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Charcot-Marie-Tooth disease type 1E: Clinical Natural History and Molecular Impact of PMP22 Variants

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Charcot-Marie-Tooth disease type 1E (CMT1E) is a rare, autosomal dominant peripheral neuropathy caused by missense variants, deletions, and truncations within the peripheral myelin protein-22 (PMP22) gene. CMT1E phenotypes vary depending on the specific variant, ranging from mild to severe, and there is little natural history and phenotypic progression data on individuals with CMT1E. Patients with CMT1E were evaluated during initial and follow-up visits at sites within the Inherited Neuropathy Consortium. Clinical characteristics were obtained from history, neurological exams, and nerve conduction studies. Clinical outcome measures were used to quantify baseline and longitudinal changes. The trafficking of PMP22 variants in transfected cells was correlated to disease severity. Twenty-four presumed disease-causing PMP22 variants were identified in 50 individuals from 35 families, including 19 missense variants, three in-frame deletions, and two truncations. Twenty-nine patients presented with delayed walking during childhood. At their baseline evaluation, the mean CMTESv2-R in 46 patients was 16 ± 7.72 (out of 32), and the mean CMTPedS from 17 patients was 28 ± 6.35 (out of 44). Six individuals presented with hearing loss, eleven with scoliosis, three with hip dysplasia, and one with both scoliosis and hip dysplasia. Twenty variants were localized within

in transmembrane domains; 31 of 35 individuals with these variants had moderate to severe phenotypes. Three variants were found in the extracellular domain and were associated with milder phenotypes. Reduced expression of PMP22 at the cell surface, and the location of missense variants within in the transmembrane domain correlated with disease severity. Pathogenic PMP22 variants located within the transmembrane regions usually cause a moderate to severe clinical phenotype, beginning in early childhood, and have impaired trafficking to the plasma membrane.