Meta-analysis of the association between CHCHD10 Pro34Ser variant and the risk of frontotemporal dementia

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Review question / Objective: Previous studies investigated the contribution of Pro34Ser mutation in the pathogenesis of ALS. Nevertheless, no comprehensive analysis of Pro34Ser mutation has been reported in FTD patients, hence, this meta-analysis aims to investigate the role of CHCHD10 Pro34Ser mutation in FTD.

Condition being studied: Frontotemporal dementia (FTD) is characterized by a range of clinical manifestations including an insidious progressive degeneration in behavior, executive function, and language. FTD is the 3rd most prevalent form of dementia across all age groups, after Alzheimer's disease and dementia with Lewy bodies, besides, it is the major type of dementia in patients below the age of 65 years. Based on estimation by the US and European populations, this disease occurs in between 4 and 15 cases per 100,000. Notably, FTD is classified into 4 clinical variants, i.e., behavioral-variant FTD (bvFTD), non-fluent variant primary progressive aphasia (nfvPPA), semantic-variant primary progressive aphasia (svPPA) and logopenic variant primary progressive aphasia (lvPPA). Despite genetic inheritance playing a vital role in the pathogenesis of FTD, studies on its underlying pathology has not matured. Previous studies investigated the contribution of Pro34Ser mutation in the pathogenesis of ALS. Nevertheless, no comprehensive analysis of Pro34Ser mutation has been reported in FTD patients, hence, this meta-analysis aims to investigate the role of CHCHD10 Pro34Ser mutation in FTD.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 May 2021 and was last updated on 25 May 2021 (registration number INPLASY202150090).
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Rationale: Reports indicate that 10% - 20% of FTD cases are caused by mutation in MAPT (encoding microtubule-associated protein tau), GRN (encoding progranulin, also known as acrogranin), and C9orf72 (encoding protein C9orf72) genes. CHCHD10 gene, located on 22q11.23 and encodes a mitochondrial protein located in the intermembrane space and is enriched at the cristae junction, was identified to be associated with FTD and amyotrophic lateral sclerosis (ALS) in a large family in 2014. Thereafter, subsequent studies have identified the association between CHCHD10 mutations with FTD and ALS. Previous studies investigated the contribution of Pro34Ser mutation in the pathogenesis of ALS. Nevertheless, no comprehensive analysis of Pro34Ser mutation has been reported in FTD patients, hence, this meta-analysis aims to investigate the role of CHCHD10 Pro34Ser mutation in FTD.

METHODS

Search strategy: “Frontotemporal dementia” or “FTD” and “Pro34Ser” or “CHCHD10”.

Participant or population: 1,408 FTD patients.

Intervention: FTD with Pro34Ser variant.

Comparator: FTD without Pro34Ser variant.

Study designs to be included: Observational studies.

Eligibility criteria: The inclusion criteria were as follows: (a) use of a case-control study design or a genome-wide association studies (GWAS) design to analyze patients with FTD and healthy controls; (b) evaluation of the association between Pro34Ser variant and FTD risk; (c) report on frequency of a minor allele distribution for both cases and controls or other data necessary for estimating odds ratio (OR) at 95% confidence interval (CI). Notably, only large studies were enrolled for studies with overlapping cohorts. On the other hand, studies that had not reported the frequency of minor alleles in Pro34Ser and those that cannot calculate the frequency of minor alleles based on the data provided by the author were excluded.

Information sources: PubMed, Web of Sciences, Embase databases were searched for studies on the potential association between CHCHD10 Pro34Ser variant and risk of FTD.

Main outcome(s): A total of 4 studies involving 1,408 patients with FTD and 7,511 controls were analyzed. Based on fixed-effects meta-analysis, the Pro34Ser variant was not associated with increased risk of FTD (Pro34Ser-positive vs Pro34Ser-negative: OR 0.91, 95% CI 0.41 to 2.05, P = 0.823).
Additional outcome(s): None.

Data management: We use Excel to extract the original data and Endnote to manage the data.

Quality assessment / Risk of bias analysis: Each study was given a Newcastle-Ottawa Scale quality score. Publication bias was assessed using Egger’s and/or Begg’s tests.

Strategy of data synthesis: Heterogeneity among the included studies was evaluated using the Q test and quantified using I². An I² value below 25% was considered as homogeneity; 25% to < 50%, low heterogeneity; 50% to < 75%, moderate heterogeneity; and at least 75%, substantial heterogeneity. We planned to use a fixed-effects model to meta-analyze pooled data classified as homogeneous or of low heterogeneity, and a random-effects model for data classified as showing moderate or substantial heterogeneity. Publication bias was assessed using Egger’s and/or Begg’s tests.

Subgroup analysis: None.

Sensitivity analysis: We performed a sensitivity analysis by omitting the individual studies one at a time to test the robustness of our findings.

Language: Only articles in English were included.

Country(ies) involved: China.

Other relevant information: None.

Keywords: Frontotemporal dementia, CHCHD10, Pro34Ser, meta-analysis.

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