Genetic analysis of the *CHCHD2* gene in Chinese patients with familial essential tremor

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Abstract

Recently, Funayama et al. identified *CHCHD2* as a novel causative gene of Parkinson disease (PD). However, the relationship between *CHCHD2* and essential tremor (ET) patients was still unknown. Genetic analysis of *CHCHD2* gene was conducted in 60 probands of ET families with autosomal dominant inheritance and 90 healthy controls in Chinese population. No pathogenic *CHCHD2* mutation was found in ET patients, but we identified one rare variant, c.5C>T, a reported risk variant for sporadic PD in Japanese populations, and examined the frequency of three common variants. Our results supported that *CHCHD2* mutations may be rare in Chinese familial ET patients.

Key words: essential tremor, Parkinson disease, *CHCHD2*, Chinese population

Introduction

Essential tremor (ET) is one of the most common neurological disorders characterized by postural and kinetic tremors. Although 50%~70% of ET patients have a positive family history and genetic component may play a major role in the development of ET, the main genetic basis of ET remains unclear [1, 2]. Recently, Funayama et al. identified *CHCHD2* as a novel causative gene of Parkinson disease (PD) in Japanese population [3]. They found that the causative mutation (c.182C>T, p.Thr61Ile) was not only in patients with PD, but also in a patient with ET from the same family. An association between *CHCHD2* and ET may exist. Puschmann et al. reported that no mutation was found in *CHCHD2* in the Arkansas and the Swedish family with autosomal dominant parkinsonism and essential tremor [4, 5]. However, the

relationship between *CHCHD2* and ET patients in the Chinese population was still unknown. In this study, we performed genetic analysis of *CHCHD2* in 60 ET families with autosomal dominant inheritance and 90 healthy controls.

Methods and materials

The study comprised 60 probands of ET families with autosomal dominant inheritance and 90 healthy controls. All patients and controls underwent a standardized neurological examination by two movement disorder specialists, recruited from the Neurology Department of the Second Affiliated Hospital, School of Medicine, Zhejiang University. ET diagnoses were based on Movement Disorder Society (MDS) Consensus Criteria [6]. Informed consent was obtained from each participant. The institutional ethics board committees approved the study.

Genomic DNA was isolated using standard procedures from peripheral blood leukocytes from all subjects. Exonic regions of the *CHCHD2* gene were amplified by PCR. Each PCR product was directly sequenced on an ABI 3100 automated sequencer. DNASTar was used for sequence alignment and analysis by two analysts independently. Variants frequencies of ET and control groups were analyzed using the Chi-square test. Bonferroni correction has been used and the significance level is 0.00625 (0.05/8) after correction.

Results

No causative mutation in *CHCHD2* was found in our ET patients, but we identified one rare variant, c.5C>T, a reported risk variant for sporadic PD in Japanese populations, and examined the frequency of three common variants (c.-34C>A,

c.-9T>G, c.*125G>A) (Table 1). The rare variant c.5C>T was carried by a single patient #L589 (Fig.1) and had a higher MAF of 0.0167 compared to that reported in the ExAC database (East Asian, MAF 0.008121). However, the MAF calculation of c.5C>T based on one carrier may be inconclusive. Patient #L589 developed ET at the age of 48 years old and his mother is also suffering from ET. No significant difference was found between ET patients and controls in all 4 variants (P value>0.00625).

Table 1

Genotypic and allelic frequencies of the *CHCHD2* gene variants in ET patients and controls

Nucleotide change	Accession number	Amino acid	Genotype /allele	ET N (%)	Control N (%)	ET vs Controls	
						P value	OR (95% CI)
c.-34C>A	rs816407	5'UTR	AA	53(88.3)	83(92.2)	0.42	0.69(0.21-1.92)
			CA	7(11.7)	7(7.8)		
			CC	0	0		
			A	113(94.2)	173(96.1)	0.43	0.65(0.22-1.91)
			C	7(5.8)	7(3.9)		
c.-9T>G	rs10043	5'UTR	GG	53(88.3)	83(92.2)	0.42	0.69(0.21-1.92)
			GT	7(11.7)	7(7.8)		
			TT	0	0		
			G	113(94.2)	173(96.1)	0.43	0.65(0.22-1.91)
			T	7(5.8)	7(3.9)		
c.5C>T	rs142444896	Pro2Leu	CC	59(98.3)	90(100)	0.40	1.01(0.98-1.05)
			CT	1(1.7)	0		
			TT	0	0		
			C	119(99.2)	180(100)	0.40	1.00(0.99-1.02)
			T	1(0.8)	0		
c.*125G>A	rs8406	3'UTR	GG	54(90.0)	83(92.2)	0.63	0.75(0.24-2.38)
			GA	6(10.0)	7(7.8)		
			AA	0	0		
			G	114(95.0)	173(96.1)	0.64	0.77(0.25-2.35)
			A	6(5.0)	7(3.9)		

Abbreviations: ET: essential tremor; N: number; OR: odds ratio; CI: confidence

interval; NA, not applicable.

Discussion

CHCHD2 gene contains 4 exons and encodes CHCHD2 protein, characterized by an N-terminal mitochondrial targeting sequence and twin cysteine-x9-cysteine motifs which are involved in biogenesis and regulation of enzymes in the mitochondrial respiratory chain [7].

In our study, no *CHCHD2* mutation was identified, suggesting that the pathogenic mutations of this gene may be rare in ET patients. However, we identified one rare variant, c.5C>T, which was reported to be a risk variant for sporadic PD in several studies, and examined the frequency of the other three common variants (c.-34C>A, c.-9T>G, c.*125G>A). As for the c.5C>T, most studies in Asian populations have revealed that c.5C>T in *CHCHD2* is associated with PD [3, 8-10], except the study conducted in Taiwanese populations [11] and the studies in other ethnic populations [12], which may partly due to ethnic difference. For the other common variants, rs10043 and rs8406 [3], which were also reported as risk single nucleotide polymorphisms of PD in the Japanese population, showed no significant difference between ET patients and controls in our study. For the common variants, c.-34C>A, also showed no significant difference between ET patients and controls in our study, which seemed to be in accordance with recent studies of PD [13, 14].

ET and PD are two of the most common adult onset movement disorders with overlapping clinical features. Many studies indicate the possibility of a common genetic link between ET and PD. To the best of our knowledge, this is the first cohort

study to evaluate the possible association between the *CHCHD2* gene and ET. Our results suggested that *CHCHD2* mutations may be rare in Chinese familial ET patients. The results will stimulate researches about pathogenic role of the *CHCHD2* gene. Nevertheless, our negative results can't exclude the limited sample size. Larger-scale genetic studies in multiple ethnic populations should be performed to confirm these findings.

Conclusion

CHCHD2 mutations may be rare in Chinese familial ET patients.

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Fig.1. (A1) Wild type (arrow points) and (A2) a heterozygous polymorphism, C.5C>T (arrow points).