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Demyelinating Peripheral Neuropathy Caused by the p.R160H Mutation in the *LITAF* Gene

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Abstract

We report a 62-year-old woman who presented with complaints of numbness and tingling in her feet without a family history suggestive of neuropathy. Neurological examination and electromyogram testing confirmed the presence of a demyelinating neuropathy with a mild phenotype. Extensive testing revealed no etiology and she was diagnosed and treated unsuccessfully for chronic inflammatory demyelinating polyneuropathy. Ultimately, with the availability of next-generation sequencing, genetic testing revealed a heterozygous variant, chr16:11643500C > T, c.479 G > A, p.R160H, in the *lipopolysaccharide-induced tumor necrosis factor* (*LITAF*) gene. Further analysis of this variant employing protein modeling suggests that this is a disease producing mutation causing Charcot Marie Tooth disease type 1C (CMT1C). Our study demonstrates the power of next-generation sequencing to diagnose patients with idiopathic neuropathy. This is important as it avoids unnecessary and expensive treatments for the patient and furthermore, allows genetic counseling for family members.

Keywords: Autosomal dominant genetic neuropathy, Mild demyelinating neuropathy, CMT1C, *LITAF* gene

1. Introduction

Charcot Marie Tooth disease type 1C (CMT1C) is a rare autosomal dominant genetic neuropathy caused by mutations in the gene, *lipopolysaccharide-induced tumor necrosis factor* (*LITAF*).[1] We present a patient who suffered a mild slowly progressive demyelinating neuropathy in whom genetic testing identified a mutation in the *LITAF* gene.

2. Case report

The index patient, age 63 years, was referred for a second opinion for evaluation of a neuropathy. She had been admitted to hospital at age 62 years with a myocardial infarction and the neurological review systems revealed numbness in her feet associated with complaints of gait imbalance. The exact onset of these symptoms is not clear but may have been several years earlier. She had no complaints of numbness or tingling elsewhere and the remainder of her neurological review of systems was negative for other symptoms.

Physical examination disclosed normal vital signs and evidence of pes cavus. Neurological examination revealed a normal mental status, tests of cerebellar function and the cranial nerves. Sensory examination was normal in the hands and showed a mild decrease in vibratory sense and proprioception with preservation of pinprick sensibility in the feet. Her stretch reflexes were normoactive at the biceps, brachioradialis, triceps, patellae and not obtained at the ankles. The plantar responses were flexor. Power testing showed normal strength in the arms. In the legs, testing the proximal muscles including hip flexion, extension, abduction and adduction, knee flexion and extension, foot dorsiflexion, eversion, inversion were all Medical Research Council (MRC) Grade 5/5. Plantar flexion and dorsiflexion of the great toes bilaterally displayed MRC Grade 4/5 weakness bilaterally. The patient is unable to stand

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on her toes or heels and could not perform a tandem walk. She had a mildly positive Romberg test.

Family history was undertaken of extended members including uncles, aunts and grandparents. She has no siblings and reported no other member of her family was known to suffer from symptoms suggestive of a neuropathy including the presence of high arches. Her father died at age 56 years from heart disease and her mother died at age 86 years. Neither of her parents had any history to suggest they suffered from a neuropathy. She has two daughters ages 36 and 40 years, who are asymptomatic and agreed to be genetically tested.

An electromyogram (EMG) was performed and confirmed a sensorimotor neuropathy with demyelinating features including the presence of prolonged F-wave latencies, marked slowing of the conduction velocities and conduction block/temporal dispersion in the left ulnar and median nerves (Table 1). Needle EMG showed the presence of chronic neurogenic changes (high amplitude polyphasic motor units with a decreased interference pattern with maximal effort) most marked in the distal limb muscles and more prominent in the legs.

The following tests were negative or normal: routine serum chemistries, cell count and differential, serum protein electrophoresis with immunofixation, thyroid function tests, serological tests for HIV, hepatitis C and Lyme disease, Vitamin B_{12}, folate, Vitamin E, Vitamin B_6, Vitamin B_1, hemoglobin A1c, 2 h glucose tolerance test, erythrocyte sedimentation rate, C-reactive protein, antibody tests for myelin associated glycoprotein, gangliosides (GM_1, GD_{1A}, GD_{1b}), sulfatide, ribonucleoprotein, anti-Ro, anti-La, anti-nuclear, anti-neutrophil cytoplasmic and anti-Hu antibodies.

Based on EMG testing, she was diagnosed with chronic inflammatory demyelinating neuropathy and treated with intravenous immunoglobulin (IVIG) 2 g/kg monthly for 6 months with a tapering dose of steroids added for 2 months. The IVIG was discontinued as she had no response to therapy either clinically or electrophysiologically. She was then diagnosed with an idiopathic demyelinating neuropathy.

3. Genetic analysis

Several years later, when next-generation sequencing analysis screening 80 genes known to cause neuropathy became available, a panel was ordered through a commercial company and the results analyzed in our research genetics laboratory. This testing identified a heterozygous variant, chr16:11643500C > T, c.479 G > A, p.R160H, in the *LITAF* gene, in the index patient. The p.R160H (rs864622744) variant is rare and non-synonymous. It is listed in the dbSNP database with allele frequency T = 0.000016 (4/249474, GnomAD_exome), T = 0.000021 (3/140158, GnomAD), T = 0.00004 (1/23038, ALFA), however there is no associated clinical data. This variant was not found in our internal database, which is a collection of rare gene variants with frequency of less than 3% generated from whole exome sequencing data of seventy-two individuals with neurological disorders. The variant was further analyzed using protein analysis tools, SIFT,[2] Polyphen[3] and Mutation Taster[4] and was

Table 1. Nerve conduction studies in the index patient.

Nerve	Distal latencies, ms	Response amplitude, mV	Conduction velocity, m/s	F-wave latency, ms	Comments
Motor					
Right Median	**4.8** (<4.2)	**7.2** (>4.0)	**46** (>50)	**35** (<30)	
Left Median	**5.2** (<4.2)	**7.1** (>4.0)	50 (>50)	**38** (<30)	
Left Ulnar	**4.3** (<3.3)	**3.6** (>3.5)	**30** (>50)	**38** (<30)	
		1.4 (BE) (>3.5)	**21**(>50)		
		1.0 (AE) (>3.5)			
Bilateral Peroneal	**NR** (<6.2)	**NR** (>2.6)	**NR** (>40)	**NR**	No response recording the extensor digitorum brevis
Bilateral Tibial	**NR** (<6.0)	**NR** (>4.0)	**NR** (>40)	**NR**	
Sensory					
Bilateral Sural	**NR**				
Bilateral Peroneal	**NR**				
Left Median		**10.2** (>20 uV)	**38** (>50)		
Left Ulnar		**2.7** (>17 uV)	50 (<50)		
Left Radial		**5.0** (>15 uV)	**44** (>50)		

(nl)-normal values.
NR-no response.
AE-above elbow.
BE-below elbow.

predicted to be damaging and disease causing by all three tools. Testing for the *LITAF* gene variant showed that both the daughters carried the wild type allele.

4. Discussion

We analyzed the c.479 G > A, p.R160H variant in the *LITAF* gene, following guidelines for interpretation of sequence variants,[5,6] our analysis indicates that p.R160H is a disease producing mutation and the cause of neuropathy in our patient. The absence of a family history could indicate that this is a spontaneous mutation. Alternatively, given the mild phenotype of the neuropathy in this patient, it is possible that her father also carried the mutation but died before significant symptoms developed. In addition, neither of the daughters have neurological symptoms and do not carry this mutation.

The largest report of patients with CMT1C is from a referral center for neuromuscular disorders in France.[7] In this study, eighteen patients from 13 different families are reported and of these, 5 were identified by family survey. The age at onset of first symptom ranged from birth to age 58 years and the majority of patients did not require any assistance with walking. An earlier publication, also from France,[8] in a series of 968 unrelated patients with autosomal dominant demyelinating neuropathy, 6 patients were identified with CMT1C, representing 0.6% of the total. Interestingly, in another study of 17,000 patients with neuropathy, 0.5% were identified with *LITAF* mutations confirming that this is a rare cause of CMT.[9] It has been suggested that the prevalence of *LITAF* as a cause of CMT1C is in the order of <1/1,000,000.[10]

In research papers published in the 1980s and 1990s, after thorough investigations, up to 24% of patients were diagnosed with idiopathic peripheral neuropathy.[11,12] In a more recent study in 2013, 28.5% of patients studied with neuropathy remained idiopathic.[13] A study published in 2016 reported that after investigations, 32.7% of 373 patients initially without a diagnosis remained idiopathic.[14] The authors suggest that this number is higher than prior studies because of the inclusion of small fiber neuropathy which frequently remains idiopathic. However, even in this most recent study, the use of genetic testing in these cases is limited. In the last few years, the cost of whole exome genetic testing has decreased significantly making it affordable in patients to pay even if their medical insurance does not cover the cost. In our practice, this is the third patient identified through gene testing in the last few years.[15,16] The identification of these patients would not have been possible five years earlier due to cost issues. It can be anticipated that more of the patients with idiopathic neuropathy will be diagnosed by genetic testing.

In our patient, a potential genetic diagnosis was considered less likely without a clear family history. However, this lack of family history may be due to a mild phenotype. Nevertheless, there is a role for genetic testing in such patients which ultimately confirmed the diagnosis. This confirmation is important as it avoids unnecessary investigations that could include invasive tests such as a nerve biopsy. In addition, a diagnosis prevents the administration of expensive treatments such as intravenous immunoglobulin therapy. Finally, it facilitates genetic counseling that in turn may expedite confirmation of a genetic diagnosis for family members. Although at present there are no specific treatments available for this form of CMT, a confirmed genetic diagnosis may allow participation in future therapeutic clinical trials and eventually, a more personalized approach to specific treatment.

Our study demonstrates the power of next generation sequencing to identify the genetic basis of patients with CMT even when the frequency is rare. We also expand the spectrum of mutations that can cause CMT1C, and the clinical phenotype associated with these mutations.

Statement of ethics

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of JFK Medical Center, Edison, New Jersey (protocol code FWA00001350 and date of approval, January 15, 2007). Informed consent was obtained from all individuals who participated in this study.

Data availability statement

The final data generated and analyzed are included in the paper. Further enquiries for accessing the data and the analysis results can be directed to the corresponding author.

Conflicts of interest

The authors have no conflict of interest to report.

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