Understanding the pathomechanisms of Charcot-Marie-Tooth neuropathies

Vincent Timmerman, PhD

Peripheral Neuropathy Group, VIB Department of Molecular Genetics, University of Antwerp, Belgium

Most genes for CMT and related hereditary peripheral neuropathies where identified through positional cloning or via a candidate gene approach. Different CMT phenotypes can be caused by mutations in the same gene, and conversely mutations in different genes may result in the same phenotype. This is further complicated by the fact that some mutations are private and occur in specific subtypes. Mutations in more than 20 genes cause primary alterations of the myelin sheath. Well-known examples are MPZ, PMP22 and GJB1. Mutations in genes (NFL) with a function in the axon however, result in axonal CMT phenotypes. Their products have cell type specific functions and therefore the underlying disease pathomechanisms can be logically inferred. Other mutations have been reported to cause intermediate CMT, with both myelin and axonal phenotypes. More recently, CMT mutations were found in ubiquitously expressed genes coding e.g. amino-acyl tRNA synthetases, small heat shock proteins and enzymes involved in sphingolipid metabolism, where the resulting gene products have housekeeping functions and pleiotropic activities. Therefore, these genes were not the obvious candidates for peripheral nerve degeneration and it remains an enigma why the mutant proteins cause such specific length-dependent degeneration of peripheral nerves. To find novel functional candidate genes, but also to identify peripheral nerve specific molecular pathways, we aimed to pinpoint differential protein–protein interaction networks starting from the ubiquitously expressed genes (wild type versus mutant proteins). The identification of interacting molecular partners and higher-order molecular complexes they form part of will provide novel insights in regulatory pathways in health and disease, and contribute to new candidate genes for CMT. Interacting proteins, and their encoding genes, are also potential candidates for other hereditary or sporadic peripheral neuropathies. Altogether, this will ultimately result in the identification of CMT gene networks which can provide insights in finding molecular targets for therapeutic intervention, not only for one type of CMT, but hopefully for several subtypes, including the more rare and/or complex phenotypes. During my presentation, I also highlighted the similarities in the molecular pathology underlying CMT neuropathies and hereditary spastic paraplegias (Timmerman, Clowes & Reid; in Experimental Neurology, January 2012: http://dx.doi.org/10.1016/j.expneurol.2012.01.010).