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Poster P1

CMT1E Under the Reflex Hammer and the Microscope: A Clinical and Biological Analysis

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PMP22 point mutations cause the rare dysmyelinating Charcot-Marie-Tooth type 1E neuropathy (CMT1E), with the more severe cases also classified as Dejerine-Sottas syndrome (DSS).

The underlying molecular mechanisms are still unknown but studies in different models suggested that mutant PMP22 protein mistrafficking and activation of the unfolded protein response (UPR) may play a role.

We investigated five index patients, carrying either the already described PMP22 mutations W28R, S72L, L80P or the novel variants A106V, A113P. All the subjects were clinically and neurophysiologically characterized: three cases were sporadic; for the remaining two, family members were also evaluated. We performed molecular modelling evaluation of mutant PMP22 proteins and in vitro studies; moreover, we collected serum and plasma for biomarkers' assessment and skin biopsies for immunohistochemical and fibroblasts analysis.

Four patients (W28R, S72L, L80P, A113P) showed early-onset and moderate-to-severe phenotype (CMTES range 9-20/28). Motor nerve conduction velocities (MCV) were in the DSS range (2.1-7.3 m/s). The youngest A106V subject was characterized by later onset (~14 years) and a very mild phenotype (CMTES=1, MCV=49.8 m/s), though 2 of 4 affected family members showed an aggressive demyelinating neuropathy. Molecular modelling suggested that all the mutations alter aminoacidic interactions, increasing protein rigidity, and negatively affecting plasticity and functionality. In in vitro studies, RT-4 Schwannoma cells were transfected with WT or mutant PMP22. Unlike PMP22-wt, which reached the membrane, mutants were intracellularly retained, co-localized with ER or Golgi markers, and triggered a UPR, as confirmed by CHOP staining in patient skin biopsies.

Our results strongly suggest a shared mechanism involving mistrafficking and ER stress for PMP22 mutations causing DSS/CMT1E. Ongoing studies on patient-derived cells will be crucial to confirm the UPR activation in humans.