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Original articles

Molecular genetics of inherited peripheral neuropathies : who are the actors ?

Jan MEULEMAN[1], Vincent TIMMERMAN[1], Eva NELIS[1] and Peter DE JONGHE[1,2]

[1]Flanders Interuniversity Institute for Biotechnology (VIB), Born-Bunge Foundation (BBS), University of Antwerp (UIA), Antwerpen, Belgium ; [2]Division of Neurology, University Hospital Antwerpen (UZA), Antwerpen, Belgium

Abstract

Charcot-Marie-Tooth disease, the most common variant of the inherited peripheral neuropathies, has a prevalence of 1/2500. Clinical, electrophysiological, neuropathological and molecular genetic studies have demonstrated extensive heterogeneity. Currently, 30 genetic loci are known for distinct CMT types and related inherited peripheral neuropathies, while many other types have been excluded for linkage to these loci. Recent molecular genetic studies have demonstrated the involvement of 8 genes that encode proteins with very diverse functions. These include a structural protein confined to the compact myelin, a cytoskeletal protein, an adhesion molecule, a gap-junction protein, a transcription factor, a receptor for a neurotrophic factor, a phosphatase and a protein involved in signal transduction and cell cycle regulation.

The inherited peripheral neuropathies

In 1968, Dyck *et al.* classified the inherited neuropathies of the peripheral nervous system into three large groups, i.e., hereditary motor and sensory neuropathies (HMSN), hereditary motor neuropathies (HMN), and hereditary sensory neuropathies (HSN) or hereditary sensory and autonomic neuropathies (HSAN) (Dyck *et al*., 1993). This classification is based on clinical features, mode of inheritance, neuropathological and electrophysiological findings. Subsequent molecular genetic studies have confirmed the extensive heterogeneity. Currently, 30 distinct genetic loci for inherited peripheral neuropathies have been mapped. However, many types have been excluded for linkage to the known loci or have not been studied at the molecular genetic level. An overview of the loci for CMT and related disorders is shown in Table 1. So far mutations in 8 genes have been identified as the cause of distinct inherited peripheral neuropathies. These genes include : peripheral myelin protein 22 (*PMP22*), myelin protein zero (*MPZ/P0*), connexin 32 (*GJB1/Cx32*), early growth response element 2 (*EGR2*), myotubularin-related protein 2 (*MTMR2*), N-myc downstream-regulated gene 1 (*NDRG1*), neurofilament-light gene (*NEFL/NF-L*), and tyrosine kinase receptor type 1 (*NTRK1/TrkA*). All known mutations in these genes and the corresponding phenotypes are regularly updated in the database of inherited peripheral neuropathies (IPNMDB, http://molgen-www.uia.ac.be/CMTmutations/). In this review, we will focus on the genes involved in inherited peripheral neuropathies. Other aspects of the inherited peripheral neuropathies have been addressed in recent reviews (De Jonghe *et al*., 2000 ; Nelis *et al*., 1999b).

Peripheral Myelin Protein 22

The *PMP22* gene was first cloned as the human homologue of the mouse growth arrest-specific 3 gene (*Gas3*) (Martinotti *et al*., 1992). The gene is located on chromosome 17p11.2, and encodes a membrane protein comprising 2-5% of total peripheral myelin protein content (Pareek *et al*., 1993). The *PMP22* gene has 2 tissue-specific promoters, one being nerve-specific (Suter *et al*., 1994). PMP22 expression in the peripheral nervous system (PNS) is most likely regulated by axonal contact (Spreyer *et al*., 1991). The 160 amino acids comprising PMP22 protein is a highly hydrophobic protein with a molecular mass of 22 kilodalton (kDa). It has four transmembrane domains, two extracellular loops, and cytoplasmic amino and carboxy termini (Fig. 1). After synthesis in the rough endoplasmic reticulum, the majority of PMP22 gets rapidly degraded and only a small fraction is processed in the Golgi apparatus and transported to the cell membrane (Pareek *et al*., 1997).

Although PMP22 has been known for almost a decade, its function is still under debate. Initial studies showed that PMP22 is a growth arrest- and apoptosis-specific protein (Manfioletti *et al*., 1990). Mouse pmp22 has been detected during development and in distinct adult neural and non-neural tissues. The zebrafish orthologue of PMP22 also shows expression in embryonic neural crest cells, suggesting a role in the early development of the PNS (Wulf *et al*., 1999). Moderate overexpres-

Table 1

Loci and genes for CMT and related peripheral neuropathies

Locus symbol	chromosome	mutation/gene
Hereditary motor and sensory neuropathies type I (HMSN type I)		
Autosomal dominant		
CMT1A	17p11.2-p12	1.5 Mb tandem duplication / dosage of PMP22
CMT1A	17p11.2-p12	PMP22 mutations
CMT1B	1q22-q23	MPZ mutations
CMT1C	?	?
CMT1D	10q21.1-q22.1	EGR2 mutation
Autosomal recessive		
CMT4A	8q13-q21	?
CMT4B.1	11q22	MTMR2 mutations
CMT4B.2	11p15	?
CMT4C	5q31-q33	?
CMT4D/ HMSN-L	8q24.3	NDRG1 mutations
CMT4E/ HMSN-R	10q21-q22	?
CMT4F	19q13.1-q13.3	?
CCFDN	18qter	?
X-linked		
CMT1X	Xq13.1	Cx32 mutations
Hereditary motor and sensory neuropathies type II (HMSN type II)		
Autosomal dominant		
CMT2A	1p35-p36	?
CMT2B	3q13-q22	?
CMT2C	?	?
CMT2D	7p14-p15	?
CMT2E	8p21	NEFL mutations
HMSN-P	3q13.1	?
Autosomal recessive		
CMT2	1q21.2-q21.3	?
X-linked		
CMT2X	Xq24-q26	?
Hereditary motor and sensory neuropathies type III (HMSN type III)		
Autosomal Recessive		
DSS	17p11.2-p12	PMP22 mutations
DSS/CH	1q22-q23	MPZ mutations
DSS/CH	10q21.1-q22.1	EGR2 mutations
Autosomal dominant		
DSS/CH	17p11.2-p12	PMP22 mutations
DSS/CH	1q22-q23	MPZ mutations
DSS/CH	10q21.1-q22.1	EGR2 mutations
AD-DSS	8q23-q24	?
distal Hereditary Motor Neuropathy (distal HMN)		
Autosomal dominant		
distal HMN II	12q24	?
distal HMN V	7p	?
congenital distal HMN	12q23-q24	?
Autosomal recessive		
distal HMN-J	9p12-p21	?
Hereditary Sensory Neuropathy (HSN)		
Autosomal dominant		
HSN I	9q22	?
Autosomal recessive		
HSAN III	9q31	?
HSAN IV	1q21-q22	NTRK1/TrkA mutations

Table 1 (continued)

Recurrent neuropathies		
Autosomal dominant		
HNPP	17p11.2-p12	1.5 Mb deletion / dosage of PMP22
HNPP	17p11.2-p12	PMP22 mutations
HNA	17q25	?
Others		
GAN	16q24.1	?

Legend : HMSN-L = HMSN-Lom ; HMSN-R = HMSN-Russe ; CCFDN = congenital cataracts facial dysmorphism neuropathy syndrome ; HMSN-P = HMSN proximal ; HMN-J = HMSN-Jerash type ; GAN = giant axonal neuropathy ; HNA = hereditary neuralgic amyotrophy.

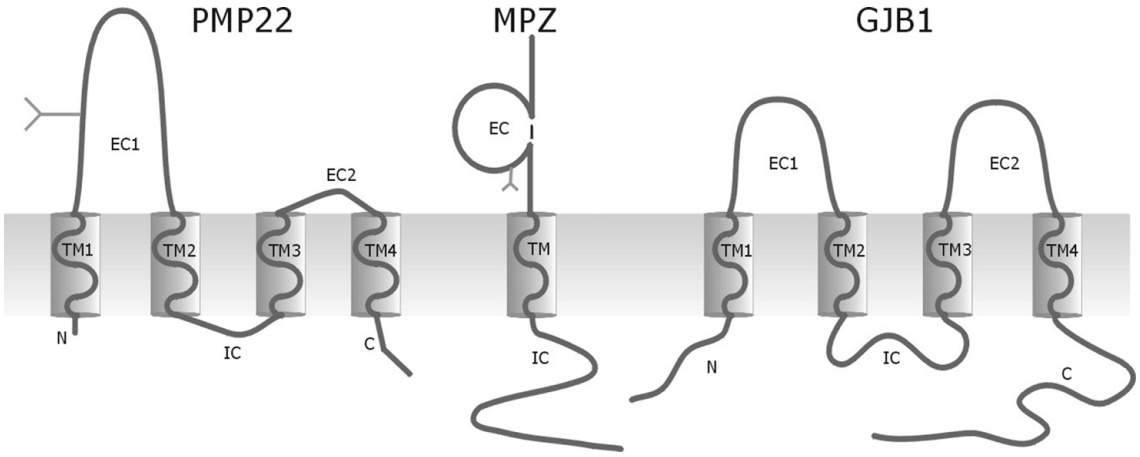

FIG. 1. — Structural overview of the myelin membrane proteins PMP22, MPZ/P0 and GJB1/Cx32. N = amino terminus; TM = transmembrane domain; EC = extracellular loop; IC = intracellular loop; C = carboxy terminus.

sion of PMP22 can induce susceptibility to apoptosis in some cell types. When this apoptotic response is counteracted, PMP22 can still modulate cell shaping and cell spreading. Therefore, PMP22 may have an important role in Schwann cell differentiation and myelination (Brancolini *et al*., 1999).

In the adult PNS, PMP22 most likely functions as an integral membrane protein since it is confined to the compact myelin of Schwann cells (Kuhn *et al*., 1993 ; Snipes *et al*., 1992). Recently, co-immunoprecipitation and confocal microscopy experiments demonstrated that PMP22 and P0, the major component of the peripheral myelin membrane, form complexes suggesting a complementary role of both proteins in cell adhesion of compact myelin (D'Urso *et al*., 1999).

PMP22 is the first identified culprit gene for CMT (CMT1A, OMIM # 118220). A 1.5-megabase (Mb) tandem duplication on chromosome 17p11.2-p12 (Lupski *et al*., 1991 ; Raeymaekers *et al*., 1991), containing the *PMP22* gene (Matsunami *et al*., 1992 ; Patel *et al*., 1992 ; Timmerman *et al*., 1992 ; Valentijn *et al*., 1992), is present in 71% of patients with the classical demyelinating form of CMT. The same region is deleted in the overwhelming majority of patients with hereditary neuropathy with liability to pressure palsies (HNPP, OMIM # 162500) (Nelis *et al*., 1996). The rare smaller duplications and deletions still contain the *PMP22* gene (Palau *et al*., 1993 ; Valentijn *et al*., 1993), suggesting a gene dosage effect as the disease mechanism (Lupski *et al*., 1992). Over- and underexpression of *PMP22* has been confirmed at the protein and mRNA level (Vallat *et al*., 1996). The dosage sensitivity of *PMP22* is nicely illustrated by the genotype-phenotype correlations in man and rodents over- and underexpressing *PMP22*, as reviewed by Nelis *et al.* (Nelis *et al*., 1999b). Furthermore, 37 distinct mutations have been described (IPNMDB), resulting in distinct phenotypes : classical CMT1 (CMT1A), the more severe Dejerine-Sottas syndrome (DSS, OMIM # 145900) and occasionally HNPP. *In vitro* studies have demonstrated that missense mutations lead to impaired intracellular trafficking of PMP22 resulting in an accumulation of the mutant protein in the endoplasmic reticulum (ER) and Golgi apparatus. The mutant protein also traps normal PMP22 resulting in a decreased amount of PMP22 available for incorporation in the myelin membrane (Naef and Suter, 1999). Mutations leading to HNPP are predicted to result in a truncated or severely altered protein that gets rapidly degraded, mimicking underexpression resulting from the

HNPP deletion. Apparently, some mutations produce a loss of function and result in HNPP, while other mutations lead to CMT1 or DSS by a gain of function, either by increased dosage of a normal PMP22 protein or by a toxic effect of the mutated PMP22 molecule.

Myelin Protein Zero

The myelin protein zero gene (*MPZ*, *P0*) is located on chromosome 1q22-q23. It encodes a 219 amino acid, 28-30 kDa glycoprotein that accounts for more than 50% of total PNS myelin protein. P0 has one transmembrane domain, an extracellular amino- terminus and an intracellular carboxy-terminus (Fig 1). Crystallographic 3-D structural analysis of the extracellular domain shows similarity to an immunoglobulin variable domain (Shapiro *et al*., 1996).

During Schwann cell development, *P0* is simultaneously induced with genes encoding other myelin proteins, such as *PMP22*, myelin basic protein (*MBP*) and myelin-associated glycoprotein (*MAG*) (Lemke *et al*., 1988). *P0* is upregulated at the onset of myelination.

As a compact myelin protein, P0 most likely acts as a 'double adhesive protein'. It holds myelin together at the intraperiod line through interactions of its extracellular (Shapiro *et al*., 1996), self-adhesive immunoglobulin domain and at the major dense line via interactions of its cytoplasmic domain (Ding and Brunden, 1994).

Apart from its structural role in myelination, P0 plays a regulatory role as well. *P0* overexpressing mice show failure in axon sorting and a myelination arrest at early mesaxon formation. In early developing Schwann cells, high *P0* overexpression inhibits polarization of Schwann cell membranes into appropriate functional domains, dynamic axonal interaction and Schwann cell membrane expansion required for appropriate axonal sorting and myelination (Yin *et al*., 2000).

Up to now, 73 distinct *P0* mutations have been identified. Most of these mutations cause a classical CMT1 phenotype (CMT1B, OMIM # 118200). However, some *P0* mutations lead to a CMT2 phenotype or a more severe DSS phenotype or congenital hypomyelination (CH, OMIM # 605253), as reviewed by Nelis *et al.* (Nelis *et al*., 1999a). Mutant P0 could affect myelin formation in three ways : (1) by not reaching the myelin membrane, (2) by reaching the myelin membrane but having lost its adhesive properties, or (3) by reaching the myelin membrane and having a dominant negative effect on the wildtype P0. The recently demonstrated complex-formation between PMP22 and P0 might clarify the remarkable similarity between the CMT1A and CMT1B phenotypes (D'Urso *et al*., 1999). Alterations in either protein may interfere with the normal association of P0 and PMP22 into one functional complex. The disturbed interaction would subsequently result in demyelination as a common pathological pathway in CMT1A and CMT1B.

Connexin 32

The *Cx32* gene is located on Xq13.1. The Cx32 protein has 4 transmembrane domains, 2 extracellular loops and cytoplasmic and carboxy termini (Fig. 1). The connexin family consists of homologous integral membrane proteins that form channels providing low resistance pathways for the transmission of electrical signals and the diffusion of small ions and non-electrolytes between coupled cells. Gap junctions are channels between adjacent cells. Six monomeric connexins form a hemi-channel, also called a connexon. Gap junctions are formed when a connexon in the plasma membrane of one cell docks with a connexon in the plasma membrane of an adjacent cell (Bruzzone *et al*., 1996).

Cx32 has two cell-type specific promoters. The first is used in all cells expressing Cx32, except in Schwann cells, while the second is used in brain, spinal cord and peripheral nerve (Sohl *et al*., 1996). Cx32 is expressed in many different cell types, ranging from Schwann cells and oligodendrocytes, to pancreatic cells and hepatocytes, from where it was first cloned (Kumar and Gilula, 1986). Cx32 expression in Schwann cells is upregulated during myelination and nerve regeneration, and reduced during Wallerian degeneration (Scherer *et al*., 1995).

The function of Cx32 as part of a gap junction is straightforward. Immunohistochemistry has located Cx32 in non-compacted myelin, around the nodes of Ranvier and at the Schmidt-Lanterman incisures (Bergoffen *et al*., 1993 ; Scherer *et al*., 1995). Injection of dyes with different sizes proved that Cx32 forms reflexive intracellular channels that provide a radial pathway traversing the myelin sheath (Balice-Gordon *et al*., 1998).

All disease-causing mutations in *Cx32* result in CMTX (OMIM # 302800). This X-linked disease presents as a classical CMT phenotype, which is usually more severe in male than in female patients. Currently 202 mutations have been described scattered throughout the whole gene. Although Cx32 is widely expressed, the effect of *Cx32* mutations is limited to the peripheral nervous system.

Cx32 mutations have different functional consequences. Some mutations lead to a loss of function with no transcription of Cx32 (Ainsworth *et al*., 1998). Other mutations cause normal transcription of *Cx32*, but virtually no protein is found in the cell. This can be due to a nonsense mutation leading to the insertion of a stop codon at the beginning of the protein, or instability of the mRNA or protein. Protein can be synthesized but not properly

transported to the membrane. Abnormal accumulation of Cx32 in the Golgi apparatus or cytoplasm, due to altered trafficking, may be toxic to the cell or hamper transport of other myelin proteins (Deschenes *et al*., 1997). Normally transported protein can be unable to form functional gap junctions. Mutated Cx32 can fail to build connexons, to dock connexons to the hemi-channels of adjacent cells, or to form functional gap junctions (Castro *et al*., 1999). Some mutated Cx32 proteins do insert in the plasma membrane and form functional gap junctions. However, these channels have altered gating, permeability or biophysical properties (Oh *et al*., 1997).

Early growth response element 2 gene

The *EGR2* gene is located on chromosome 10q21.1-q22.1 (Joseph *et al*., 1988) and encodes a 51 kDa protein of 475 amino acids. *EGR2* is the human homologue of the mouse *Krox20* gene (Chavrier *et al*., 1989), with an overall amino acid identity of 89% (100% in the zinc finger domain) (Warner *et al*., 1999). *EGR2* is a member of the *EGR* family.

The EGR proteins encode transcription factors containing Cys_2His_2 zinc finger domains, which bind a GC-rich consensus binding site (Swirnoff and Milbrandt, 1995). Analysis of homozygous and heterozygous *Krox20* knockout mice has shown that *Krox20* is important in the development and segmentation of the hindbrain (Schneider-Maunoury *et al*., 1993 ; Swiatek and Gridley, 1993). Surviving homozygous *Krox20* knockout mice have hypomyelination of the PNS with Schwann cells blocked at an early stage of differentiation, causing a trembling phenotype (Topilko *et al*., 1994). Krox20 expression is activated before onset of myelination in the PNS and is essential for the final differentiation of myelinating Schwann cells (Zorick *et al*., 1996). These data suggest that Krox20 and its human homologue EGR2 are transcription factors required for the transactivation of PNS myelination-specific genes.

The target genes of EGR2 are still unknown. Krox20 regulates the transcription of HoxB2 and Hox-1.4, genes required for segmentation in the CNS, but the PNS target genes are still unknown (Chavrier *et al*., 1990).

Several mutations in *EGR2* have been described in patients with different phenotypes i.e. classical CMT1, DSS and CH (Timmerman *et al*., 1999 ; Warner *et al*., 1998). Some of these mutations were present in the homozygous and others in the heterozygous state. One mutation causes a CMT1 phenotype with cranial nerve deficits (Latour *et al*., 1999 ; Pareyson *et al*., 2000). This additional clinical involvement of cranial nerves is unusual for CMT1 and may demonstrate a similar role for *Krox20* and *EGR2* in brainstem and cranial nerve development (Pareyson *et al*., 2000).

The effect of some mutations on the DNA binding capacities of EGR2 has been studied in order to correlate the residual DNA binding capacities to the clinical severity (CMT1 < DSS < CH). The results confirm an allelic series with increasing functional defects (R409W < R359W < S382R/D383Y) (Warner *et al*., 1999). The dominant nature of these mutations seems to be in contrast with the *Krox20* heterozygous knockout mouse, which shows no phenotypical abnormalities (Schneider-Maunoury *et al*., 1993). This suggests that these mutations do not cause a loss of function, but rather have a dominant negative or a gain of function effect. Another mutation was shown to interfere with the binding of NAB (NGFI-A Binding) proteins, possible co-repressors of *EGR2*, probably leading to increased transcription of *EGR2* (Warner *et al*., 1999).

Myotubularin-related protein-2

MTMR2 was initially cloned as a cDNA related to the *myotubularin* (*MTM1*) gene, in which mutations cause X-linked myotubular myopathy (OMIM # 310400). The gene was mapped to chromosome 11q22 (Laporte *et al*., 1996). The full-length cDNA defines an open reading frame of 1716 basepairs (bp), encoding a protein of 571 amino acids.

MTMR2 is a member of the myotubularin dual specificity phosphatase (DSP) gene family, comprising at least 8 human and 6 mouse genes (Laporte *et al*., 1998). The MTMR2 protein is therefore characterized by a protein tyrosine phosphatase (PTP) / DSP signature and a SET (Suvar3-9, Enhancer-of-zeste, Trithorax) interaction domain (SID) (Cui *et al*., 1998 ; Hunter, 1998). The exact function and substrate of MTMR2 still need to be determined. A putative function of MTMR2 is to interact via a phosphorylation cascade with proteins involved in cell proliferation.

Five homozygous *MTMR2* mutations have been found causing autosomal recessive demyelinating neuropathy with myelin outfoldings (CMT4B.1, OMIM # 601382) (Bolino *et al*., 2000). The exact effect of these mutations has not yet been studied but one can speculate that disturbed Schwann cell proliferation could lead to overgrowth of myelin, as observed in the nerve biopsies of CMT4B.1 patients (Bolino *et al*., 1996).

N-myc Downstream-Regulated Gene 1

NDRG1 was identified in several independent *in vitro* studies of human cell lines (Kokame *et al*., 1996 ; Kurdistani *et al*., 1998 ; van Belzen *et al*., 1997). The gene is located on chromosome 8q24.3. The existence of a *Ndr* gene family in mice (van Belzen *et al*., 1997) led to the discovery of the

human homologues *NDRG2* and *NDRG3*. The encoded protein is highly conserved in evolution (Shimono *et al*., 1999). It is ubiquitously expressed, as determined by various experimental systems (Kokame *et al*., 1996). Expression studies demonstrate an abundant expression of *NDRG1* in peripheral nerves. Preliminary immunocytochemistry studies localize NDRG1 in the Schwann cell cytoplasm, without evidence of axonal expression (Kalaydjieva *et al*., 2000). The predicted functions of NDRG1 are based on studies of non-neural tissues. NDRG1 expression cycles with cell division (Kurdistani *et al*., 1998), is repressed in cell transformation and upregulated in growth-arrested differentiating cells (Kurdistani *et al*., 1998 ; van Belzen *et al*., 1997). These data suggest the involvement of NDRG1 in growth-arrest and cell differentiation, and in the maintenance of the differentiated state.

Until now, only one *NDRG1* mutation has been described as the cause of HMSN-Lom (OMIM # 601455), an autosomal recessive HMSN variant confined to in-bred Gypsy families. This suggests that all these families originate from a common founder. The mutation segregated in the homozygous state in all affected individuals (Kalaydjieva *et al*., 2000). Since the function of NDRG1 has only been studied in non-neural tissue, it is currently impossible to predict the functional consequences of this mutation, either for the peripheral neuropathy, or the hearing loss that is an invariant feature of the phenotype.

Neurofilament-Light Gene

Neurofilament-light (*NEFL*), neurofilament-medium (*NEFM*) and neurofilament-heavy (*NEFH*) form together the neurofilament family, in humans the most abundant subclass of the cytoplasmic intermediate filaments (IF). The *NEFL* gene is located on chromosome 8p21 (Hurst *et al*., 1987 ; Somerville *et al*., 1988). *NEFL* encodes a 68 kDa protein, which is the most abundant protein of the three neurofilament proteins.

The neurofilaments share a central coiled domain, which is involved in the assembly of 10-nm filaments (Julien, 1999). NEFL seems to be the key-player in the neurofilament assembly, since it is the only neurofilament protein capable of organizing filaments by itself (Carpenter and Ip, 1996 ; Geisler and Weber, 1981). Homozygous *NEFL* knockout mice show that NEFM and NEFH cannot form 10-nm neurofilaments in the absence of NEFL. Furthermore, the homozygous *NEFL* knockout mice express only 5% of the normal level of NEFM and NEFH and exhibit reduced axonal radial growth and delayed nerve regeneration. This demonstrates that *NEFL* can also influence the expression of the other neurofilament proteins (Ohara *et al*., 1993 ; Zhu *et al*., 1997). A targeted Leu394Pro mutation in mice has more devastating consequences than the null mutation. It shows a permanent loss of mostly large, neurofilament-rich motor axons (Cleveland *et al*., 1996 ; Lee *et al*., 1994). Therefore, NEFL seems to be important for the structure and function of axons and may be responsible for effective transport, axon regeneration and axonal longevity. Recently, NEFL has been shown to be a protein-phosphatase-1-binding protein, associated with the neuronal plasma membrane (Terry-Lorenzo *et al*., 2000).

Currently, two mutations in the *NEFL* gene have been described in association with an autosomal dominant CMT2 phenotype (Mersiyanova *et al*., 2000). One mutation is situated in the highly conserved coil 2B domain, which is responsible for the neurofilament assembly (Carpenter and Ip, 1996). The second mutation most likely destabilizes the head domain. However, these predicted pathogenic effects have not yet been studied in functional assays.

Tyrosine kinase receptor, type 1

The gene for neurotrophic tyrosine kinase receptor, type 1 (*NTRK1/TrkA*) (Martin-Zanca *et al*., 1986) is located on chromosome 1q21-q22 (Weier *et al*., 1995).

The *NTRK1* gene is expressed in the nervous system (Martin-Zanca *et al*., 1990) and encodes a transmembrane receptor tyrosine kinase, that is phosphorylated in response to nerve growth factor (NGF) (Kaplan *et al*., 1991 ; Klein *et al*., 1991). Homozygous *Trka* knockout mice show a phenotype resembling autosomal recessive congenital insensitivity to pain (CIPA) (Swanson, 1963), also known as hereditary sensory and autonomic neuropathy type IV (HSAN-IV, OMIM # 256800). The animals show loss of responses to painful stimuli, but no anhidrosis (Smeyne *et al*., 1994).

In humans, distinct NTRK1 mutations have been found to cause HSAN-IV. In contrast to the homozygous knockout mice, patients show anhidrosis in addition to congenital insensitivity to pain. Most mutations are present in the homozygous state. Compound heterozygous double and triple mutations have been reported (Mardy *et al*., 1999 ; Miura *et al*., 2000). The mutations are distributed in the extracellular domain involved in binding of nerve growth factor, as well as in the intracellular signal transduction domain (Mardy *et al*., 1999), suggesting a loss of function hypothesis (Greco *et al*., 2000).

Conclusions

Molecular genetic studies have identified mutations in 8 genes as the cause of inherited peripheral neuropathies. It turns out that the underlying dis-

ease mechanisms are highly diverse. The genes not only encode proteins that are involved in distinct biological pathways but mutations in the same gene exert their pathogenic effect in very different ways. Some are dosage sensitive, while others result in a loss or gain of function effect. The molecular genetic studies of the inherited peripheral neuropathies have certainly provided us with important new tools for accurate DNA diagnosis of these disorders, especially for the most common forms such as CMT1. However, extensive functional studies need to be performed in order to unravel the underlying disease mechanisms and the complex molecular interactions. Only then, treatment for inherited peripheral neuropathies will become a reality.

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P. DE JONGHE,
Peripheral Neuropathy Group,
Laboratory of Molecular Genetics,
Department of Biochemistry,
University of Antwerp (UIA),
Universiteitsplein 1,
B-2610 Antwerpen (Belgium).