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Case Report

Intrafamilial Phenotypic Variability Associated with the I1739V Mutation in the SCN9A Gene

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Abstract
The *SCN9A* gene encodes a voltage gated sodium channel Nav1.7 in which mutations can result in a wide variety of phenotypes ranging from congenital insensitivity to pain to small fiber neuropathy. We report the genotype phenotype analysis in a family carrying a specific mutation, I1739V, in the *SCN9A* gene. Neurophysiological studies have documented the gain of function impact of this mutation on this sodium channel. Interestingly, there is significant interfamilial phenotypic variability in individuals carrying this mutation. In our family, a father daughter combination had identical genotypes analyzing the *SCN9A* gene and multiple other genes known to cause neuropathy. Both of them carry the I1739V mutation but exhibit significant phenotypic variability with complaints of decreased sensitivity to discomfort in the father while the daughter has the clinical and laboratory features consistent with a small fiber neuropathy. We hypothesize that there are modifiers of the I1739V mutation that could involve intronic or exonic gene variants which contribute to this intrafamilial phenotypic variability. Our study has implications for genetic counseling, personalized medicine and the development of drugs to treat neuropathic pain.

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Introduction

The voltage gated sodium channel Nav1.7, encoded by the *SCN9A* gene, is expressed in subcortical brain structures [1] and particularly enriched in the dorsal root ganglion and sympathetic ganglion neurons. Interestingly, mutations in this gene have been reported associated with a wide variety of phenotypes including erythromelalgia, insensitivity to pain, hereditary sensory and autonomic neuropathy, small fiber neuropathy, paroxysmal extreme pain disorder and certain forms of epilepsy [2, 3]. We report our genotype phenotype analysis of a family carrying the I1739V mutation in the *SCN9A* gene.

Case Presentation

The index patient is 55-year-old woman who has a long history of a complaint of "muscle cramps" for more than 10 years. Specifically, these episodes consisted of muscle tightening but without a muscle cramp and occurred mainly, but not exclusively, at night. Independent from these episodic symptoms were those of a squeezing sensation in her feet aggravated by wearing any kind of shoe. Both of these symptoms were slowly worsening prompting medical attention and evaluation by a neurologist who subsequently referred her for neuromuscular evaluation. The remainder of the neurological review of systems revealed no complaints suggestive of insensitivity to pain, paroxysmal extreme pain disorder, autonomic dysfunction or epilepsy. Her neurological examination revealed no abnormalities of the mental status, cranial nerves, power, cerebellar testing or reflexes. Sensory examination was normal testing light touch, vibration and proprioception. Perception of pin prick and temperature were also normal. Her gait tested with shoes was tentative consistent with discomfort in her feet. No trophic changes were noted in her hands or feet. She underwent neurophysiological testing that revealed normal motor (bilateral fibular and tibial) and sensory nerve (sural and superficial fibular) conduction parameters. Needle electromyogram of selected muscles of both legs revealed no abnormalities. Overall, the study showed no evidence of a large fiber neuropathy.

Further testing was done investigating a small fiber neuropathy including a quantitative sudomotor axon reflex test that showed significantly decreased sweat production in both proximal and distal segments of the right leg. A skin biopsy was performed and showed significant reduction in the epidermal nerve fiber density 0.93 (nl>8.3) in the distal thigh and 0.88 (nl>4.3) in the distal leg. Her symptoms and the results of these tests are consistent with a diagnosis of small fiber neuropathy.

Family history reveals that her parents are both in their eighties and that her mother has no neurological complaints. Her father has a history of decreased sensitivity to extremes of hot or cold extending back for decades. He could walk in these extremes without adequate protection on his feet and by history has decreased pain sensitivity. He had been told that he had a neuropathy and repeat tests for diabetes mellitus were negative. He had no symptoms of pain or imbalance and did not have any clinical features to suggest paroxysmal itch. Although he declined neurological examination or electrophysiological testing, he did agree to genetic testing. The patient has two siblings, ages 58 and 60 years who have no history of any neurological or pain disorder.

Routine serum chemistries showed that the following tests were normal or negative: complete and differential blood count, comprehensive metabolic panel, serology for hepatitis

C, HIV, anti-Ro(SSA) and anti-La(SSB), rheumatoid factor, antineutrophil cytoplasmic antibodies (ANCA) panel and a 2-h glucose tolerance test.

Genetic Testing

The patient underwent commercial genetic testing analyzing 53 genes known to cause neuropathy and a number of variants were detected. A c.2215 A>G (rs182650126) variant resulting in p.Ile739Val was detected in the *SCN9A* gene. This is a known disease causing mutation reported in the heterozygous state in a number of unrelated patients with clinical diagnosis of small fiber neuropathy [4, 5]. The I739V substitution alters a highly conserved position in the transmembrane segment S1 in the second homologous domain of the Nav1.7 protein. Protein modelling analysis with SIFT [6] predicts this variant to be tolerated, PolyPhen [7] predicts it as probably damaging, and mutation taster analysis [8] predicts this as a disease causing variant. This is a rare variant reported in various genetic databases (https://www.ncbi.nlm.nih.gov/snp/rs182650126), with a frequency ranging from C = 0.0010 (5/5008, 1000G) to C = 0.009 (9/998, GoNL). The ExAC database (https://gnomad.broadinstitute.org/) reports two homozygotes and a frequency C = 0.002470 (597/241656), without any clinical data. In addition to this mutation, other polymorphisms were detected including a c.365 A>T variant in the *HINT1* and a c.380 G>A variant in the *FAM124B* genes. Mutations in the *HINT1* gene can result in an axonal neuropathy with or without the presence of neuromyotonia when they are transmitted in an autosomal recessive inheritance pattern. While mutations in the *FAM124B* gene can result in autonomic neuropathy, they are also typically transmitted in an autosomal recessive pattern of inheritance. There is no second variant identified in the index patient in either of these genes strongly suggesting that they are not likely to be disease producing in this family. Targeted analysis of these variants was performed in both of her parents and revealed that she inherited all of the variants from her father.

Discussion

The I1739V mutation identified in this family has been reported in a number of studies over the years. It was first noted in a study of Dutch patients and detected in a 51-year-old woman who had complaints suggestive of autonomic neuropathy including dry eyes, dry mouth, orthostatic dysfunction and joint and muscle pain. Her sister and two sons had similar complaints [4]. This mutation was also described in a family with paroxysmal itch [3]. Interestingly, it was identified in 7 patients, 5 of whom developed a painful neuropathy. Subsequently, some of them were diagnosed with diabetes mellitus suggesting the potential importance of this mutation in the development of painful diabetic neuropathy [9]. Electrophysiological voltage clamp studies of this mutation show a gain of function with an increased hyperexcitability and a reduced current threshold with increased firing frequency when responding to depolarizing stimuli [5]. These studies, in combination with the genotype/phenotype reports, strongly indicate a potential role of this mutation in some patients with pain syndromes.

In our family, it is interesting to note that although all the variants on the neuropathy panel were transmitted paternally, the phenotype of the father and daughter is different. The

father has no complaints of pain but rather a decreased sensitivity to heat or cold while his daughter, the index patient, has a pain syndrome. Intra- and inter-familial phenotypic variability has been previously reported in a family carrying mutation I1228M in the *SCN9A* gene [10]. Our study indicates for the first time that intra-familial variability can also occur with the I739V mutation. This suggests that other genetic modifiers contribute ultimately resulting in a particular phenotype. It is possible that the *HINT1* and *FAM124B* variants could modify the expression of the I739V mutation. However, they are all inherited paternally making the likelihood that they are potential modifiers of gene expression unlikely. Other exonic variants in genes that are highly expressed in dorsal root ganglion cells and not analyzed in this study could be modifiers of the expression of this mutation. Alternatively, intronic variants in genes expressed in these neurons could also modify the expression of the I739V mutation contributing to the variability of the observed phenotype.

A recent investigation of more than 400 individuals with peripheral neuropathy, the patients were subjected to next-generation sequencing which identified the I739V mutation in about 1% of patients [11]. In these patients, there was little difference in the frequency between those suffering pain compared to those without discomfort. The detailed analysis of the I739V mutation in our family supports and extends the results of this prior research. Collectively this research is important and has implications for personalized medicine and for the development of drugs to treat neuropathic pain.

Statement of Ethics

Written informed consent was obtained for the case report publication from the individuals who participated in this study. The study was conducted following policies and procedures approved by the local Institution Review Board.

Conflict of Interest Statement

The authors have no conflicts of interest to report.

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Author Contributions

Both authors (R.P.G. and L.R.P.) contributed to the initial draft of this publication and revised the later drafts. All authors reviewed and approved the final draft.

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