Novel Mutations in SCN4A Gene Cause Myotonia Congenita with Scoliosis

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Myotonia congenita (MC) is a group of genetically and clinically heterogeneous congenital neuromuscular channelopathies, typically characterized by the delayed relaxation of the muscles after voluntary contraction, stiffness, hypertrophy, transient weakness, and cramping. MC is caused by mutations in the skeletal muscle chloride channel gene (*CLCN1* [OMIM 118425]) and the skeletal muscle sodium channel gene (*SCN4A* [OMIM 603967]). The Nav1.4 voltage-gated sodium channel encoded by *SCN4A* is a transmembrane complex that consists of an α subunit associated with an auxiliary β subunit in the muscle. The α subunit is composed of four homologous domains (I–IV), and each domain contains six α-helical transmembrane segments (S1–S6). Mutations clustered in specific areas of the Nav1.4 channel associate with distinct phenotypes according to their positions in the protein.

In this study, we reported the clinical characterization of a new *SCN4A* mutation p.P1158A with symptoms assembling congenital myotonia, with additional symptoms of scoliosis and peripheral contracture deformities. The phenotype was very consistent in his sister carrying the same mutation. By summarizing the reported literatures of *SCN4A*-related myotonia and accompany symptoms of scoliosis and peripheral contractures, we have a new understanding to the genotype–phenotype correlations of *SCN4A*.

The 21-year-old male patient was referred for a consultation due to his slow walking and stiffness for 20 years and scoliosis for 14 years. He tended to fall and trip often and feel tired after a long distance walking (>1000 m) since he was a child. His muscle stiffness was worse on the initiation of exercise and relieved by repetitive contractions. The activities of his upper limbs were so restricted that they could not straighten up to the top of head and extend to the backward for the limbs' stiffness. No pain was related to stiffness. In addition, he had a sense of facial muscle tightness which could be alleviated by relaxation and massage. His parents reported that he possessed pectus carinatum at age of 2 years and scoliosis at age of 8 years.

Neurological examination disclosed that the patient possessed short stature (143 cm), dental dysplasia, short neck, and obvious scoliosis [Figure 1d]. He showed proximal muscular hypertrophy and distal amyotrophy of upper limbs. He had difficulty opening his mouth when started speaking, but his speech articulation was not affected after that. It would take several seconds for him to open his eyes after he closed. Besides, warm-up phenomena and grips myotonia were demonstrated. Moreover, the limb muscle tone increased obviously. Tendon reflexes were weakened in upper limbs and were not induced in lower limbs. The limbs' activities were restricted accompanying foot drop.

Other accessary examinations were as follows: The spine X-ray of the patient showed obvious scoliosis [Figure 1f]. His creatine kinase levels were 441 U/L (CK, normal range <170 U/L). Muscle biopsy was nonspecific, revealing increased variation in fiber diameter that ranged from 30 μm to 80 μm and the atrophy of Type I muscle fiber with a reduced proportion. Electromyographic investigation demonstrated profound myotonia, and there were no clear signs of myopathic motor units.

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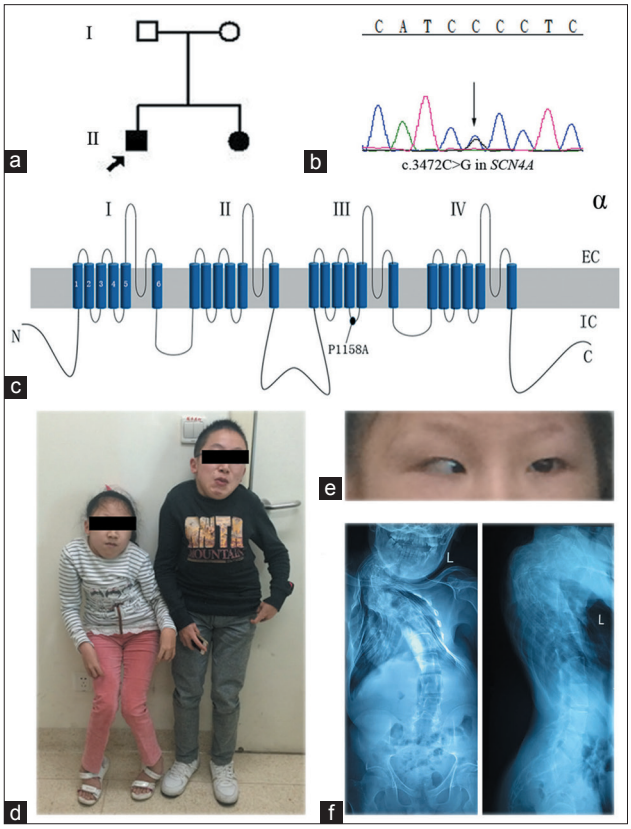

Figure 1: (a) Pedigree of the family. The one marked with arrow is the proband. (b) Sequencing chromatogram indicates that a heterozygous missense mutation c.3472C>G in *SCN4A* is identified in the proband. (c) The site of the mutation in Nav1.4 channel identified in the study. The mutation is indicated by small black cycle. (d) Short neck, scoliosis, and dwarfism. (e) Strabismus of her right eye in the younger sibling. (f) Thoracolumbar spine X-ray of the elder brother shows severe scoliosis.

The 18-year-old younger sibling developed the similar symptoms of myotonia and skeleton deformities for 16 years. She was found to possess pectus carinatum at age of 2 years and scoliosis at age of 6 years. She underwent an emergency tracheotomy for respiratory difficulty at age of 17 years. Moreover, she possessed strabismus of the right eye [Figure 1e], slurred speech and weak voice, claw finger deformity, and strephenopodia. Her daily life required to be facilitated for the stiffness. Clinical examinations also revealed prominent limb myotonia accompanying skeleton deformities.

We identified the *SCN4A* (RefSeq: NM_000334) mutation (c.3472C>G, p.P1158A) in the older sibling by performing the whole exome sequencing. *SCN4A* p.P1158A was not found in 100 healthy controls, Exome Aggregation Consortium, and 1000 Genomes Project (1000G). Silico predictions also suggested a pathogenic effect (Polyphen-2: 0.990; SIFT: 0). Moreover, MutationTaster predicted to be disease causing. Genetic testing revealed that the affected sister also harbored the mutation whereas their parents did not. We interpreted this mutation to be pathogenic according to the American College of Medical Genetics and Genomics standards and guidelines.[1]

SCN4A-associated disorders include hyperkalemic periodic paralysis (hyperPP, OMIM: 170500), hypokalemic periodic paralysis Type 2 (OMIM: 613345), paramyotonia congenita (PMC, OMIM: 168300), sodium channel myotonias (SCM, OMIM: 608390), and congenital myasthenic syndrome (OMIM: 614198). More than 40 dominant mutations have been identified in *SCN4A*. The mutation P1158A in *SCN4A* is predicted to lie intracellularly between the fourth and fifth transmembrane segments of domain III [Figure 1], which involves fast inactivation of the Nav1.4 channel.[2] Moreover, p.P1158A may disrupt this process leading to the disorder.

The mutation p.P1158A detected in this study has not been described in previous literatures. Mutation Pro1158Ser, with a different amino acid substitution in the position, associates with an atypical periodic paralysis plus myotonia phenotype and another phenotype of SCM. The near site mutation, Ala1156Thr, was presented in a family with variable features of hyperPP and PMC, and Ile1160Val resulted in potassium-aggravated paramyotonia.[3] The patients in this study were characterized of facial stiffness, eye closure myotonia, and serious limbs' stiffness supporting the diagnosis of MC. All these demonstrate the considerable phenotype variability of *SCN4A* mutations.

Interestingly, a British pediatric cohort observed that limb myotonia, strabismus, and respiratory symptoms are common among children with sodium channelopathy. Moreover, scoliosis and/or contractures were demonstrated in 6 of 38 children.[4,5] In line with these observations, our study highlights that conspicuous limb myotonia, scoliosis, peripheral contractures, and strabismus are nonnegligible features in children with skeletal muscle channelopathies [Supplementary Table 1].

In conclusion, p.P1158A in *SCN4A* was first explored in our patients with MC. Particularly, the recurrence of the same mutation in the younger sibling suggests the existence of germ line mosaicism in one of the asymptomatic parents. Our observations indicate that, in young patients with prominent myotonia and accompany symptoms of skeleton and contracture deformities, the genetic sequencing of *SCN4A* gene is essential for the diagnosis.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: The clinical features of *SCN4A*-myotonia with skeleton and peripheral contracture deformities

Items	The older sibling in present family	The younger sibling in present family	Fusco *et al*.[5]
Ethnicity	Chinese	Chinese	Italian
SCN4A mutation	p.P1158A	p.P1158A	p.N1180I
Family history	Yes	Yes	Yes
AO	1 year	2 years	Birth
Aggravating factors	None	None	Cold
Relieving factors	Repetitive muscle contraction	Repetitive muscle contraction	Repetitive muscle contraction
Painful myotonia	None	None	None
Strabismus	None	Yes	None
Respiratory symptoms	None	Yes	None
Skeleton deformities	Scoliosis	Scoliosis	Clubfoot deformity, high arched palate and clinodactyly
Peripheral contractures	Yes	Yes	Yes
Diagnosis	MC	MC	SCM

AO: Age at onset; MC: Myotonia congenita; SCM: Sodium channel myotonia.