GENETIC DOSAGE COMPENSATION VIA CO-OCCURRENCE OF PMP22 DUPLICATION AND PMP22 DELETION

Charcot-Marie-Tooth disease type 1 A (CMT1A, OMIM #118220) and hereditary neuropathy with liability to pressure palsies (HNPP or tomaculous neuropathy, OMIM #162500) are autosomal dominantly inherited neuropathies caused by genomic rearrangements on chromosome 17p11.2-p12 containing PMP22. Heterozygous PMP22 duplications result in a peripheral neuropathy characterized by distal muscular atrophy, foot deformities, sensory deficits, and generally reduced nerve conduction velocities in the demyelinating range (CMT1A). In contrast, a heterozygous PMP22 deletion results in HNPP that is characterized by recurrent transient episodes of transient focal compressive neuropathies manifesting as weakness, sensory loss, or both, with electrophysiology showing multifocal slowing at the sites of compression.

We report a large 3-generation family including several patients with CMT1A or HNPP, as well as 2 unaffected sisters, both with co-occurrence of a PMP22 duplication and a PMP22 deletion.

Case report. We first examined 4 siblings (II-2, II-3, II-4, II-5, figure) of a 55-year-old female index patient (II-1) with CMT1A by performing a multiplex ligation-dependent probe amplification (MLPA) assay (Kit P033-B3, MRC-Holland, Amsterdam, Netherlands). As expected, one sister (II-4) with typical features of CMT1A carried a PMP22 duplication. MLPA analysis of another sister (II-2) who reported transient numbness of the palms and feet, probably caused by chemotherapy, revealed a normal genotype. The second clinically unaffected sister (II-5) also had normal MLPA results. Remarkably, one brother (II-3) carried a PMP22 deletion, which was consistent with his focal neuropathic symptoms due to traumatic compression.

Subsequently, further relatives were examined (figure, table e-1 on the Neurology® Web site at Neurology.org). The father (I-1) of the siblings was deceased; further paternal family members were not available. The mother (I-2) with CMT1A carried a PMP22 duplication, as expected. The daughter (III-1) and son (III-3) of individual II-5 carried a PMP22 deletion, as did their uncle (II-3). We therefore assumed the co-occurrence of a maternally inherited PMP22 duplication and a paternally inherited PMP22 deletion in their mother (II-5).

To verify this hypothesis, we performed segregation analysis with 3 polymorphic microsatellite markers (CMT 4A, CMT 9A, and CMT 9B) within the segment in region 17p11.2-p12 in all of the above-mentioned family members. This analysis confirmed that the unaffected sisters II-5 and II-2, both with normal MLPA results, carried the maternal duplication of PMP22 and the paternal deletion of PMP22. There was no clinical or electrophysiologic evidence for CMT1A or HNPP in the sisters (table e-1).

Discussion. To our knowledge, this is the first report of a co-occurrence of PMP22 duplication and PMP22 deletion in the same individual. There is one family in the literature with a de novo PMP22 duplication of paternal origin in a girl, whose mother had HNPP, but transmitted the normal allele to her daughter. Patients with homozygous mutations of PMP22 are rarely reported (summarized in reference 3) and are mostly compound heterozygotes with mutations that produce deletion of PMP22 in one allele and a different mutation on the second PMP22 allele. These patients generally present with severe sensory and motor deficits in early childhood. One patient with a homozygous PMP22 deletion also had an infantile neuropathy that was less severe than in the compound heterozygous patients. The authors argue that truncated PMP22 from one of the alleles may cause toxic gain of function that leads to a more severe phenotype than if there was no PMP22 protein at all. Previously reported patients with PMP22 duplication and a second mutation in another neuropathy gene showed a more severe phenotype than expected, with each individual disease underscoring the important impact of each gene on peripheral nerve function. While separate, neuropathy-causing mutations generally result in a more severe phenotype, this is an exceptional situation where increased protein expression from the duplicated allele seems to be fully compensated by the lack of expression of the deleted allele. Pointing in a similar direction, a mother–daughter pair was observed who carried a heterozygous duplication of PMP22 and the heterozygous PMP22 mutation p.T118M on the same chromosome. Both patients showed an unusually
mild CMT1A phenotype with electrophysiologic features usually found in HNPP. Despite the fact that the pathogenicity of the mutation p.T118M is not fully clarified, this could be another example of partial compensation of PMP22 overexpression.

The co-occurrence of PMP22 duplication and PMP22 deletion in a patient might also be a rare source of a false-negative result in CMT/HNPP diagnostics. This should be considered particularly in unusual cases of familial neuropathy.

This case report highlights the relevance of therapeutic strategies that aim at genetic correction of the gene copy number, since genetic dosage compensation in CMT1A/HNPP patients seems to be effective.

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