PMP22 single exon deletion in a proband with hematologic malignancy and family history of Charcot-Marie-Tooth disease

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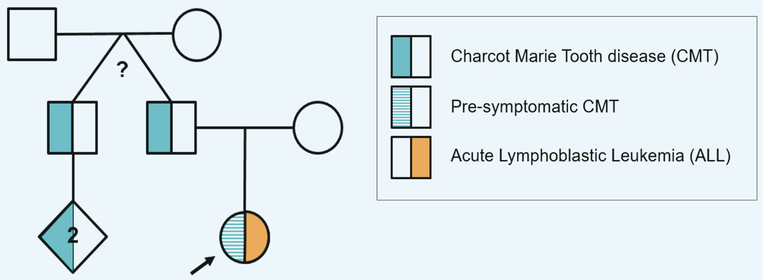
BACKGROUND

Charcot-Marie Tooth disease (CMT) is a group of hereditary sensory polyneuropathies that characteristically result in distal muscle weakness and atrophy alongside impaired deep tendon reflexes and pes cavus formation. Symptoms typically occur in the first to third decade and are slowly progressive but can be exacerbated by neurotoxic chemotherapeutic agents. Duplications or gain-of-function variants in the *PMP22* gene cause autosomal dominant CMT types 1A and 1E, while loss-of-function changes underlie the allelic condition Hereditary Neuropathy with Liability to Pressure Palsies (HNPP).

CASE SUMMARY

A four-year-old female presented with acute lymphoblastic leukemia (ALL) and a family history of CMT (Figure 1). The proband's father had experienced delayed walking, toe walking, and frequent falls since childhood; he and his similarly affected twin brother with clinical diagnoses of CMT were both found to carry a *PMP22* exon 4 deletion. Although this variant results in the loss of *PMP22* material, previously reported functional studies in unrelated patients with CMT type 1E suggest that this in-frame *PMP22* exon 4 deletion invokes a toxic gain-of-function effect via protein retention in the endoplasmic reticulum (Figure 2). The proband, who did not show signs of CMT, required a timely assessment of the known familial *PMP22* variant to guide her chemotherapy treatment. A custom, high-resolution chromosomal microarray (CMA) with >400k probes and exon-targeted coverage detected the familial single exon deletion of less than 1 kb in size (Figure 3). No additional copy number variants related to her ALL diagnosis were identified. The detection of the familial *PMP22* exon 4 deletion resulted in the selection of a chemotherapeutic agent with a reduced risk of neurotoxicity to not hasten the onset of CMT symptoms in the proband.

Figure 1. Pedigree



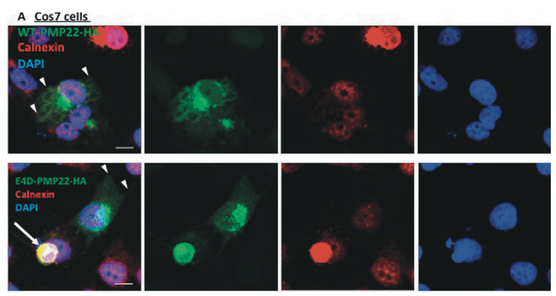


Figure 2A. Wang et al. (PMID: 28382305) showed *PMP22* without exon 4 (E4D mutation-PMP22) localized to the endoplasmic reticulum (ER, red calnexin signal) instead of the plasma membrane.

PMID: 28382305

Figure 2B. RT4 cells transfected with *PMP22* DNA constructs lacking exon 4 (E4D mutation-PMP22) were retained in the ER more than cells with wild type *PMP22*. *PMP22* ER retention is thought to result in a toxic gain-of-function effect through increased ER stress leading to neuropathy.

PMID: 28382305

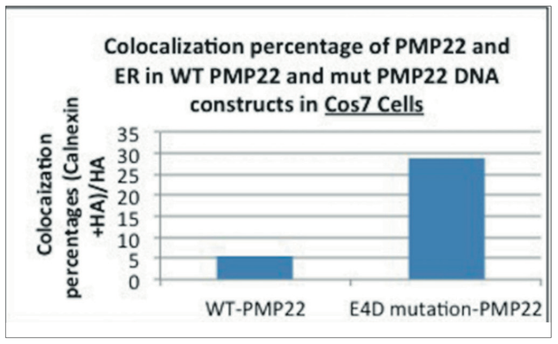


Figure 3. High-resolution Chromosomal Microarray Analysis (CMA) showing a loss of exon 4 of the *PMP22* gene.

DNA samples extracted from the patient's peripheral blood and a genotyped normal control were differentially labeled and co-hybridized to a 400K BGL custom Agilent oligonucleotide array to assay copy number changes. Results are displayed as log 2 ratios of the proband's versus the control's signal strength at each probe location.

CONCLUSIONS

This case provides **an example of an atypical gain-of-function change** caused by an intragenic *PMP22* loss that results in a CMT type 1E phenotype. High-resolution exon-level CMA coverage is critical for the detection of such single exon variants. Moreover, **this case highlights the importance of testing for familial CMT variants before chemotherapy treatment to avoid symptom exacerbation**, especially in cases of pediatric malignancy occurring before the natural onset of any CMT symptoms.