PMP22 Expression in CMT1a Neuropathy

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In most patients with Charcot-Marie-Tooth 1a neuropathy (CMT1a) the gene of the peripheral myelin protein 22 (PMP22) is duplicated. Few patients show point mutations in the PMP22 gene or other myelin genes [1]. With great interest we read the article by H. Yoshikawa and colleagues [2] concerning PMP22 gene expression in CMT1 patients carrying the duplication in chromosome band 17p11.2 (CMT1a). Determining the levels of PMP22 expression in these patients is essential for understanding how duplication of the gene for the myelin protein PMP22 leads to the demyelinating neuropathy of the Charcot-Marie-Tooth type. Yoshikawa and colleagues [2] state (p 447) that the mean relative ratio of PMP22 mRNA levels in CMT1a was significantly higher than that in controls, and they conclude that PMP22 mRNA is overexpressed in CMT1a. In Figure 2 of the article, they show a northern blot in which the expression of PMP22 mRNA in other demyelinating neuropathies was compared with the expression of PMP22 mRNA in CMT1a. The variation of relative PMP22 mRNA levels in neuropathies other than CMT1a is moderate. In CMT1a, however, the variation in PMP22 mRNA levels is more pronounced and the authors point out the elevated mean PMP22 mRNA expression in CMT1a. Yet the data of Figure 2B indicate that relative PMP22 mRNA levels of 3 CMT1a patients (3 of 5) overlap with the mRNA levels found in controls. In a separate investigation we recently carried out a very similar analysis [3] using slightly different methods, i.e., a different control probe (GAPDH instead of actin), calibration curves of control RNA from healthy controls, and quantification of the hybridization signals by a phosphor imager. We obtained virtually identical results. In two of four CMT1a sural nerve biopsies, normal values of PMP22 mRNA levels were detected. The remaining CMT1a nerves showed a 1.5- and a fourfold overexpression of PMP22 mRNA. Taken together, the data from Yoshikawa and colleagues [2] and from our laboratory [3] indicate that only about 50% of the CMT1a patients with duplication of the PMP22 gene express elevated PMP22 mRNA levels, whereas the other half of the patients show transcript levels in the range of normal controls.

It is interesting that we found highest PMP22 mRNA expression in the patient who was least affected. Therefore we wonder whether, in the study of Yoshikawa and colleagues [2], the two nerve biopsies showing elevated levels of PMP22 mRNA are confined to patients with the shortest duration of the disease and/or with the least severe symptoms. Since indirect evidence suggests that PMP22 may serve a dual function in myelination and cell growth, we hypothesize that PMP22 overexpression in the beginning of the disease might alter the growth behavior of Schwann cells. The abnormal Schwann cell function could subsequently impair myelination, and during disease progression the expression of PMP22 subsequently could be down-regulated. This hypothesis is further supported by the observation that immunoreactivity of PMP22 and other established myelin proteins, like myelin basic protein (MBP) and P_0, has markedly declined at advanced disease stages as could be demonstrated by immunohistochemistry [3]. Finally, it is conceivable that the CMT1a phenotype is related to a Schwann cell growth defect induced either by duplication or by mutation of the PMP22 gene.

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The Influence of Apolipoprotein E Isotypes on Alzheimer's Disease Pathology in 40 Cases of Down's Syndrome

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Linkage between one of the apolipoprotein (apo) E isotypes, apo E4, and late-onset sporadic and familial Alzheimer's disease (AD) is now established by numerous reports and has been found in different ethnic populations (for review, see [1]). It has also been suggested that the presence of the apo E2 allele is protective against AD and is associated with longevity [2]. Among late-onset AD patients, the inheritance of the apo E4 allele has been associated with an earlier age of clinical onset and a higher number of plaques. Individuals suffering from early-onset familial AD (FAD) associated with mutations at codon 717 of βPP770 have also been reported to have an earlier onset of symptoms if they have an apo E4 allele [3]. However AD is heterogeneous and not all genetic types of AD show an apo E4 association. For example, early-onset familial AD patients with linkage to chromosome 14 do not differ clinically or pathologically according to their apo E isotype [4]. We have studied another population with AD pathology, Down's syndrome (DS) patients. These individuals will all develop the neuropathological features of AD if they reach middle adult life. We evaluated the apo E isotype of 40 postmortem paraffin-embedded DS brains using

