Variations of Mitochondrial ND4 and ND5 Genes and their Association with Temporal Lobe Epilepsy in a Northern Han Chinese Population

Sir,
Temporal lobe epilepsy (TLE) is one of the most common types of epilepsy, and is often intractable.[1] Recent studies have demonstrated that mitochondria play an important role in epileptogenesis in TLE through three prominent mechanisms: adenosine triphosphate (ATP) production, calcium homeostasis, and intramitochondrial cytochrome c release.[2] The dysfunction of mitochondrial activity has been observed only close to or directly inside of the epileptic foci of patients, while there were no changes in mitochondrial pathology observed in tissues surrounding the hippocampi.[3] A diverse range of diseases with mitochondrial genetic mutations has been identified in recent decades, however, studies focusing on a link between mitochondrial genetic mutations and TLE are relatively rare. In the present study, we used polymerase chain reaction sequencing-based genotyping (PCR-SBT) to detect MT-ND4 and MT-ND5 genetic mutations in 51 TLE patients and 16 matched healthy control volunteers from their peripheral blood samples.

In terms of MT-ND4 genetic mutations, out of 119 variants in the TLE group, we found 17 nonsynonymous mutations; 1 of 35 variants in the control group was nonsynonymous. Among these nonsynonymous mutations, 8 variants were reported in the NCBI database, 7 of which were absent from the control group [Table 1]. The possible impact on protein function caused by amino acid change was predicted using the PolyPhen-2 and SIFT scores. The mutation g.11087 T > C, altering the amino acid residue from phenylalanine to leucine at position 110, was predicted to be damaging by a score of 0.917 in PolyPhen-2 (sensitivity = 0.68, specificity = 0.90) and 0.000 in SIFT (cutoff = 0.05). This variant was absent from normal controls in our cohort and was also absent from 100 normal subjects in a previous study with a Han Chinese population.[4] Conservation of amino acids for polypeptides showed that g.11087 T > C was highly conserved among human, bovine, mouse, and xenopus laevis genomes.[5] Furthermore, we searched mitochondrial genome databases (http://www.mitomap.org) to determine whether this mutation was reported in other diseases. We found that this mutation site had been reported in Leber’s hereditary optic neuropathy (LHON) patients in two previous studies of Han Chinese populations.[5,6] It was known that seizures could be the manifestation of the LHON disease. The above findings suggested that the mutation g.11087 T > C played an important role in mitochondrial function. As MT-ND4 encodes respiratory chain complex I, subunit IV, dysfunction of the protein can cause energy defects, ROS production, and damage to the mitochondria. Increased ROS production by mitochondria leads to the aggregation of oxidative stress and further neuronal damage.

Another MT-ND4 mutation, g.11969 G > A, was predicted to be damaging to complex I function by its SIFT score, but not by its PolyPhen-2 score, in the present study. Although this variant was absent from normal controls in our cohort, it was reported in 2 of 100 normal subjects in a previous study of a Han Chinese population.[7] In addition, phylogenetic analysis of these variants from other organisms showed that it was not evolutionarily conserved.[8] Overall, the association of the g.11969 G > A mutation with TLE needs to be assessed in the future.

The mutation g.11204 T > C was predicted to be damaging based on a SIFT score of 0.00; however, it scored very low (0.002) on the PolyPhen-2 system. In addition, the mutation was reported in healthy controls in the present study. We believe that its role in TLE needs to be further studied.

In addition, the same method was used to predict MT-ND5 genetic mutations in TLE. In total, out of 124 variants in the TLE group, we found 21 nonsynonymous mutations; 10 of 37 variants in the control group were nonsynonymous. The similarity of mutation rate between TLE patients and normal controls could be interpreted as the MT-ND5 gene being a genetic polymorphism
in the Northern Han Chinese population. After further analysis of the influence of the variants absent from normal controls, we failed to detect a specific variant that was linked to TLE [Table 2]. In addition, most of the MT-ND5 genetic mutations were reported in the normal population in a previous study. Overall, these results indicate that MT-ND5 genetic mutation was not associated with TLE in the present study.

In conclusion, we suggest that the MT-ND4 mutation g.11087 T > C is associated with TLE. This result provide a potential therapeutic target for the treatment of TLE, warranting further study on animal models in the future.

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Conflicts of interest
The authors declare that there is no conflict of interest to disclose.

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Table 1: The non-synonymous mtDNA variations detected in the mitochondrial MT-ND4 gene

| Position | Nucleotide change | No. of cases | Amino Acid change | Previous reported in normal population | Found in control in the present study | PolyPhen-2 score | SIFT score |
|----------|------------------|--------------|-------------------|----------------------------------------|----------------------------------------|------------------|-----------|
| 11150    | G-A              | 2            | A-T               | N                                      | N                                      | 0.03             | 0.150     |
| 12030    | A-G              | 1            | N-S               | NA                                     | N                                      | 0.003            | 0.717     |
| 11151    | C-T              | 1            | A-V               | N                                      | N                                      | 0.001            | 0.150     |
| 11696    | G-A              | 1            | V-I               | Y                                      | N                                      | 0.005            | 1         |
| 11969    | G-A              | 1            | A-T               | Y                                      | N                                      | 0.003            | 0.032     |
| 11087    | T-C              | 1            | F-L               | N                                      | N                                      | 0.917            | 0.000     |
| 11024    | T-C              | 1            | F-L               | Y                                      | N                                      | 0.002            | 0.000     |
| 11253    | T-C              | 1            | I-T               | Y                                      | N                                      | 0.005            | 0.060     |

NA: not available, N: no, Y: yes.

Table 2: The non-synonymous mtDNA variations detected in the mitochondrial MT-ND5 gene

| Position | Nucleotide change | No. of cases | Amino Acid change | Previous reported in normal population | Found in control in the present study | PolyPhen-2 score | SIFT score |
|----------|------------------|--------------|-------------------|----------------------------------------|----------------------------------------|------------------|-----------|
| 12026    | A-G              | 1            | A-T               | NA                                     | N                                      | NA               | NA        |
| 12358    | A-G              | 5            | N-S               | Y                                      | N                                      | NA               | NA        |
| 12361    | A-G              | 2            | A-V               | Y                                      | N                                      | NA               | NA        |
| 13834    | A-G              | 1            | V-I               | N                                      | N                                      | 0.024            | NA        |
| 14002    | A-G              | 1            | A-T               | N                                      | N                                      | 0.004            | NA        |
| 12338    | T-C              | 6            | F-L               | Y                                      | N                                      | NA               | NA        |

NA: not available, N: no, Y: yes.