, developing progressive memory impairment four years later. (Fig 1- A)

On physical examination, the patient showed hypertonia in the right lower limb, exaggeration of right knee and ankle reflexes, and positive Romberg's sign. Neurologic examination revealed deficits in memory, attention, executive functioning, and poor performed on the verbal fluency test. The patient was also prone to disinhibition, irritability, and aberrant motor behaviors. Brain MRI showed cortical atrophy especially in the right frontal and temporal lobes, diffusely hypodense periventricular white matter and multiple lacunar infarcts in the basal ganglia (Fig 1-F).

The proband underwent genetic testing. Target sequencing was performed on the Hiseq2000 platform (Illumina) according to the manufacturer's protocols. The panel used in this study included 95 dementia-related genes, and the gene list was shown in Supplementary Table 1. A heterozygous missense mutation (c.496C>T, p.R166C) in exon 2 of the *HTRA1* (NM_002775.5) gene was detected in the proband which was confirmed by Sanger sequencing (Fig 1-B). This mutation was not detected in data from the Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org), NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS) or 1000 Genomes Project. It is not located in domains of HTRA1 protein (Fig 1-C), but alters a conserved amino acid (Fig 1-D) and is predicted to generate a putative pathological effect by all in silico tools (Fig 1-E). The proband was homozygous for APOE allele ε3 and did not carry mutations in any other screened dementia-related genes. Family segregation could not be

performed because of failing obtain additional DNA from his brother and other siblings due to their refusal.

HTRA1 gene encodes a member of the trypsin family of serine proteases which is composed of an insulin-like growth factor-binding protein domain, Kazal-type serine protease inhibitor motif, trypsin-like serine protease domain and C-terminal PDZ domain. To date, more than 40 mutations of *HTRA1* have been identified associated with cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy type 2 (CADASIL2)(6). The molecular mechanisms underlying heterozygous *HTRA1* mutations associated CADASIL2 might result in an impaired HTRA1 protease activity or the inability of the protein to form stable trimers(7). Trimerization of HTRA1 monomers is mediated by ring-stacking interactions of N-terminal residues Tyr169, Phe171 and Phe278 of each monomer(8). The p.R166C missense mutation described here was close to the key sites for HTRA1 trimerization. In addition, a different heterozygous *HTRA1* missense mutation at the same residue (c.497G>T, p.R166L) found in a CSVD family has been identified to reduce proteolytic activity of HTRA1(9). Therefor it is reasonable to declare the pathogenic role of the heterozygous p.R166C mutation in our family.

Clinical data of five families with *HTRA1* p.R166C mutation was shown in Fig1-G. The median age of onset was 45 years (ranging from 29 to 78 years). Most of the mutation carriers were with a history of cerebrovascular event and half of them presented with hair loss and back pain. Brain MRI was characterized by diffuse white matter hyperintensities and multiple lacunar infarcts. Cognitive impairment was reported in all patients.

In conclusion, we reported a Chinese CADASIL2 family with atypical clinical characteristics caused by heterozygous *HTRA1* mutation. The present study expands the phenotype spectrum of *HTRA1* gene related CSVDs.

Abbreviations

CSVDs: Cerebral small vessel diseases; MRI: Magnetic Resonance Imaging; CARASIL: cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CADASIL2: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy type 2

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Renmin Hospital of Wuhan University in China, and written informed consent was obtained from the patient and his guardians.

Consent for publication

Written informed consent was obtained from the patient and his guardians.

Availability of data and materials

The datasets used during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

Zhang JQ: Study conception; acquisition of data; drafting of the manuscript. Nie SK, Li ZN, Zhang XY and Zhang ZT: critical revision of the manuscript for important intellectual content. Xiao TT: Study conception, design, and organization; critical revision of the manuscript for important intellectual content; study supervision. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

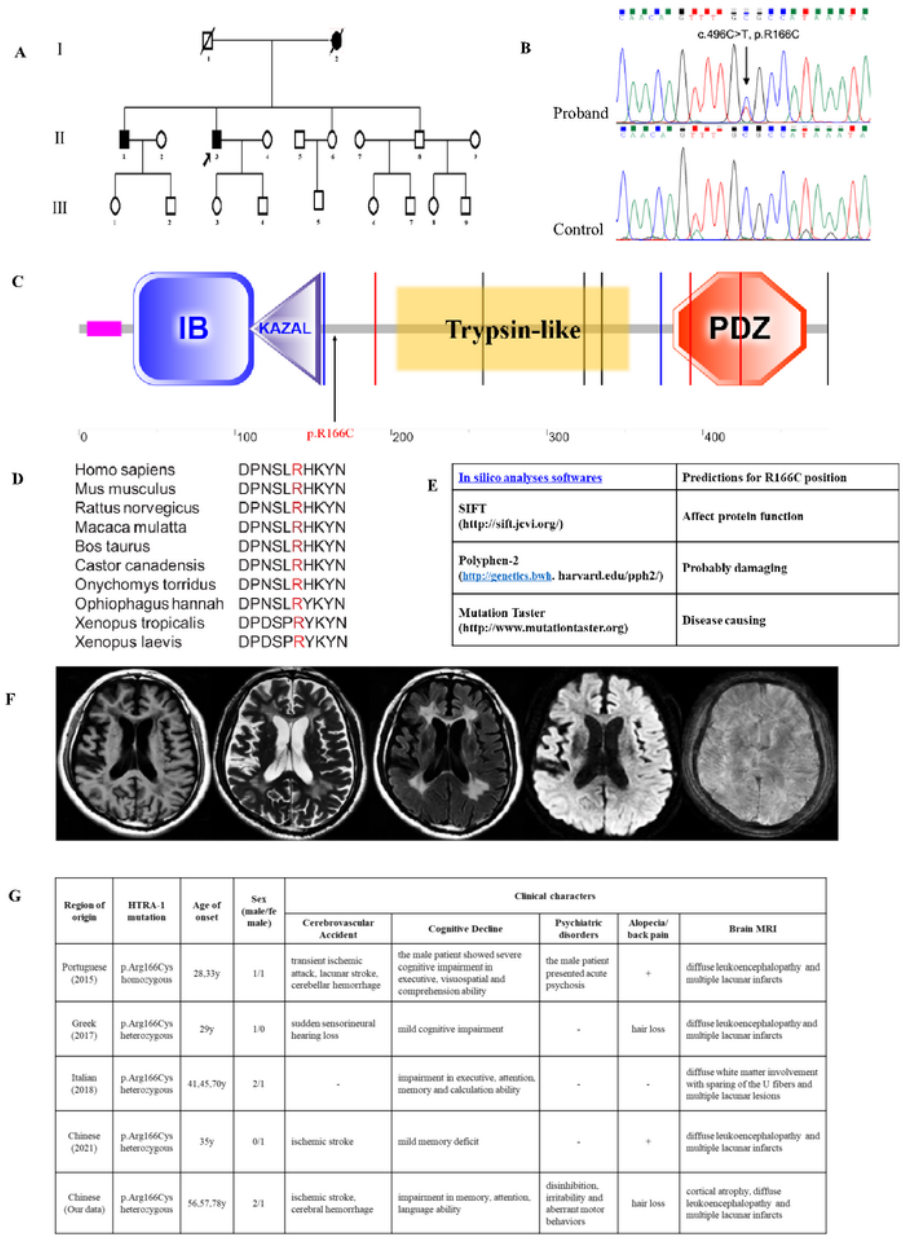

Figure 1

Pedigree and R166C mutation. (A) Pedigree of the family, proband was indicated by an arrow. (B) Mutation in HTRA1 (c.496C>T, p.R166C) was identified in proband. (C) Schematic representation of the conserved domains of HTRA1 protein. The previously identified mutation was located in the second exon of HTRA1 gene. (D) R166C was highly conserved residue across species. (E) In silico analyses of the

R166C mutation in HTRA1 gene. (F) Brain MRI of the proband. (G) Clinical characteristics of families with HTRA1 p.R166C mutation.

Supplementary Files

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