A Novel Mutation in the Gene for the Adult Skeletal Muscle Sodium Channel α-Subunit (SCN4A) That Causes Paramyotonia Congenita of von Eulenburg

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Background: Paramyotonia congenita (PMC) of von Eulenburg is an autosomal dominant muscular disease characterized by exercise- and cold-induced myotonia and weakness. To date, 18 missense mutations in the adult skeletal muscle sodium channel α-subunit (SCN4A) gene have been identified to cause a spectrum of muscular diseases, including PMC of von Eulenburg, PMC without cold paralysis, potassium-aggravating myotonia, and hypokalemic periodic paralysis. However, no obvious correlations can be made between the location or nature of amino acid substitutions in SCN4A and its clinical phenotypes.

Objective: To describe clinical and genetic features of a family with PMC of von Eulenburg.

Results: A Japanese family with cold-induced myotonia and weakness was diagnosed as having PMC of von Eulenburg. This phenotype was identified to be caused by a novel mutation that substituted a glutamic acid residue for a highly conserved glycine residue in the fourth transmembrane segment (S4) of domain IV. This predicted a decrease in positive charge specific for the S4.

Conclusion: In addition to the G1456E identified in this study, 4 mutations that cause a decrease in positive charge in the S4/D4 are associated with the phenotype of PMC of von Eulenburg. This provides an important genotype-phenotype correlation in sodium channelopathies.

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Paramyotonia congenita (PMC) is an autosomal dominant muscular disease characterized by paradoxical and cold-induced myotonia. Paramyotonia congenita has been subdivided into PMC of von Eulenburg (Mendelian Inheritance in Man [MIM 168300])—accompanied by cold-induced paralysis—and PMC without cold paralysis (MIM 168350). Hyperkalemic periodic paralysis (MIM 170500) is also a dominantly inherited disease in which periodic paralysis is associated with hyperkalemia. Because hyperkalemic periodic paralysis can occur in some families with PMC, it has been suggested that the 2 diseases share a common etiologic basis. In fact, PMC and hyperkalemic periodic paralysis have been genetically mapped to the same locus on chromosome 17q23-25, and various missense mutations in the gene for the subunit of the skeletal muscle sodium channel (SCN4A) at this locus have been identified as causative mutations for both diseases. Furthermore, other autosomal dominant myotonias characterized by potassium sensitivity (potassium-aggravated myotonia) have also been demonstrated to be caused by mutations in the SCN4A gene.

Although 18 missense mutations in the SCN4A gene have been identified in various forms of sodium channelopathies, no obvious correlations have been demonstrated between the location or nature of amino acid substitutions in SCN4A and the clinical phenotypes. Herein, we describe a novel mutation in the SCN4A gene in a Japanese family with PMC of von Eulenburg. This observation provides an important insight into the genotype-phenotype correlation of sodium channelopathies.

RESULTS

CLINICAL FEATURES

The proband (IV-2) was a 16-year-old girl who began to experience muscle stiffness that affected her face and limbs in a cold environment, such as being outdoors in the winter (approximately 5°C-10°C), at the age of 4 years. She also experienced stiffness and concomitant weakness in her hands after immersing them in ice-cold water. She had not experienced episodes of
generalized flaccid weakness. On examination, she showed grip and percussion myotonia in her hands in a warm environment (approximately 20°C), which was further exacerbated by exercise. Serum sodium, potassium, and chloride levels were normal, and serum creatine kinase level was 83 U/L (normal range, 7-160 U/L). Needle electromyographic studies revealed myotonic discharges at rest but otherwise normal findings. The amplitude of compound muscle action potentials of the thenar muscles that were elicited by electric stimulation of the left median nerve was 26.6 mV, which decreased to 1.0 mV after immersing her left hand in ice-cold water for 10 minutes.

In addition to the proband (IV-2), 5 members of her family (III-1, III-4, III-6, IV-3, and IV-4) interviewed experienced cold-induced muscle stiffness in their faces and hands with onsets in infancy, and 3 other members (I-2, II-2, and II-3) were thought to have cold-induced muscle stiffness based on information obtained from the interviewed family members (II-1 and IV-2). These members (I-2, II-2, II-3, III-1, III-4, III-6, IV-3, and IV-4) were also judged to be affected (Figure 1, A). Two members (III-4 and IV-3) experienced stiffness in their throats when eating ice cream. Perspiration and grip myotonia were observed in all the affected members examined (III-6, IV-2, and IV-4); none was aware of any food that exacerbated muscle stiffness, except ice cream.

Only 3 (III-1, III-6, and IV-4) of the affected members reported episodes of severe generalized paralysis—always muscle stiffness after exposure to cold such as air conditioning in summer—and never while resting after exercising or eating large meals. Serum potassium levels during generalized paralyses were not measured.

**LINKAGE ANALYSIS TO THE SCN4A LOCUS AND MUTATIONAL ANALYSIS OF THE SCN4A GENE**

Results of the analysis of the (dGda)_n and (dGdT)_n dinucleotide markers are shown in Figure 1, A. The highest pairwise lod scores of 1.84 (θ = 0.0) and 1.81 (θ = 0.0) were obtained for the (dGda)_n and (dGdT)_n markers, respectively. Single strand conformation polymorphism analysis of the SCN4A gene of the proband and other members of this family revealed aberrantly moving bands in 2 regions, one of which represented a G to A polymorphism at nucleotide position 4869 in exon 24 of SCN4A complementary DNA.20 Haplotype analysis ([dGda]_n-[dGdT]_n-G-A) revealed perfect cosegregation of a haplotype of GA4-GT9-G with the disease in this family (Figure 1, A). The other aberrant conformer also segregated with the disease in all affected members of this family (Figure 1, B), but not in 90 unrelated Japanese individuals. Nucleotide sequence analysis revealed that this
aberrant conformer contained a G to A transition at nucleotide position 4367 in SCN4A complementary DNA, which was predicted to result in glutamic acid substituting for glycine at amino acid position 1456 in SCN4A (G1456E) (Figure 2). Alignment of amino acid sequence of the SCN4A (GeneBank, National Library of Medicine, Bethesda, Md, M81758) with that of other voltage-gated sodium channel α-subunits, including the human heart (GeneBank, M77235), rat brain isoform II (GeneBank, M22254), rat sensory nerve (GeneBank, U53833), drosophila (GeneBank, M24285), and cyanea jellyfish (GeneBank, L15443) sodium channels revealed that the glycine at position 1456 in the SCN4A was highly conserved.

This family exhibited various forms of myotonia, including cold-induced myotonia, grip and percussion myotonia, and paradoxical myotonia. The mode of inheritance is consistent with autosomal dominant inheritance. The proband experienced cold-induced muscle stiffness and weakness only in her hands, and the 3 other affected members experienced attacks of cold-induced muscle stiffness followed by generalized weakness. Interestingly, muscle weakness was always associated with exposure to cold temperature and never with rest after exercising or eating large meals. Although the clinical presentations associated with mutations in the SCN4A gene can vary, the clinical features of the affected individuals in this family are close to that described by von Eulenburg.

Linkage and haplotype analyses suggested that the disease was linked to the SCN4A gene. The mutation that segregated with the disease in this family substituted a glutamic acid for a glycine at position 1456, which is highly conserved among voltage-gated sodium channels. This mutation was not found in 90 healthy Japanese individuals. These observations strongly support this mutation being the pathogenic mutation, although we analyzed only exons 22 and 24 in the SCN4A gene.

SCN4A has 4 similar domains (D1-D4) connected by cytoplasmic loops (Figure 2), each domain consisting of 6 transmembrane segments (S1-S6). Their function is not fully understood. The S4 segments, which have a positive charge due to repeats containing positively charged amino acids (X-X-R-K), are thought to act as voltage sensors for channel activation and to be involved in activation-inactivation coupling. The present mutation (G1456E) is located in the D4/S4 and predicted to alter the charge of the D4/S4 by substituting negatively charged glutamic acid for glycine. Interestingly, 3 mutations (R1448C, R1448H, and R1448P) affecting the same arginine at position 1448 in the D4/S4 are reported to be associated with the phenotype of PMC of von Eulen-
These mutations, including the G1456E identified in the present study, are all predicted to alter the charge of the D4/S4 (Figure 2). These observations suggest that mutations causing a decreased positive charge in the S4/D4 are associated with the phenotype of PMC of von Eulenburg. Other mutations not located in the D4/S4 have also been described to cause cold-sensitive myotonia.7-10,15,17 However, some of them, including S804F13 and G1306V,11 are reported to be associated with potassium-aggravated myotonia without cold sensitivity in some families. Our observation that mutations identified in the D4/S4 are associated with PMC of von Eulenburg provides an important genotype-phenotype correlation in sodium channelopathies.

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