LETTER TO THE EDITOR

High prevalence of CHCHD10 mutation in patients with frontotemporal dementia from China

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Sir,

Data recently published in Brain indicate that the CHCHD10 gene (NM_213720.2) plays an important role in frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) (Bannwarth et al., 2014; Johnson et al., 2014; Muller et al., 2014; Dols-Icardo et al., 2015; Marroquin et al., 2015). The CHCHD10 gene is located on chromosome 22q.11.23 and encodes a protein enriched at cristae junctions in mitochondria. Mutations in this gene cause mitochondrial dysfunction, which leads to disease. The study is the first report proposing that mitochondrial dysfunction contributes to the pathogenesis of ALS and FTD. The prevalence of the CHCHD10 mutation has been reported in a number of nationalities, including German (2.3%), French (2.6%), Spanish (0.68%) and Italian (1%) populations (Chaussenot et al., 2014; Muller et al., 2014; Chio et al., 2015; Dols-Icardo et al., 2015). However, no mutation analysis has been performed in Asian populations, and most variants have been on the ALS or ALS-FTD spectrum. Here, we present data showing that the CHCHD10 mutation is common in patients with the pure FTD phenotype in China.

Patients with ALS (n = 165) and FTD (n = 65) were recruited at the outpatient clinic of Xiangya Hospital, China. The patients with ALS did not have mutations in SOD1, FUS, C9orf72 and TARDBP. Additionally, the patients with FTD did not have any variants of MAPT, GRN and C9orf72. We screened all of the exons in the CHCHD10 gene using Sanger sequencing. The analyses also included 500 unaffected individuals with matched geographical ancestry as healthy controls. This study was approved by the ethics committee of Xiangya Hospital, Central South University in China. All patients provided written informed consent.

In this study, the age at onset of disease in patients with ALS was 48.9 ± 12.8 years (male = 71.5%). There were 15 patients (9.1%) with a positive family history of neurological disease. The age at onset in the patients with FTD was 56.3 ± 10.3 years (male = 49.2%). These patients were classified into the following clinical phenotypes: behavioural variant FTD (n = 42), progressive non-fluent aphasia (n = 6), semantic
We identified five novel missense mutations in CHCHD10 in five unrelated patients with sporadic FTD. The mutations included the following: c.64C>T, p.H22Y; c.67C>T, p.P23S; c.68C>T, p.P23L; c.95C>A, p.A32D; and c.170T>A, p.V57E (Fig. 1). All of the variants were heterozygous except for the P23S homozygous mutation. Furthermore, all of the variants were located in CHCHD10 exon 2. These mutations were not detected in patients with ALS. We subsequently screened exon 2 in 500 healthy individuals and the results showed the variant was absent. Additionally, these variants were not detected in data from the National Heart Blood and Lung Institute Exome Sequencing Project (ESP6500), 1000 Genomes Project [result in different dataset: Asian, 2012 Apr; CHB (Northern Chinese); JPT (Japanese); CHS (Southern Han Chinese)] or the Single Nucleotide Polymorphism Database (dbSNP137). The functional predictions using the MutationTaster tool revealed all variants were damaging (http://www.mutationtaster.org) (Table 1).

The mutation carriers (male = 4/5), including four patients with behavioural variant FTD and one patient with semantic dementia, had an average age at onset of 61.6 ± 9.7 years (range 52–76 years). The average disease duration was 4.6 ± 3.1 years (range 2–10 years). The H22Y mutation (Patient 2-A6) was identified in a patient with sporadic behavioural variant FTD, who had been bright and sociable as an accountant. However, at 54 years of age, he presented progressively bizarre behaviours including withdrawal from social engagements. The patient also began laughing and speaking loudly at inappropriate occasions and then lost interest in family events. After 4 years, he became aggressive and irritable. By the age of 60 years, his memory and executive function had substantially declined. MRI showed bilateral frontotemporal atrophy. The patient did not develop ALS or other neurodegenerative disorders. We also detected a homozygous (c.67C>T, p.P23S) and a heterozygous (c.68C>T, p.P23L) mutation in the same codon. However, the clinical presentations were different. The P23S mutation carrier (Patient 2-B7) was initially misdiagnosed as having schizophrenia due to the predominant symptoms of hallucinations and delusions at the age of 66 years. However, there was no change found after 3 months of risperidone treatment. At 68 years of age, the patient subsequently presented apathy and inappropriate behaviours. MRI indicated bilateral frontal lobe atrophy. The P23L mutation carrier (Patient 3-C10) had a typical language impairment syndrome. At 52 years of age, the patient displayed initial symptoms such as difficulties finding words and reduced comprehension. The patient’s family could not understand his speech due to the use of meaningless words. At 55 years of age, the patient manifested increased sexual activity. MRI
revealed bilateral temporal lobe atrophy and moderate frontal atrophy. These two carriers did not have any family history of neurological disease. The patients and their relatives were all free from ALS and other neurodegenerative disorders. The A32D mutation carrier (Patient 2-D10) had been an introverted person. However, the patient began to speak with strangers (especially female) and invite them to dinner. A neurological assessment indicated that memory and other cognitive abilities remained intact, and the MRI result was negative. Considering the disease duration was 1 year, we should follow-up to observe whether the patient develops an ALS phenotype. Finally, there was one patient with behavioural variant FTD and a V57E mutation (Patient 2-C12) who was a teacher. At the age of 60 years, she became easily irritable and lost her job due to poor attention span. The patient subsequently presented compulsive stereotyped movement at the age of 62 years. A neurological assessment revealed there was cognitive impairment in memory, execution and visual-spatial function. MRI showed asymmetrical frontal-temporal atrophy. The patient and her family members did not suffer from ALS.

CHCHD10 is the second most important gene linked to ALS and FTD beside the C9orf72 gene. C9orf72 mutations are rare in Asian populations (Jiao et al., 2014). However, the prevalence of CHCHD10 mutations is up to 7.7% (5/65) in Chinese patients with FTD and is higher than in European populations (range 0.68–2.6%). In previous work, we demonstrated the prevalence of MAPT, GRN and C9orf72 mutations were responsible for 2.8%, 1.4% and 2.8% of FTD cases, respectively (unpublished data). Therefore, we suggest that genetic testing should first be conducted for CHCHD10 before evaluating MAPT, C9orf72 and GRN. This proposed strategy should improve the genetic diagnosis workflow for Chinese patients with FTD.

There are more than nine rare variants of CHCHD10 that have been identified in patients with broad phenotypes including ALS, FTD, Parkinson’s disease, myopathy and late-onset spinal motor neuronopathy. These variants were predominantly detected in patients with ALS or ALS-FTD. However, we did not detect any variant in patients with ALS, including the S59L mutation that was first identified in a large family of patients with ALS-FTD. There are at least two reasons that account for our data, small sample size and different ethnicities. Interestingly, all identified variants were from the patients with a pure FTD phenotype. Zhang et al. (2015) previously reported two cases of behavioural variant FTD that had mutations within a cohort of 158 Canadian patients with FTD. Additionally, a study from Dols-Icardo et al. (2015) reported that three patients with pure FTD had variants in a cohort of 876 Spanish patients with FTD (Dols-Icardo et al., 2015; Zhang et al., 2015). Although only 65 patients with FTD were enrolled in this study, the higher prevalence suggested CHCHD10 frequently has gene variants in patients with FTD.

In summary, we identified four novel heterozygous variants and one homozygous variant in five unrelated patients with FTD. We cannot easily conclude that CHCHD10 was associated with ALS due to the limited sample size. We found that the CHCHD10 mutation is common in patients with a pure FTD phenotype. Our study provides additional genetic support for CHCHD10 as a novel FTD gene and extends the phenotype–genotype correlation of CHCHD10-related disorders.

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**References**


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<th>Case</th>
<th>Gender</th>
<th>Age at onset (years)</th>
<th>Diagnosis</th>
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<th>Amino acid change</th>
<th>Inherited model</th>
<th>Damaging prediction</th>
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**Table 1** Novel variants identified in all subjects


