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INTRODUCTION

Molecular Genetics, Biology, and Therapy for Inherited Peripheral Neuropathies

Vincent Timmerman,*[,1,2] James R. Lupski,[†,3] and Peter De Jonghe[†,2,4,5]

[1]Peripheral Neuropathy Group, Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology, University of Antwerp, Antwerpen, Belgium; [2]Laboratory of Neurogenetics, Institute Born–Bunge, University of Antwerp, Antwerpen, Belgium; [3]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX; [4]Neurogenetics Group, Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology, University of Antwerp, Antwerpen, Belgium; and [5]Department of Neurology, University Hospital Antwerpen, Belgium

This issue reviews the most recent findings in the molecular genetics, biology, and therapy for inherited peripheral neuropathies. The best-known form is Charcot-Marie-Tooth disorder (CMT), an inherited neuropathy first described in 1886 (Charcot and Marie, 1886; Tooth, 1886). Most patients have progressive weakness and wasting of foot and hand muscles. Sometimes patients need walking aids or rarely become wheelchair dependent even at a young age. The clinical variability and genetic heterogeneity in CMT often poses difficult diagnostic challenges. Treatment is currently supportive and a therapy that fundamentally alters the course of CMT neuropathy is still lacking but recent studies in animal models show promising results. A better understanding of the molecular architecture of the peripheral nerve, the functional pathways, the myelination process, and the complex interaction between the myelinating Schwann cells, the axon, and muscle is crucial to identify targets for therapeutic interventions. The identification of loci, genes, and disease-causing mutations involved toward inherited peripheral neuropathies is the first step toward this understanding, and in the mean time provide tools for molecular genetic diagnosis. Genotype/phenotype correlations guide the selection of specific mutations suitable for functional analysis in cellular and animal models. These models are instrumental in the search for therapies, as it was very recently demonstrated in both a CMT rat and mouse model. The knowledge gained from the molecular genetic and biological research of inherited peripheral neuropathies will also help to make progress in the study of acquired neuropathies. Some of these neuropathies are often therapy-resistant and have a profound influence on the quality of life of the affected individuals.

According to the well-known classification of Dyck (Dyck et al., 2005), inherited peripheral neuropathies can be categorized as hereditary motor and sensory neuropathies (HMSN), hereditary motor neuropathies (HMN), and hereditary sensory neuropathies (HSN). HMSN, HMN, and HSN are further subdivided in several subtypes. All these neuropathies show a progressive course. Other inherited neuropathies follow a relapsing-remitting course; including hereditary neuropathy with liability to pressure palsies and hereditary brachial

*Author to whom all correspondence and reprint requests should be addressed. E-mail: vincent.timmerman@ua.ac.be
[†]Also for correspondence: E-mail: peter.dejonghe@ua.ac.be (De Jonghe); jlupski@bcm.tmc.edu (Lupski).

plexus palsy or hereditary neuralgic amyotrophy. Using positional cloning methods, the chromosomal localization (locus) of more than 40 inherited peripheral neuropathies was found in the last 15 yr. However, these genetic analyses also show that many entities do not show linkage to the known loci. A conservative estimate would predict that a total of 50–100 genes are involved in distinct forms of inherited peripheral neuropathies. Since the recent advances in the *Human Genome Project*, the number of genes identified for peripheral neuropathies has increased considerably with currently 34 genes. Several of these genes were previously unknown or their expression in the peripheral nervous system had not been demonstrated. Diagnostic work-up and genetic counseling can be complicated owing to this enormous heterogeneity. Furthermore mutations in the same gene can lead to demyelinating or axonal neuropathies, or even both, making the pathogenesis complex.

This issue contains 17 review articles dealing with different topics, starting with a clinical, electrophysiological and pathological survey of CMT and related disorders. The following sections are dedicated to the most recent molecular genetic findings in HMSN, HMN, HSN, and recurrent neuropathies. The pathomechanism of mutant proteins is discussed and correlations are made between the different neuropathy phenotypes and model organisms. Sections are dedicated to the interaction between Schwann cells and the axon in the developing nervous system, and to the role of the immune system related to the pathomechanism. Finally, future perspectives are presented regarding diagnostic and therapeutic approaches based on the molecular findings.

References

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