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Coexistence of a T118M *PMP22* missense mutation and chromosome 17 (17p11.2-p12) deletion

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Abstract

We describe a 6-year-old girl with a T118M *PMP22* mutation and heterozygous deletion of *PMP22* on chromosome 17 (17p11.2-p12) resulting in a severe sensorimotor polyneuropathy.

Methods—Case Report

Results—Foot pain, cavovarus feet, tibialis anterior atrophy, absent reflexes, and inability to walk were found at age 6. Nerve conduction studies showed evidence of a sensorimotor polyneuropathy and compressive mononeuropathies of bilateral median nerves at the wrist and ulnar nerves at the elbow. Genetic testing revealed a deletion of a *PMP22* allele and T118M *PMP22* mutation in the remaining allele.

Conclusions—The severe presentation of sensory motor polyneuropathy and HNPP in this patient is likely a consequence of both decreased expression of *PMP22* causing features consistent with HNPP, and unopposed expression of the T118M mutant form of *PMP22* that is relatively benign in the heterozygous state. The T118M mutant form of *PMP22* can be disease-modifying in the appropriate circumstances.

Keywords

HNPP; T118M mutation; *PMP22*; Loss of Function Mutation; Neurogenetics

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Introduction

Hereditary neuropathy with liability to pressure palsy (HNPP) is caused by heterozygous deletion of *PMP22* on chromosome 17 (17p11.2-p12). Patients have a typical phenotype with focal episodes of weakness and/or sensory loss and nerve conduction slowing at common compression sites such as the fibular nerve at the knee and the median nerve at the wrist. HNPP symptoms typically present from the late teens to early twenties [1]. In the absence of these episodes patients are usually asymptomatic or, at most, have evidence of a mild, predominantly sensory neuropathy as they age [1]. Therapy involves avoiding repetitive injury or pressure on the nerves, as this makes symptoms worse.

The threonine 118 methionine mutation (T118M) of *PMP22* causes a mild, often asymptomatic dominantly inherited neuropathy in humans. It has been reported previously to cause a partial loss of *PMP22* function, behaving like a milder form of HNPP in the heterozygous state [2] [3] [4].

We report here a patient who has both a chromosome 17 (17p11.2-p12) deletion and a T118M mutation who presented with a severe length-dependent demyelinating neuropathy with electrodiagnostic features consistent with HNPP. This case demonstrates that the T118M mutant form of *PMP22* is not a benign polymorphism but can be disease-causing and/or disease-modifying in the appropriate circumstances.

Case Report

Informed consent was obtained from the patient and parents. The proband is a 6 year-old girl of German, Hungarian, and Welsh/English descent who was the product of a 35 week twin pregnancy and was delivered by caesarian section. Her mother was hospitalized for nausea early in pregnancy and went into early labor at 25 weeks. She was placed on bedrest and delivered at 35 weeks. Our patient and her twin brother had a 2.5 week stay in the NICU for respiratory and feeding difficulties, but then had a benign neonatal course. She reached developmental milestones on time and walked at age 13 months. She did not toe walk but had difficulty hopping. At age 3.5 years, she tripped frequently while climbing stairs. Her toes would catch on the ground while walking and running. At age 4.5 years, her feet turned inwards, and she wore braces intermittently. She started to develop pain in her feet and would get cramps weekly. At age 6 years, she could barely walk without braces.

The first visit to our clinic was at 6 years of age. Neurological exam revealed significant tibialis anterior atrophy, and weakness in the tibialis anterior and fibularis longus (1/5) bilaterally (Figure 1). No abnormality in the hand strength or sensation was found. She had tight Achilles tendons, cavovarus feet, and could not toe, heel, or tandem walk. She was able to walk only 318 meters in 6 minutes with a bilateral steppage gait (normal, 600 meters) [5]. All reflexes were absent except the patellar reflexes, which were intact. Cranial nerves, mentation, sensation, and strength in her upper extremities were normal. She did not have scoliosis. She did not have a Romberg sign. Her CMT pediatric score (CMTPedS) was 26 (out of 44), which was associated with moderate impairment [6].

Prior work up included a normal MRI brain and lumbar spine. She had been treated with physical therapy and bilateral ankle foot orthotics as well as stretching. She was ambulatory and not disabled but would tire and have some leg pain with walking.

Electrodiagnostic exam

Electrodiagnostic testing was obtained from an outside facility (Table 1). No needle electromyography was performed. Compound muscle action potentials (CMAPs) were reported to be absent in bilateral tibial and right fibular nerves with recording from the extensor digitorum brevis muscle. When recording from the tibialis anterior, however, left fibular nerve stimulation produced a reduced amplitude CMAP at 0.6 mV, and a conduction velocity of 53 m/s with a latency of 4.8 ms at the knee. Motor nerve conduction velocities and CMAP amplitudes were decreased at common compression sites (Table 1). Bilateral median nerve distal latencies were prolonged; those of the ulnar nerve were normal. Minimum F-wave latencies were prolonged (right median nerve, 26.4 ms and right ulnar nerve, 21.6 ms; normal, 19.4 ms and 17.6 ms, respectively). Sensory nerve action potentials (SNAP) amplitudes were reduced (Table 1). Right superficial fibular sensory nerve conduction velocity was normal, but the remaining sensory nerve conduction velocities were slowed. (Table 1) Left sural and right ulnar SNAPs were absent. Nerve conduction studies were consistent with bilateral compressive mononeuropathies of the median nerve at the wrist and ulnar nerve at the elbow as well as an underlying predominantly demyelinating sensorimotor polyneuropathy.

Family history

A family history of HNPP was observed on the maternal side (Figure 2). The patient's maternal grandmother was diagnosed with HNPP upon developing a foot drop after wearing a cast. There is no family history of the T118M mutation; both parents have declined further genetic testing.

Genetic testing

Analysis of the PMP 22 gene was performed by PCR amplification of highly purified DNA followed by bi-directional DNA sequencing of the coding region of the *PMP22* gene. The test revealed a *PMP22* deletion and a threonine to methionine mutation at codon 118 in the remaining *PMP22* allele (T118M mutation).

Follow up

The patient underwent multiple orthopedic procedures for cavovarus feet including a bilateral plantar fascia release, bilateral fibularis longus to brevis transfers, bilateral posterior tibialis tendon transfers to the dorsum of the foot, bilateral Dwyer calcaneal osteotomy, bilateral cuboid closing wedge osteotomy, bilateral flexor digitorum longus lengthening, bilateral flexor hallucis longus lengthening, and bilateral first metatarsal dorsal closing wedge osteotomy (see Figure 3 for before and after x-rays). Recent communication with the parents indicates that her walking has improved markedly after the surgical procedure (supplementary video, available online). Given this improvement, it is likely that the severity of her presentation at such a young age could be attributed partly to a structural

etiology. Although her walking has improved functionally, she still exhibits significant dorsiflexion weakness.

Discussion

In this report we describe a patient with both a deletion of a 1.5 Mb region on 17p11.2-p12 and a T118M point mutation on the remaining *PMP22* allele (Figure 4). This combination of a 17p11.2-p12 deletion and a T118M point mutation has been reported only once previously [3,7]. Although the previous patient was 76 years-old, the physical exam was similar to that of our patient, including distal muscle weakness, atrophy, pes cavus deformity, and absent deep tendon reflexes. Both patients thus had a clinical phenotype more severe than that what is usually caused by either mutation individually [1, 8]. Interestingly, our patient had both reduced nerve conduction velocities at common compression sites, whereas the previously reported patient had only uniformly reduced motor nerve conduction velocities. The reason for this difference is not known, but it could be due to the difference in their ages.

A T118M mutation by itself is a partial loss of function mutation and results in a mild HNPP phenotype with focal nerve conduction slowing similar to patients with HNPP (Figure 4) [3].

The molecular genetic mechanism producing the severe neuropathy in these cases is likely 2-fold. First there is reduced expression of *PMP22* caused by the 17p11.2-p12 deletion that leads to structurally altered myelin with susceptibility to pressure. Second, as a result of the deletion, the mutant T118M protein is expressed and incorporated into myelin without its wild type counterpart. Since this mutant protein has been shown previously to have a partial loss of function, the resulting myelin sheaths in these patients are additionally altered, leading to more severe myelin dysfunction and neuropathy.

Conclusion

The combination of chromosome 17 (17p11.2-p12) deletion and a T118M mutation causes a more severe neuropathy than either mutation alone. Taken together with previous analyses, these data suggest that the T118M mutant form of *PMP22* is not a benign polymorphism but can be disease-causing and/or disease-modifying in the appropriate circumstances.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HNPP	Hereditary neuropathy with liability to pressure palsies
T118M	A recessive missense mutation at codon 118 of the PMP 22 gene producing a threonine to methionine amino acid substitution
CMAP	compound muscle action potential
SNAP	sensory nerve action potential

Figure 1. Appearance of legs in proband with distal lower extremity muscle atrophy, and cavovarus feet (left). She had difficulty walking without ankle foot orthotics (right).

Figure 2. Family Pedigree. Gray indicates HNPP, and black a T118M mutation. An arrow indicates the proband. A star indicates a first trimester spontaneous abortion.

Figure 3.
A) Pre- and B) post-surgical X-rays.

Figure 4.

Genetic schematic of chromosome 17 showing the normal *PMP22* gene (pink arrow), a deletion of the *PMP22* allele (green arrow), duplication of the *PMP22* allele (pink arrow), T118M missense mutation (yellow line, blue star), both the T118M missense mutation (yellow line, blue star) and CMT 1A (pink arrow), and both T118M missense mutation (yellow line, blue star) and HNPP (green arrow).

Table 1
Nerve Conduction data of the patient

	Right		Left	
	Latency	Amplitude	NCV	NCV
Motor NCS				
Median nerve				
APB	5.5 ms	3.3 mV	5.4 ms	1.3 mV
Wrist, elbow	8.7 ms	2.6 mV	8.0 ms	2.3 mV
Ulnar Nerve				
ADM, wrist	2.9 ms	6 mV	2.9 ms	6.9 mV
Wrist below elbow	4.6 ms	5.5 mV	4.6 ms	4.9 mV
Below elbow-above elbow	6.6 ms	5.1 mV	6.7 ms	4.6 mV
Fibular Nerve				
EDB, ankle	NR		NR	
Ankle, fibular Head	NR		NR	
Tibialis Anterior	NR		3.7 ms	0.6 mV
Tibial Nerve				
AH, ankle	NR		NR	
Ankle, knee	NR		NR	
Sensory NCS				
Median Nerve				
Finger, wrist	4.7 ms	4 uV	38 m/s	25 uV
Ulnar Nerve				
Finger, wrist	NR		NR	
Radial	2.1 ms	7 uV	35 m/s	
Sural nerve	3.1 ms	1 uV	36 m/s	
Superficial fibular			3.1 ms	4 uV

NCS; nerve conduction study, APB; abductor pollicis brevis, ADM; abductor digiti minimi, EDB; extensor digitorum brevis, AH; abductor hallucis, NR; not recordable, Abnormal values in **Bold**