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Alterations of functional connectivity density in a Chinese family with a mild phenotype associated with a novel inherited variant of SCN8A

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ABSTRACT

Objective: Only a few heritable SCN8A variants have been described in patients with a mild phenotype of epilepsy. Here, we describe a Chinese family with a novel inherited SCN8A variant and investigate changes in spontaneous cerebral activity during the resting-state in magnetic resonance imaging (MRI)-negative patients with epilepsy and their unaffected siblings.
Methods: A gene panel targeting 535 epilepsy genes was performed on the proband and his parents. The identified variant was confirmed in other affected members by Sanger sequencing. Resting-state functional MRI (fMRI) data were gathered from the family (4 affected individuals and 3 unaffected siblings) and 72 healthy controls (HCs). Functional connectivity density (FCD) was used to assess whether distant or local functional network changes occurred in patients with epilepsy.
Results: A heterozygous missense variant (c.4568C>A; p.A1523D) in SCN8A was identified in the Chinese family, with a total of 7 members who presented with a mild phenotype (childhood seizures and normal cognition). All patients remained seizure-free, and one patient remained seizure-free without medication. Increased FCD values in the thalamocortical network and basal ganglia network were observed in both patients with epilepsy and their unaffected siblings compared with the HCs. Direct comparison between SCN8A variant patients and unaffected siblings showed that more serious and distributed abnormal changes occurred in the mesial frontal regions of patients with epilepsy.
Conclusions: We identified a novel SCN8A variant with a mild familial epilepsy phenotype. A similar pattern of FCD alterations in patients and their unaffected siblings might represent an endophenotype of benign epilepsy associated with the SCN8A inherited variant, and more extensive alterations in mesial frontal regions may help us to further understand the pathogenesis of SCN8A-related mild epilepsy.

1. Introduction

The voltage-gated sodium channel gene, SCN8A, encodes the Nav1.6 α subunit, which is widely expressed in the central nervous system [1]. Pathogenic SCN8A variants in humans can cause a broad spectrum of epilepsy phenotypes, including severe early-onset developmental and epileptic encephalopathies (DEEs) [2], treatable seizures and mild intellectual disability [3], as well as benign familial infantile seizures (BFISs) [4,5]. In addition, these variants can also cause a few cases with no epilepsy [6,7]. To date, more than 100 SCN8A variants have been identified, and most of which were de novo [8–10]. Moreover, most de novo SCN8A variants in patients present with intractable epilepsy and serious intellectual disability [10], and these variants account for approximately

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1% of epileptic encephalopathies (EEs) [11]. Recently, there has been an increasing number of patients with an intermediate SCN8A epilepsy phenotype, in which the majority presented de novo SCN8A variants [3]. However, few inherited SCN8A variants have been reported. Three recent reports have described five unrelated families with autosomal dominant heterozygous SCN8A variants associated with a milder phenotype of epilepsy with no developmental delay, and the brain magnetic resonance imaging (MRI) scans of these family members were all normal [12]. In the present study, we identified a novel inherited SCN8A variant in a Chinese family with a milder clinical pattern.

Although conventional MRI showed a normal structure in patients with SCN8A variants [13], functional profiles remain unexplored. The functional connectivity density (FCD) of resting-state functional MRI (fMRI) signals has been identified as an effective parameter to investigate dysfunction in patients with epilepsy [14–17], and we utilized this parameter to assess functional connectivity changes in patients with the SCN8A variant and their asymptomatic siblings compared with healthy controls (HCs).

2. Materials and methods

2.1. Subjects and study design

A Chinese family with seven individuals with epilepsy was recruited. Seizures were categorized according to the International League Against Epilepsy classification [18]. Eleven members of the family were recruited for gene testing, including 5 patients with epilepsy and 6 unaffected individuals (Fig. 1A). Seven members of the family were also enrolled in the fMRI study, including four patients (II8, II10, III5, and III9) with epilepsy and three unaffected siblings (III6–III8) of these patients. Seventy-two HCs had no history of seizures or a family history of epilepsy and no other neurological disease. This study was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The Institutional Review Boards of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital provided ethical approval for this study. Informed consent was signed by all individual participants.

2.2. Gene study

2.2.1. Collected samples and DNA extraction

According to a standard extraction protocol, genomic deoxyribonucleic acid (DNA) was extracted from peripheral leukocytes using the QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany). Agarose gel electrophoresis was used to assess DNA integrity, and the DNA samples were stored at −80 °C until use.

2.2.2. Gene sequencing

Targeted sequencing was performed on genomic DNA samples from the proband and his parents for 535 epilepsy genes (Appendix Table 1) by MyGenostics Technology, Inc. (Beijing, China). Sequencing data analysis and annotation of variants were carried out as previously described [19]. Variants were categorized as benign, likely benign with uncertain significance, likely pathogenic, and pathogenic according to the interpretation guidelines of the American College of Medical Genetics and Genomics [20].

2.3. fMRI study

2.3.1. Data acquisition

An echo-planar imaging sequence and a 3-dimensional fast spoiled gradient echo sequence were used for collecting resting-state functional data and axial anatomical T1-weighted images. All data were collected in a 3-T GE MRI scanner with an eight-channel phased array head coil (MR750; GE Discovery, Milwaukee, WI) in the University of Electronic Science and Technology of China. Detailed acquisition parameters are illustrated in the Supplementary Materials.

2.3.2. Data preprocessing

The NIT software package (http://www.neuro.uestc.edu.cn/NIT.html) was used to preprocess fMRI data. Deletion of the first five volumes, slice-timing, realignment, normalization, and nuisance regression were performed in the present study. A detailed illustration of preprocessing is presented in Appendix B. The preprocessing procedure was the same as the one described in our previous study [21].

2.3.3. FCD analysis

Functional connectivity density calculation was performed using a neuroscience information toolbox (http://www.neuro.uestc.edu.cn/NIT.html). Functional connectivity density measures the functional interaction between a given voxel and lFCD and gFCD. Pearson's correlation coefficient was used to qualify the connectivity, and 0.6 was selected as the correlation threshold for the connectivity strength as commonly used in other studies [22]. For the gFCD of a given voxel, the number of voxels connected with the given voxel was computed as higher than the threshold (0.6). For the lFCD, the correlation coefficients were calculated between a given voxel and its immediate neighbors. The voxels with supra-threshold connection to the given voxel were added to its neighbor cluster. Next, the same calculation was performed for every voxel in the neighbor cluster to extend the size of neighbor clusters until no additional voxel was added. Then, the number of voxels in the final neighbor cluster was used to map the local FCD. The lrFCD was generated by subtracting lFCD from gFCD [23]. To reduce the variability of FCD across subjects, mean FCD values were divided from the FCD maps in each individual. Finally, spatial smoothing was performed in the present study using a Gaussian kernel with a full-width half maximum of 8 mm.

2.3.4. Statistical analysis

A one-sample t-test was performed to investigate the significantly high FCD values in the HC group. Crawford's t-test is an optimal statistical method to address a comparison between a single subject against a group of controls [24]. Because of the small sample size of the family with epilepsy, Crawford's t-test was performed for each of the seven subjects to investigate abnormally altered FCD with a threshold of $p < 0.005$. Then, a binary mask was generated for each statistical map. The voxels with statistical significance were assigned a value of 1, and the others were assigned a value of 0. Four statistically significant masks of patients with epilepsy and three masks of unaffected siblings were overlapped and transformed to binary images separately, generating group-level result maps. Finally, the group-level maps were further overlapped for a comparison of the spatial distributions of FCD disturbances in patients with epilepsy and their unaffected siblings.

3. Results

3.1. Clinical findings

In this family, the males and females were both affected and aged from 10 to 84 years old (Fig. 1A). The family members presented with normal motor and intellectual development. No family member had febrile seizures. Neurological and general examinations were unremarkable. All routine brain neuroimaging findings were normal. The proband (III5) had have seizures at the age of 2 years. Clinical manifestations included motor arrest, speechless sense, reduced responsiveness, and unilateral clonic convulsions. A 24-hour video-electroencephalogram (video-EEG) of the proband at the age of 22 years on lamotrigine (LTG) at 100 mg/day showed a normal background and occasional epileptiform discharges on the left mid-frontal and central areas (Appendix Fig. 1). The detailed clinical information of the seven patients with epilepsy and three

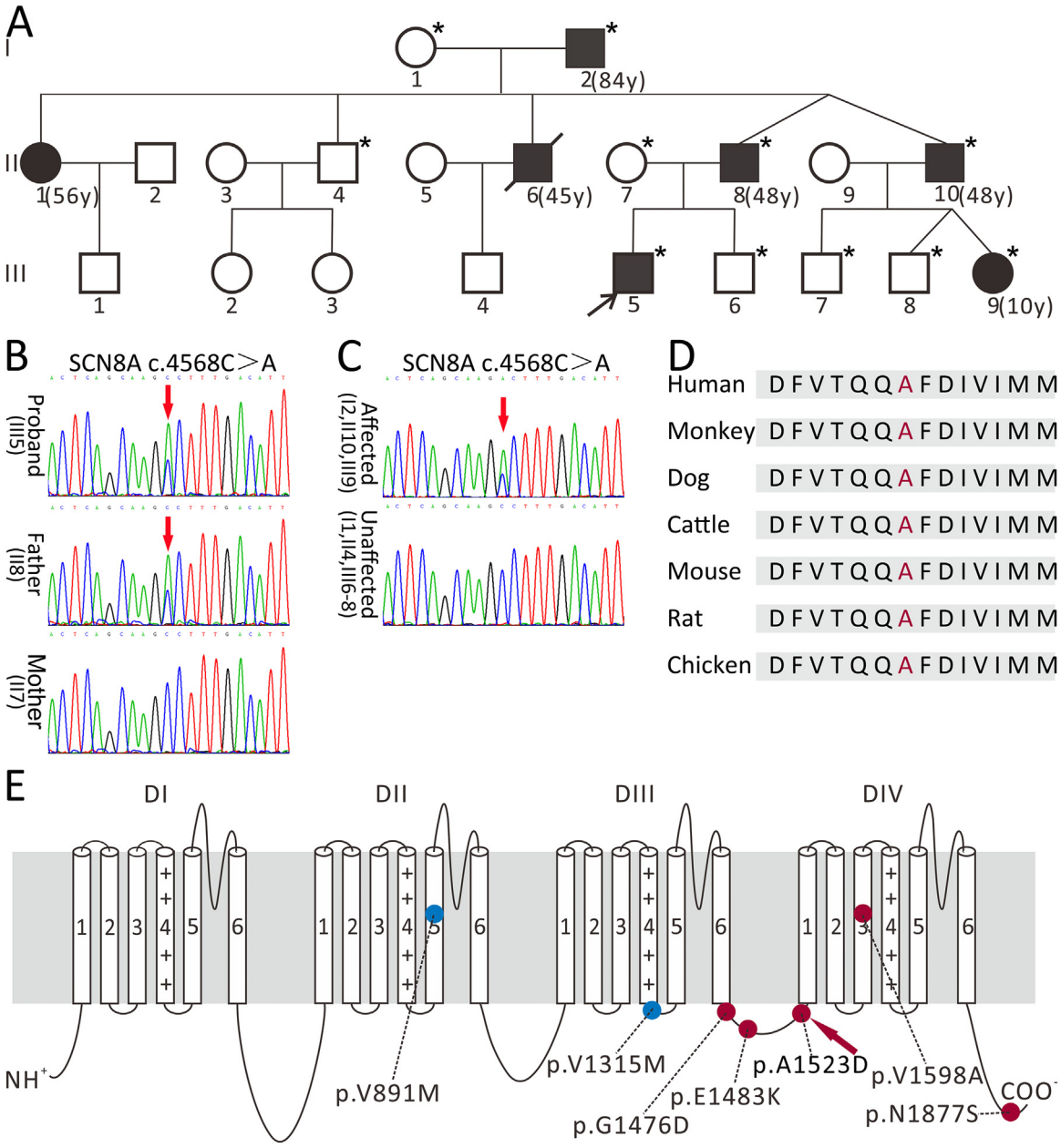

Fig. 1. Pedigree of the family and a novel SCN8A variant identified in this family. (A) The figure demonstrates the affected status of all family members. The available blood samples for gene study are marked with asterisks. (B) A novel heterozygous SCN8A variant c.4568C>A (p. Ala1523Asp) found in the proband and his parents (indicated by an arrow) by targeted next-generation sequencing. (C) The variant was identified in other affected members and was not detected in the unaffected members by Sanger sequencing. The arrow shows the position of the variant. (D) SCN8A protein sequences from different species. The protein sequence of the p. Ala1523Asp residue is highly evolutionarily conserved across the species compared, which is highlighted in red. (E) Variants in SCN8A described in patients with a mild seizure phenotype in relation to the location in the Nav1.6 channel. Blue indicates de novo variants. Red indicates inherited variants. Red and an arrow denote the variant identified in this study. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

unaffected siblings is summarized in Table 1, Appendix A, and Appendix Table 2.

In the fMRI study, all HCs demonstrated normal neurologic examination and MRI findings of the brain. These patients with epilepsy had a mean age of 32.3 ± 16.4 years, and there were 3 males and 1 female in this group. The mean age of unaffected siblings was 12.3 ± 1.7 years and consisted of 3 males. The HCs had a mean age of 26.1 ± 8.7 years, and there were 40 males and 32 females.

3.2. Genetic analysis

A heterozygous missense variant (c.4568C>A, p.A1523D) in exon 26 of SCN8A was identified in five affected individuals (I2, II8, II10, III5, and III9) from this family, whereas the variant was not found in the unaffected individuals (I1, II4, and III6–III8) (Fig. 1B, D and Appendix B).

3.3. fMRI findings (within- and between-group FCD values)

In our subjects, no excessive head motion was observed.

3.3.1. Within- and between-group FCD values

The results of the one-sample t-test in HCs showed that the voxels with high FCD values were mainly located in the posterior parietal, occipital, and prefrontal cortices (Fig. 2A). The FCD maps of four patients with epilepsy and three unaffected siblings are shown in Appendix

Table 1
Clinical features of the affected individuals of SCN8A mutation in the pedigree.

Patient	Gender	Age (death)	Age at SZ onset	SZ type	Video-EEG (age)	Respond to AEDs
I-2	F	84 y	1y	Focal to bilateral tonic–clonic SZ	nd	Untreated, SZ resolved
II-1	M	56	<1 y	Focal SZ	nd	SZ-free after PHT
II-6	F	(47 y)	2 y	Focal to bilateral tonic–clonic SZ	nd	Untreated
II-8	F	48	<1 y	Focal to bilateral tonic–clonic SZ	Normal	Not controlled by taking PHT irregularly; no SZs after 40 years old with nontreatment
II-10	F	48	<1 y	Focal to bilateral tonic–clonic SZ	Normal	SZ-free after PHT
III-5	F	23	2 y	Focal to bilateral tonic–clonic SZ	Abnormal (22 y)	Not controlled by VPA; No SZ after 19 years old with LTG
III-9	M	10	6 m	Focal SZ	Normal	SZ-free after OXC

AED, antiepileptic drug; EEG, electroencephalogram; F, female; LTG, lamotrigine; M, male; OXC, oxcarbazepine; y, years; m, months; PHT, phenytoin; SZ, seizure(s); VPA, valproic acid; nd, not done.

Fig. 2. Seven t maps from the Crawford's t-test are also shown in Fig. 2B, suggesting that all of the patients with epilepsy showed increased values for the three types of FCD in the mesial frontal cortex, anterior cingulate cortex, and basal ganglia relative to HCs. In addition, two of the patients with epilepsy also showed higher FCD values in the occipital lobe than the controls. Moreover, two of the patients with epilepsy demonstrated increased FCD values in the cerebellum. With regard to the unaffected siblings, a few alterations in the cerebral cortex were observed, which were located at the frontal and parietal lobes. In addition, the subcortical regions, including the basal ganglia and thalamus, and the cerebellum still showed increased FCD values in unaffected siblings compared with the HCs. Overlapping the integration results of patients with epilepsy and their unaffected siblings revealed that patients with epilepsy demonstrated more extensive alterations in crucial regions (mesial frontal regions) compared with their unaffected siblings (Fig. 2C).

4. Discussion

In this study, we described a novel inherited pathogenic variant (c.4568C>A) in SCN8A that changed alanine to aspartic acid at position 1523 in the present pedigree. Position 1523 is located in the intracellular loop between domains III and IV, a highly conserved portion of the inactivation gate in the Nav 1.6 channel (Fig. 1D and E). Here, we reported the clinical features of six affected members in a Chinese family. These features included early onset, good response to sodium channel blockers (SCBs; even seizure-free without treatment in I1), normal brain MRI, normal cognitive milestones, and normal motor milestones.

To date, only a few inherited SCN8A variants have been reported, including p.Glu1483Lys, p.Asn1877Ser, p.Val1598Ala, p.Gly1476Asp, and p.Val1315Met [4,5,10,25,26]. These variants, which are associated with a mild seizure phenotype, were distributed throughout the SCN8A channel (Fig. 2D). Similar to p.Gly1476Asp and p.Glu1483Lys, p.Ala1523Asp identified in this study was located in the cytoplasmic loop between domains III and IV. Based on its variant residue close to the inactivation gate, we speculated that p.Ala1523Asp might disturb the inactivation of $Na_V1.6$. Thus far, these three SCN8A variants at or close to the inactivation gate of the sodium channel (p.Gly1476Asp, p. Glu1483Lys and p.Ala1523Asp) have been found in mild epilepsy phenotypes, such as BFIS and infantile convulsions and paroxysmal choreoathetosis (ICCA) [4,12]. Moreover, some variants (p.Ile1464Thr, p.Asn1466Lys, p.Asn1466Thr, p.G1475R, p.Ile1479Val, p.A1491V, pGlu1483Lys, and p.K1498M) have also been identified close to or at the inactivation gate in patients with DEE and intermediate epilepsy [3]. Compared with the reported cases from Gardella et al. and Anand G et al. [4,5], the majority of the patients in our study had a milder phenotype than BFIS. However, the case characteristics in our study were similar to those reported by Wang J et al. (except for II3) and Han JY et al. [10,25]. The Korean family study included a relatively small number of patients. Moreover, all patients in the family enrolled in our study had become seizure-free at the time of study, which may be associated with the stages of the disease, variant site, or race.

To our knowledge, this was the first study to evaluate alterations in spontaneous brain activity during the resting-state in inherited SCN8A variant patients, their unaffected siblings, and HCs. Nav1.6 is strongly expressed in the cerebral cortex, subcortical structures, cerebellum, and hippocampus [1,27]. A recent study has suggested that the E1483K (Glu1483Lys) variant causing mild epilepsy in vitro revealed no obvious biophysical changes but increased neuronal firing in neurons [28]. In a previous study, significantly altered lrFCD in the cerebrum and cerebellum have been described in patients with generalized tonic-clonic seizures (GTCS) [15]. In addition, significantly increased lFCD in some arousal structures (such as midbrain/hippocampal/parahippocampal gyrus, thalamus, bilateral cerebellum, prefrontal cortex, left superior temporal pole, and posterior insula/rolandic operculum) have been found in patients with temporal lobe epilepsy (TLE) [16]. In our previous study, patients with idiopathic generalized epilepsy (IGE) showed reduced amplitude of low-frequency fluctuation and increased coupling with FCD in the cerebellum, implying that the abnormality of the cerebellum might participate in the regulation of generalized spike-and-wave discharges [14]. Previous evidence has also revealed that the cerebellum and basal ganglia might be related to propagation and modulation of epileptic discharges in IGE [14,29]. Consistently, the present fMRI results demonstrated increased FCD in the thalamocortical network and basal ganglia network in the SCN8A variant patient. Moreover, increased FCD values were also found in the basal ganglia, thalamus, and cerebellum in subjects without seizures when compared with HCs. Previous studies have shown temporal cortex morphologic alterations and significant deficits in cerebral white matter in patients with TLE and their unaffected siblings [30,31]. In a functional MRI working memory task, altered functional connectivity and motor system activation are common in patients with juvenile myoclonic epilepsy (JME) and nonaffected siblings [32]. Recently, Lorenzo Caciagli et al. [33] assessed the hippocampal structure and function in JME and their unaffected siblings by using multimodal MRI and neuropsychological measures, and they found abnormal hippocampal shape, volume, and positioning in patients with JME and their unaffected siblings. The above research suggests that these similar imaging alterations in patients with epilepsy and unaffected siblings may be an endophenotype of patients with TLE or JME. Thus, our findings suggested that increased FCD of the basal ganglia, thalamus, and cerebellum in patients and unaffected siblings is not seizure- or medication-related but represents an endophenotype of benign epilepsy caused by the SCN8A-inherited variant. Qualitatively, the patients with seizures showed more serious and distributed abnormal changes in the mesial frontal lobe, which is a key region for epileptogenesis in patients with epilepsy [34,35]. Interestingly, the video-EEG of the proband at the age of 22 years showed occasional epileptiform discharges on the left mid-frontal and central areas. Based on these findings, it is tempting to hypothesize that increased FCD in the mesial frontal regions could be related to epileptic actions and may be a neuroimaging biomarker for SCN8A-related epilepsy with a mild phenotype. However, combining video-EEG and MRI, Gardella et al. [2] observed an elective impairment of the temporo-occipital regions in patients with DEE with de novo SCN8A heterozygous variants. Thus, we considered that different electroclinical features between the

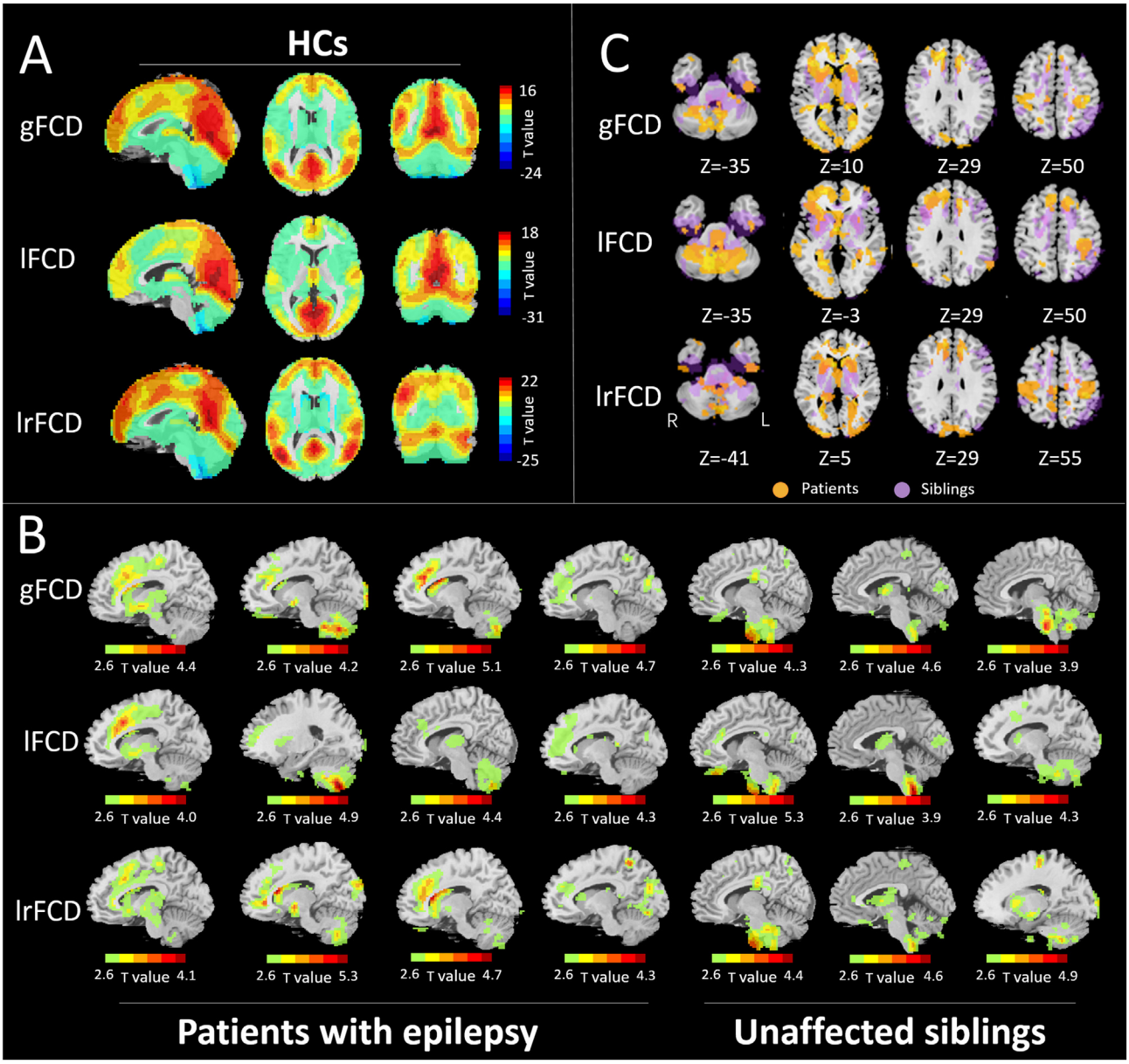

Fig. 2. FCD values within the HC group and alterations in patients with epilepsy and their unaffected siblings. (A) In HC, high FCD values were mainly located in the posterior parietal, occipital, and prefrontal cortices. (B) Using Crawford's t-tests, with a significance threshold of $p < 0.005$, increased FCD values in the thalamocortical network and basal ganglia network were observed in both patients with epilepsy and their unaffected siblings when compared with HC. (C) Overlaps of changed FCD in four patients with epilepsy and three unaffected siblings. Yellow represents patients with epilepsy, and purple represents unaffected siblings. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

patients with DEE and BFIS may be associated with the variant pattern of SCN8A loci, clinical manifestations, and research methods.

Notably, there are several limitations in our study. First, small samples of patients and unaffected siblings were brought into our fMRI research study. Thus, we cannot group them and discuss them further, which might decrease the reliability of the findings. Second, our study did not allow regulation of the confounding effects of antiepileptic drugs, which can affect normal neuronal function [36]. Thirdly, we only used a single threshold to construct FCD maps. A series of thresholds will be chosen to verify the stability of results in future studies.

In conclusion, we report a novel inherited SCN8A variant in a Chinese family with a mild epilepsy phenotype. Increased FCD values in the basal ganglia, thalamus, and cerebellum were found in both patients with epilepsy and their unaffected siblings, but these patients showed more serious and distributed abnormal changes in the mesial frontal lobe. Our findings indicated that common damage in patients with the SCN8A variant and their unaffected siblings might represent an endophenotype, while more widespread alterations of the mesial frontal lobe in patients might be a pivotal region in the pathogenesis of SCN8A-related mild epilepsy. Considering the small sample size, the inference cautiously proposed in the present study needs to be further verified in future research with a large sample size.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2020.107379.

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Declaration of competing interest

None of the authors have any conflicts of interest to disclose.

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