Inherited peripheral neuropathies: a myriad of genes and complex phenotypes

Inherited peripheral neuropathies form a sizable group of disorders that are known for their remarkable clinical and genetic heterogeneity. A common feature is the progressive length-dependent neurodegeneration in the peripheral nervous system (PNS). As a group, inherited peripheral neuropathies are the most common hereditary neuromuscular disorders with an estimated prevalence of one in every 2500 individuals. The inherited peripheral neuropathies are subdivided in hereditary motor and sensory neuropathy...
(HMSN), which is also known as Charcot–Marie–Tooth disease; hereditary motor neuropathy; and hereditary sensory and autonomic neuropathy (HSAN) based on clinical and electrophysiological findings. Further refinement of HMSN into demyelinating (HMSN-I), axonal (HMSN-II) and intermediate forms can be made when applying criteria to nerve conduction studies. These subdivisions stem from the pre-genetic era and were laid down in seminal reports based on detailed description in patients and families (Harding and Thomas, 1980; Dyck, 1993; Harding, 1993).

The first and still major causal genetic defect for inherited peripheral neuropathies, the CMT1A duplication, was discovered two decades ago (Lupski et al., 1991; Raeymaekers et al., 1991). Since that time, our knowledge of the molecular genetic groundwork of this group of diseases has grown considerably with well over 40 causal genes now identified. Genetic heterogeneity is such that, for a given subgroup of phenotypes, numerous candidate genes still have to be considered. Conversely, pronounced clinical heterogeneity can be observed among patients carrying mutations in the same gene with phenotypes sometimes conforming more closely to another subgroup within the classification of inherited peripheral neuropathies. The interrelationship between mutations in the known genes and their respective clinical phenotypes has led to a highly intricate classification. There are countless examples of this clinical and genetic heterogeneity: dominant mutations in HSPBI, HSPP8 and GARS can cause both HMSN-II and hereditary motor neuropathy; mutations in genes like EGR2, NEFL and GDAP1 can be transmitted as dominant or recessive traits; phenotypes associated with heterozygous MPZ mutations can range from typical HMSN-I to intermediate types and HMSN-II, and with age at onset from infancy to late adulthood (Reilly and Shy, 2009).

In spite of the common occurrence of inherited peripheral neuropathies in neuromuscular clinics and the widespread availability of genetic testing, establishing the molecular diagnosis in patients and families can be a cumbersome task. The prospects are brighter for some subforms of inherited peripheral neuropathy: well over 80% of patients with dominantly inherited HMSN-I (or CMT1) can be diagnosed genetically by screening only a handful of genes (Saporta et al., 2011). However, for other more rare subtypes (e.g. hereditary motor neuropathy and HSAN), 70–80% of patients do not carry mutations in any of the known genes (Dierick et al., 2008; Rotthier et al., 2009).

There is a constant need for studies that further refine existing genotype–phenotype correlations and describe new associations between mutations in genes that are already known and unexpected phenotypes. Such studies are valuable for several reasons: first, a more detailed knowledge on the various inherited peripheral neuropathy phenotypes helps neurologists to reach a clinical diagnosis in a particular patient. Secondly, these studies are instrumental in the design of rational screening strategies for genetic testing and counselling. Thirdly, as genetic knowledge grows exponentially, there is an ever-increasing need for ways to handle the complexity; these studies are the starting point for more in-depth research seeking to understand the basic biology and pathophysiology of the PNS, which may ultimately provide targets for therapeutic strategies.

In this issue of Brain, Auer-Grumbach et al. (2011) report on heterozygous mutations in the fibulin-5 (FBLN5) gene that cause a variety of phenotypes including variants of Charcot–Marie–Tooth disease, but surprisingly also hyperelastic skin and age-related macular degeneration. FBLN5 was previously implicated in hereditary disease with both recessive and dominant mutations causing generalized cutis laxa (Loeys et al., 2002; Markova et al., 2003) and heterozygous mutations underlying age-related macular degeneration (Jones et al., 2010). FBLN5 is a calcium-binding glycoprotein of the extracellular matrix and is a key regulator of development and maintenance of elastic fibre-rich tissues (Yanagisawa et al., 2009).

The study by Auer-Grumbach et al. (2011) was organized around two CMT1 families that were suitable for linkage studies. After whole-genome single nucleotide polymorphism genotyping and multipoint linkage analysis, a 4.5 Mb region on chromosome 14q32 could be delineated. Subsequent target capturing and parallel resequencing revealed a single novel missense variant in exon 10 of FBLN5 segregating with the disease. From a technological point of view, this approach very elegantly illustrates how next-generation sequencing approaches can be applied for gene discovery and mutation detection. The current next-generation sequencing platforms are in fact robust and versatile enough to be tailored to a number of different approaches, such as locus capturing and resequencing (Guelly et al., 2011), whole exome (Montenegro et al., 2011) and ultimately whole-genome sequencing (Lupski et al., 2010). Although studies such as that now reported by Auer-Grumbach et al. remain focused on families with prior locus information, they do pave the way for the more systematic application of genome wide-sequencing technologies to isolated patients with Mendelian disease who often remain without a molecular diagnosis (Visser et al., 2010). When applied more extensively, this could revolutionize the field of rare inherited diseases.

The phenotypes associated with the FBLN5 mutations identified in this study are very diverse and in fact transcend the classic features of hereditary neuropathy due to the variable co-occurrence of skin hyperlaxity and age-related macular degeneration. The FBLN5-associated diseases rather represent a novel spectrum of ‘oculo-neuro-cutaneous’ syndromes. This is in fact reminiscent of another recent example of such overlap syndromes namely the ‘neuro-skeletal’ phenotypes caused by dominant mutations in TRPV4 (Chen et al., 2010; Zimon et al., 2010).

The neuropathy constituent of the FBLN5 disease spectrum not only includes demyelinating CMT1 but also pure motor neuropathies (hereditary motor neuropathy) and possibly even a few patients with late-onset axonal neuropathies. In addition, a number of mutation carriers in this study do not show an overt phenotype at all. In such conditions, proving pathogenicity of sequence variants can be troublesome. In fact, the authors comment extensively on one such FBLN5 sequence variant namely Val126Met that may either be a causal variant, a genetic risk factor for age-related macular degeneration or a benign polymorphism (Lotery et al., 2006).

The interpretation of genetic data in any given family may therefore be greatly facilitated by information on phenotypes and mutations in other families. This underscores the fact that
for such studies of clinically diverse Mendelian disorders strength indeed is in the numbers. Clinical variability, allelic diversity and reduced penetrance are known phenomena in the field of hereditary neuropathies. In addition to variability of disease severity between and within families with inherited peripheral neuropathy, there are numerous examples of allelic disorders caused by mutations in the same gene (TRPV4, ATP7A, LMNA, DNLM2, ATL-1 and BSCL2); genes in which both dominant and recessive mutations can cause inherited peripheral neuropathy (NEFL, EGR2, MFN2 and GDAP1); and overlap syndromes consisting of inherited peripheral neuropathy and non-neuronal features (TRPV4 and now FBLN5). This wide range of clinical features and their corresponding genetic findings are a major challenge for diagnostic screening and genetic counselling in patients.

Finally, the most intriguing question remains how mutations in a broadly expressed gene like FBLN5 can give rise to such specific yet variable clinical phenotypes. Although of course beyond the scope of the current work, Auer-Grumbach et al. (2011) touch on this matter in their discussion. Decreased secretion of FBLN5 and the ensuing disturbances in formation of elastic fibres may be the underlying disease mechanism of age-related macular degeneration and cutis laxa (Jones et al., 2010). The identification of FBLN5 mutations in Charcot-Marie-Tooth disease shows for the first time that extracellular matrix genes might indeed be implicated in inherited peripheral neuropathy as well. Myelination in the PNS requires interaction between Schwann cells and the extracellular matrix that may well be regulated by FBLN5 (Berti et al., 2006). Disturbances of this interaction may indeed cause myelin abnormalities. If that were the case, one expects demyelinating forms of neuropathy, as was the case in at least two of the reported families. It is however less obvious if and how this mechanism applies to the reported FBLN5 mutation carriers with axonal neuropathies.

By applying next-generation genetic techniques in their study, Auer-Grumbach et al. (2011) not only enlarge our understanding of the genetic basis and the remarkable phenotypic diversity of inherited peripheral neuropathies, but also hint at a pivotal role for regulators of the extracellular matrix in the fundamental biology and pathophysiology of the PNS.

**Funding**

J.B. is supported by a fellowship of the Fund for Scientific Research (FWO-Flanders).

Jonathan Baets1,2,3 and Vincent Timmerman2,4

1VIB Department of Molecular Genetics, Neurogenetics Group, University of Antwerp, Antwerpen, Belgium

2Laboratory of Neurogenetics, Institute Born-Bunge, University of Antwerp, Antwerpen, Belgium

3Department of Neurology, University Hospital Antwerpen (UZA), Antwerpen, Belgium

4VIB Department of Molecular Genetics, Peripheral Neuropathy Group, University of Antwerp, Antwerpen, Belgium

Correspondence to: Vincent Timmerman, PhD, VIB Department of Molecular Genetics, University Neuropathy Group, University of Antwerp, Universiteitsplein 1, 2610 Antwerpen, Belgium

E-mail: vincent.timmerman@molgen.vib-ua.be

doi:10.1093/brain/awr114

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