CHAPTER 5

AUTOSOMAL RECESSIVE CHARCOT-MARIE-TOOTH NEUROPATHY

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Abstract: Charcot-Marie-Tooth (CMT) disease, a hereditary motor and sensory neuropathy that comprises a complex group of more than 50 diseases, is the most common inherited neuropathy. CMT is generally divided into demyelinating forms, axonal forms and intermediate forms. CMT is also characterized by a wide genetic heterogeneity with 29 genes and more than 30 loci involved. The most common pattern of inheritance is autosomal dominant (AD), although autosomal recessive (AR) forms are more frequent in Mediterranean countries. In this chapter we give an overview of the associated genes, mechanisms and epidemiology of AR-CMT forms and their associated phenotypes.

INTRODUCTION

Peripheral neuropathy is one of the most common referrals to neurologists and within this group of disorders, genetic cause is common. Inherited peripheral neuropathies present with varied symptoms and temporal course and represent one of the groups of Mendelian neurological disorders with higher prevalence. They are clinically and genetically heterogeneous disorders and lead to a progressive degeneration of the peripheral nerves. Hereditary neuropathies are classified into hereditary motor neuropathies (HMN), hereditary sensory neuropathies (HSN), hereditary motor and sensory neuropathies (HMSN) and hereditary sensory and autonomic neuropathies (HSAN).

Charcot-Marie-Tooth (CMT) disease is an HMSN that comprises a complex group of more than 50 disease entities and it is the most common inherited neuropathy with

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Table 1. Classification of CMT forms

	Inheritance	Hystological Features	CMT Types
CMT1	Autosomal dominant	Demyelinating	CMT1A-D, CMT1F
CMT2	Autosomal dominant	Axonal	CMT2A-N
DI-CMT	Autosomal dominant	Intermediate	DI-CMTA-D
CMTX	X linked	Demyelinating or axonal	CMTX1-5
CMT4	Autosomal recessive	Demyelinating	CMT4A-H, CMT4J
CMT4C/ AR-CMT2	Autosomal recessive	Axonal	CMT4C1-4

an estimated prevalence of 28/100 000.[1,2] Patients usually present with distal muscle atrophy in the legs, areflexia, foot deformity and steppage gait in the first or second decade of life. In most cases, hands are also involved as the disease progresses. CMT can be classified according to electrophysiological and nerve biopsy findings into three types (*Neuromuscular Disease Center*, http://neuromuscular.wustl.edu/index.html; Table 1): (i) Demyelinating CMT characterized by nerve conduction velocities (NCVs) of <38m/s and demyelinating traits on sural nerve biopsies with proliferation of Schawnn cells forming onion bulbs; (ii) Axonal CMT showing normal or slightly reduced NCV and loss of myelinated axons; and (iii) intermediate CMT in which NCV lies between 30-40 m/s and nerve pathology shows axonal and demyelinating features.[3,4]

CMT is characterized by a wide genetic heterogeneity not just because of the large number of genes/loci involved (29 genes and more than 30 loci) (*Inherited Peripheral Neuropathies Mutation Database*, http://www.molgen.ua.ac.be/CMTmutations), but also because the disease may segregate with different Mendelian patterns and even, mutations in the same gene could be inherited as a recessive and a dominant trait. The most common pattern of inheritance is autosomal dominant (AD), which can be demyelinating (CMT1) or axonal (CMT2). The main CMT form is Type 1A (CMT1A; MIM 118220) caused by a duplication of 1.4-Mb on chromosome 17 that affects the *PMP22* gene and represents approximately 70% of CMT1 cases.[3] Mutations in the *PMP22* (CMT1A) and *MPZ* (CMT1B; MIM 118220) genes are relatively frequent: 2.9% and 1.5%, respectively.[4] The remaining genes associated with CMT1 are responsible for less than 1% of the cases. Regarding CMT2, the most common form is CMT2A (MIM 118210) due to mutations in the *MFN2* gene (approximately 20%)[5,6] and to a lesser extent, CMT2I (MIM 607677) and CMT2J (MIM 607736) both caused by mutations in the *MPZ* gene.[7] The X-linked type caused by mutations in the *GJB1* gene (CMTX1; MIM 302800) is also a frequent cause of CMT and can lead to both demyelinating and axonal forms. Finally, autosomal recessive (AR) forms are frequent in countries around the Mediterranean basin,[8] and as other diseases of recessive transmission, are more severe and present with an earlier onset than the dominant ones. AR-CMT forms are named CMT4 (demyelinating, Table 2) and AR-CMT2 (axonal, Table 3). The most prevalent forms are CMT4A (MIM 214400) and their allelic variants, AR-CMT2K/CMT4C4 (MIM 606598) and CMT2K (MIM 607831), due to mutations in the *GDAP1* gene and CMT4C (MIM 601596) caused by mutations in the *SH3TC2* gene. Another point to be considered is that mutations in some CMT genes, as *MFN2, NEFL* or *HSP27*, with an autosomal dominant inheritance can also show an autosomal recessive inheritance.[9-11]

Table 2. Genes involved in demyelinating CMT with an autosomal recessive inheritance (CMT4)

Gene	CMT Type	MIM	Clinical Features	Putative Function of Protein
GDAP1	CMT4A	214400	Very early onset (<2 yo); vocal cord palsy	Maintenance of the mitochondrial network
MTMR2	CMT4B1	601382	Focally folded myelin sheaths; cranial nerve involvement	A phosphatase involved in transcription and cell proliferation
SBF2/ MTMR13	CMT4B2	604563	Focally folded myelin sheaths; early-onset glaucoma	MTMR13 interacts with MTMR2 and is involved in transcription and cell proliferation
SH3TC2	CMT4C	601596	Severe scoliosis; ataxia	Involved in vesicular transport and membrane trafficking
NDRG1	CMT4D	601455	Hearing loss; possible CNS involvement	Maintenance of the myelin sheaths, involved in cell growth arrest and differentiation
EGR2	CMT4E	605253	Congenital hypomyelinating neuropathy	Transcription factor involved in the myelination process
PRX	CMT4F	145900	Hypertrophic neuropathy of Dejerine-Sottas	Maintenance of the peripheral nerve myelin
HK1	CMT4G	605285	Prominent sensory loss	Major regulator of the cell's energy metabolism involved mainly in generation of ATP
FGD4	CMT4H	609311	Variable onset (almost congenital/ during childhood); slow progression	FGD4 is a member of the Rho family and plays a role in early stages of myelination
FIG4	CMT4J	611228	Asymmetric, rapidly progressive paralysis	A phosphatase that desphosphorylates $PI(3,5)P_2$, involved in trafficking of endosomal vesicles.

In this chapter we give an overview of the AR-CMT forms. The large number of genes involved in CMT makes for a complex genetic analysis which would be almost impossible to carry out in a single specialized laboratory. Mutations in some genes have been associated with specific CMT phenotypes, although it is usual to find variability among and within families. Moreover, if these private clinical manifestations are absent, the frequency of a CMT form or the patient ethnicity gains relevance for genetics analysis. Here, we try to emphasize that there are wide, defining features that can be common to several forms of AR-CMT.

Table 3. Genes involved in axonal CMT with an autosomal recessive inheritance (AR-CMT2)

Gene	CMT Type	MIM	Clinical Features	Putative Function of Protein
LMNA	CMT4C1/ AR-CMT2A/ CMT2B1	605588	Rapid evolution involvement of proximal muscles	Nuclear lamina component, transcription factor
MED25/ ARC 92/ ACID1	CMT4C3/ AR-CMT2B/ CMT2B2	605589	Typical CMT2 phenotype	Coactivator involved in regulating transcription of RNA polymerase II-dependent genes
GDAP1	CMT4C4/ AR-CMT2K	606598	Very early onset (<2 yo); vocal cord paresis	Maintenance of the mitochondrial network
Unknown	CMT4C2/ ARCMT2H/ ARCMT2C	607731	Brisk patellar and upper limbs reflexes absent, plantar anattainable	

THE MOST PREVALENT AR-CMT FORMS

CMT4A, CMT2K and AR-CMT2K: the *GDAP1*-Associated Neuropathies

Mutations in the *GDAP1 (ganglioside-induced differentiation-associated protein-1)* gene are responsible for both the demyelinating and axonal autosomal recessive forms, CMT4A (MIM 214400) and AR-CMT2K/CMT4C4 (MIM 606598), respectively and for CMT2K (MIM 607831) an autosomal dominant axonal form. Among them, the most prevalent form is AR-CMT2K.[12] Moreover, in a number of *GDAP1* cases nerve pathology shows an intermediate phenotype with axonal as well demyelinating findings.[13-17]

Different mutations have been described in the *GDAP1* gene. Inheritance in most of *GDAP1* mutations is autosomal recessive, although in a minor number of cases mutations are transmitted in a dominant mode of inheritance.[18-21] So far, three founder mutations have been described in *GDAP1*: p.Q163X in Spanish families and in North American Hispanic families,[18] p.S194X in families from Maghreb countries and in families with Moroccan ancestry,[15,18] and p.L239F in Central and Eastern European population.[22]

The *GDAP1* gene encodes for a protein of 40 kDa, localized in the outer mitochondrial membrane and is expressed in both the peripheral nervous system and central nervous system (brain and cerebellum).[23] GDAP1 participates in the dynamics of mitochondrial network, probably in the fission pathway of mitochondria without increasing the risk of apoptosis.[24-27] According to the inheritance pattern, different possible functions for GDAP1 have been postulated. Recessive mutations seem to cause a loss of fission activity and dominant mutations may affect to mitochondrial fusion because they lead to mitochondrial aggregation.[27]

Clinical Features of the GDAP1-Associated Neuropathies

Clinically, patients with mutations in the *GDAP1* gene show a relatively uniform phenotype in terms of age at onset and pattern of muscle involvement. Autosomal recessive

GDAP1 mutations are associated with a severe phenotype that is characterized by disability due to weakness of limb muscles that usually begins before the age of 3 years and patients are wheelchair-bound in the second decade of life. In some cases, however, disease evolved at a slower pace even among patients belonging to the same family.[28,29] Affected subjects with inherited dominant *GDAP1* mutations show much milder phenotypes and onset during the second decade of life.[18,19] Moreover, in *GDAP1*-associated neuropathy vocal cord palsy and diaphragmatic dysfunction are frequent clinical features.[28,30] In fact, respiratory function should be evaluated in these patients because life span could be compromised due to respiratory failure.

CMT4C, a Common Neuropathy in Several Populations

Mutations in the *SH3TC2* gene have been reported to be responsible for a demyelinating CMT neuropathy (CMT4C, MIM 601596) and also for intermediate phenotype.[31,32] In both forms, mutations are transmitted as an autosomal recessive trait. CMT4C has been described as one of the most frequent autosomal recessive demyelinating CMT forms in several populations as in England and in countries from North Africa.[33,34]

The *SH3TC2* gene encodes for a protein that contains multiple SH3 and TPR domains therefore may be a constituent of multiprotein complexes.[31] SH3TC2 protein is highly conserved in vertebrates. Northern blot and RT-PCR analysis showed that SH3TC2 protein is strongly expressed in neural tissues, including brain, spinal cord and sciatic nerve.[31] SH3TC2 participates in the endocytic pathway of cellular traffic and is also anchored to plasma membrane.[32] Recently a small GTPase, Rab11, has been reported as an effector of SH3TC2, which mediates its localization.[35,36] A *Sh3tc2* knockout mouse study revealed that *Sh3tc2* is specifically expressed in Schwann cells and the pathology of the peripheral nerve has revealed lengthened nodes of Ranvier.[37]

To date more than 20 different *SH3TC2* mutations have been reported in Caucasian non-Gypsy families from Turkey, Germany, Italy, Greece, Iran, UK, Czech Republic and Spain.[31-33,38-40] Moreover, the *SH3TC2* p.R954X mutation, a recurrent change detected in different studies,[31,33] has been postulated as a founder event in a French-Canadian cohort,[38] and other two *SH3TC2* mutations, p.C737_P738delinsX and p.R1109X, have been exclusively associated with Gypsy population (see *HMSN-Lom, HMSN-Russe and CMT4C, three CMT forms in Gypsy population*).[41]

Clinical Features of CMT4C

CMT4C presents with an early onset although is less severe than other autosomal recessive demyelinating CMT forms as CMT4A in which there is often an early loss of ambulation. Spine deformities are a hallmark of CMT4C.[33,34] Almost all patients develop severe scoliosis and foot deformities (pes cavus or planus). Moreover, hypoacusia and facial paresis have been observed in some patients, although they have also been found in other CMT patients as HMSN-Lom ones (MIM 601455).[42] Sural nerve neuropathology show private features: very thin myelin sheaths with extensive Schawnn cell proliferation with multiple small onion bulbs.[34,43] As in the *Sh3tc2* knockout mouse, biopsies from patients have also revealed that the nodes of Ranvier show an abnormal organization, providing a new marker to diagnose CMT4C.[37]

THE MOST SEVERE AR-CMT FORMS

CMT4B1 and CMT4B2, the Myotubularin Disorders

CMT4B is genetically heterogeneous: mutations in *MTMR2 (myotubularin-related 2*) and *MTMR13/SBF2 (myotubularin-related 13/set-binding factor 2*) genes can lead to CMT4B1 (MIM 601382)[44,45] and CMT4B2 (MIM 604563),[46] respectively.

MTMR2 is synthesized in fetal liver and brain and in several adult tissues, mainly in brain, spinal cord and corpus callosum. MTMR13 is mainly detected in cerebellum, placenta, testis, fetal brain and sciatic nerve. Homodimeric MTMR2 interacts with homodimeric MTMR13 to form a tetrameric complex.[47] This interaction increases the activity of the MTMR2, a lipid phosphatase that dephosphorylate PI3P and PI(3,5)P2 and that could be implicated in vacuolar fusion.[48] When MTMR13, a catalytically inactive protein is mutated, the MTMR2 PI3P activity could be misregulated leading to anomalous levels of PI3P and/or PI(3,5)P2 and subsequent membrane trafficking defects.

Clinical Features of CMT4B1 and CMT4B2

Clinically both CMT forms are similar, characterized by severe disability and cranial nerve involvement. The disease manifests in infancy. Some patients present with a very severe phenotype and are diagnosed as congenital hypomelinating neuropathy (CHN). Histopathology shows demyelination with outfoldings of the myelin sheaths. CMT4B2 also presents juvenile glaucoma in some patients.[44,45,49]

CMT4E, a Congenital Hypomelinating Neuropathy

The Charcot-Marie-Tooth disease Type 4E (CMT4E) is a recessive form of Congenital Hypomelinating Neuropathy (CHN) caused by mutations in the *EGR2* (*early growth response gene-2*) gene (MIM 129010). Mutations in this gene are also associated with autosomal dominant CMT1D (MIM 607678) and Déjèrine-Sottas neuropathy (MIM 145900).

The *EGR2* gene is a member of the early growth response gene family, which encodes a Cys_2His_2 zinc-finger transcription factor.[50,51] EGR2 target genes include myelin proteins and enzymes required for synthesis of normal myelin lipids, some of them as *MPZ*, *PMP22*, *CX32* and *PRX* (*periaxin*), associated with several forms of CMT.[50-52] Studies of *Erg2-null*, *Egr2 hipomorphic* and *Eg2r* mutants confirmed that EGR2 is absolutely required for both development and maintenance of proper peripheral nerve myelin.[50,51,53]

Clinical Features of CMT4E

CMT4E is characterized clinically by early onset of hypotonia, areflexia, distal muscle weakness and very slow NCV. Respiratory compromise and cranial nerve dysfunction are commonly associated with *EGR2* mutations and a lesser number of patients suffer from scoliosis.[54] To date the *EGR2* p.I268N mutation is the only one identified with an autosomal recessive inheritance pattern in three affected siblings from a consanguineous marriage.[55] They were floppy at birth, had delayed motor milestones and walk with the aid of crutches. The nerve conduction velocities were 3m/s and the sural nerve biopsies showed the absence of myelin in virtually all fibers.[56] The $Egr2^{I268N/I268N}$ mutant mouse

initially grows normally, but develops rapidly progressive weakness and finally dies in a few days, due to conduction block or neuromuscular junction failure.[57]

CMT4F, a Déjèrine-Sottas Neuropathy-Like

Mutations in the *PRX* (*periaxin*) gene lead to a broad spectrum of severe demyelinating neuropathy. Patients manifesting CMT4F or hypertrophic neuropathy of Déjèrine-Sottas (MIM 145900) have been reported with nonsense and frameshift mutations in the *PRX* gene. Curiously one Gypsy patient with a large deletion in homozygosis in the *PRX* gene has been reported.[58]

The *PRX* (*periaxin*) gene encodes two proteins, L- and S- periaxin, proteins of myelinating Schawnn cells, which are required for the maintenance of peripheral nerve system.[59] The protein has four domains: PDZ, nuclear localization signal, repeat and acidic domains.[60,61] The PDZ domain interacts with plasma membrane proteins and with the cortical cytoskeleton and has been associated with the stabilization of myelin in the peripheral nervous system.[62] Thus, periaxins are thought to play a role in stabilizating the Schwann cell-axon unit.[63]

Clinical Features of CMT4F

CMT4F phenotype is characterized by an early-onset and slowly-progressive distal motor and sensory neuropathies.[64] Histopathological examination of nerve biopsy specimens showed severe loss of myelinated fibers, onion bulb formations and folded myelin.[65] Other clinical features as areflexia, sensory ataxia and foot deformities have also been associated with CMT4F patients.[66]

CMT4H, a Neuropathy with a Slow Progression

CMT4H is a disease associated with Rho GTPase signaling. The causative gene is *FRABIN (FGD1-related F-actin binding protein) or FGD4* (*FYVE, RhoGEF and PH domain-containing protein 4*), which encodes for a ubiquitously expressed Rho GTPase.[67,68] Rho-GTPases play a role in regulating signal transduction pathways in eukaryotes. FGD4 contains a FYVE domain and two PH domains, which are known to bind to phosphoinositides.[67,68] Levels of this protein in rat are lower in postnatal and adult tissues suggesting that FGD4 may have a role in early stages of myelination.

Clinical Features of CMT4H

The hallmark of CMT4H is the slow progression of disease: patients remain ambulant into middle age.[69,70] CMT4H is an infantile neuropathy (onset from almost congenital to childhood). Skeletal deformities are not always observed. Nerve biopsy shows numerous outfoldings of the myelin sheath and redundant myelin loops.[70,71]

CMT4J, a Type Allelic with an Amyotrophic Lateral Sclerosis Form

Charcot-Marie-Tooth disease Type 4J (CMT4J; MIM 611228) is caused by mutations in the *FIG4* gene.[72] This gene is also involved in amyotrophic lateral sclerosis 11 (ALS11;

MIM 612577), an autosomal dominant ALS form.[73] To date four CMT4J families have been reported.[72]

The FIG4 is a vacuolar phosphatase, localized to plasma membrane and is involved in regulating phosphoinositides content and vesicular trafficking: this protein desphosphorylates PI(3,5)P2 and interacts with FAB1 and VAC14 in a protein complex that regulates the overall concentration of PI(3,5)P2.[74]

Clinical Features of CMT4J

The phenotype is characterized by childhood-onset and by coordination disorder and severe disability. Patients develop rapidly progressive, asymmetric motor neuron degeneration and minimal symptoms of sensory loss.[75] PI(3,5)P2 mediates retrograde trafficking of endosomal vesicles to the trans-Golgi network.[76,77]

FOUNDER MUTATIONS RELATED TO AR-CMT FORMS

HMSN-Lom, HMSN-Russe and CMT4C, Three CMT Forms in Gypsy Population

The Gypsy (Roma) is a transnational founder population of around 8-10 million people in Europe whose current genetic profile is the result of profound bottlenecks, genetic drift and differential admixture.[78-80] In Gypsy population, a number of confined disease-causing mutations inherited in an autosomal recessive way and evidence of a founder effect have been reported.[81] To date three CMT4 forms have been exclusively associated with Gypsies: (i) CMT4D/HMSN-Lom (MIM 601455) due to the p.R148X mutation in the *NDRG1* gene;[82,83] (ii) CMT4C (MIM 601596), which could be caused by the p.C737_P738delinsX and/or p.R1109X mutations in the *SH3TC2* gene; (iii) and CMT4G/HMSN-Russe (MIM 605285), which has recently been associated with a G > C change in a novel alternative untranslated exon (AltT2) in the *HK1* gene.[84]

An ancestral founder mutation was postulated as causative of HMSN-Lom, since a common haplotype on chromosome 8q24, cosegregating with the disease, was found in Gypsy patients.[82] Later the p.R148X change was characterized in the *NDRG1* (*N-myc downstreamregulated gene 1*) gene which is inherited as an autosomal recessive trait.[42] The carrier rate for this mutation has been estimated in 4.5/100 and even in some Gypsy communities it is up to 16/100.[79] The *NDRG1* p.R148X mutation, currently distributed throughout Europe, probably occurred before of Gypsy diaspora from India.[85] With the exception of this mutation, defects in the *NDRG1* gene are an extremely rare cause of CMT disease. In fact only one more mutation, g.2290787G > A, in the *NDRG1* gene has been identified in a patient affected by severe demyelinating neuropathy.[86] NDRG1 is highly expressed in the Schwann cell and appears to play a role in growth arrest and cell differentiation, therefore, these findings pointed to NDRG1 having a role in the peripheral nervous system, possibly in Schawnn cell signaling between cytoplasm and the nucleus, necessary for axonal survival.

Two mutations causative of CMT4C have been described in the *SH3TC2* gene and exclusively associated with Gypsy population: p.R1109X and p.C737_P738delinsX, being the p.R1109X mutation much more common.[41] The *SH3TC2* p.R1109X mutation is probably an ancestral founder mutation because it has been detected in Turkish families and probably is distributed across Europe.[87] In Spain, this mutation would have arrived

around the end of the 18th century due to a split from an original group.[41] What is known so far about SH3TC2 protein has been described in a previous section (see *CMT4C, a Common Neuropathy in Several Populations*).

The mutation responsible for HMSN-Russe has been recently reported: a G > C change in a novel alternative untranslated exon (AltT2) in the *HK1* (*hexokinase 1*) gene.[84] In a similar way to other confined mutations in Gypsy population, an ancestral founder event has been postulated for this mutation since all HMSN-Russe patients from several European countries share a common haplotype on chromosome 10q232-q23.[41,88,89] The mutational mechanism and functional effects could lead to disrupt translational regulation causing an increased antiapoptotic activity or an impairment of a novel *HK1* function in the peripheral nervous system.[84]

Clinical Features of HMSN-Lom, HMSN-Russe and CMT4C

The three CMT neuropathies associated with Gypsy population are demyelinating forms. The clinical aspects of CMT4C have already been described in a previous section (see *CMT4C, a Common Neuropathy in Several Populations*). Both neuropathies, HMSN-Lom and HMSN-Russe, have an onset in the first decade or early in the second decade of life.[83,89,90] Motor involvement is greater than sensory. Skeletal deformities are frequent, mainly foot deformities. The disease is steadily progressive, with later involvement of the upper limbs, which leads to disability. The clinical manifestations of both neuropathies are similar although they tend to me more severe in HMSN-Lom.[91] Sensorineural deafness usually developed during the third decade, is an invariable hallmark of HMSN-Lom.

CMT2B1 in North-Western African Population

CMT2B1/AR-CMT2A (MIM 605588), an autosomal recessive axonal type of CMT, is caused by a unique homozygous p.R298C mutation in the *lamin A/C* (*LMNA*) gene.[92] Mutations in this gene can cause more than ten different clinical syndromes (MIM 150330), many of which show overlapping features and could be classified into 4 major types: diseases of striated and cardiac muscle; lipodystrophy syndromes; peripheral neuropathy; and premature aging.[93] The p.R298C is the only known *LMNA* mutation to be responsible for a pure peripheral nerve phenotype. Two different dominant mutations in *LMNA* have been associated with peripheral neuropathy,[94,95] but always in combination with several clinical signs (such as muscular dystrophy, cardiac disease, or leuconychia). All CMT2B1 patients are from a restricted region of Northwest Algeria and Eastern Morocco and carry a homozygous common ancestral haplotype at the *LMNA locus*, which is suggestive of a founder event.[96,97]

LMNA gene encodes lamins, which are intermediate filaments of the nuclear lamina. The main isoforms in somatic cells are lamin A and lamin C.[98] The phenotypic heterogeneity of diseases resulting from a mutation in the *LMNA* gene can be explained by the numerous roles of the nuclear lamina, including a role in maintaining nuclear structure, regulating transcription, controlling differentiation and chromatin organization.[99] *Lmna* null mice present an axonal pathological phenotype that is highly similar to that presented by patients with AR-CMT2.[92] Since *LMNA* is ubiquitously expressed, the finding of site-specific amino acid substitutions indicates the existence of distinct functional domains in lamin A/C that are essential for the maintenance and integrity of

different cell lineages. The p.R298C substitution, located in the lamin A/C central rod domain, has been predicted to impair protein-protein interactions which are essential for the maintenance of cellular function.[92]

Clinical Features of CMT2B1

CMT2B1 is characterized by a variable age of onset, although the disease usually begins in the second decade. Median NCVs are either preserved or slightly reduced.[96] There is a severe rarefaction of myelinated fibers with no evidence of demyelination or remyelination processes, or of onion bulb formations.[92,100] The severity and course of the disease is highly variable. Patients can present a severe CMT phenotype with distal wasting and weakness of all four extremities and areflexia and these features can coexist with proximal muscles affection.[96,100] The impairment can become severe in patients with the longest disease duration, affecting also the scapular muscles which might be a hallmark of CMT2B1.[96]

Charcot-Marie-Tooth Disease Type 2B2 in Costa Rican Population

The Charcot-Marie-Tooth 2B2 (CMT2B2, MIM 605589) is an autosomal recessive form of CMT mapped to chromosome 19q13.3 by linkage analysis, in an extended consanguineous family of Spanish ancestry in Costa Rica.[101] The p.A335V mutation in the *MED25* (*mediator complex subunit 25*) gene is the unique homozygous change identified in the mapped region and it has been identified to be the responsible for CMT2B2.[102] To date, this unique mutation is suggested to be a founder effect.

The *MED25* gene encodes a component of the transcriptional coactivator complexes related to the yeast Mediator. RT-PCR expression analysis demonstrated that MED25 is ubiquitously expressed and underlines the sciatic nerve and dorsal root ganglia expression, which are affected in peripheral neuropathies.[102,103] Furthermore, *Med25* expression correlates with *Pmp22* gene dosage and expression in both transgenic rats and mice. After permanent sciatic nerve transsection, without allowing nerve degeneration, *Pmp22* transcrit levels were strongly reduced while *Med25* expression was only moderately decreased.[102] The p.A335V mutation resides in a proline-rich region and causes a decrease in binding specificity for SH3 domains resulting in an interaction with an extended range of SH3 domain proteins.[102]

Clinical Features of CMT2B2

According to clinical features, CMT2B2 patients present an adult onset phenotype (range, 26 to 42 years) with symmetrical weakness and atrophy in the ankles and showed sensory deficit in a symmetrical "stocking-glove" pattern. Motor-nerve conduction velocity (MCV) of the median and ulnar nerves is normal or slightly reduced, indicative of an axonal degenerative process.[101]

CONCLUSION

CMT is the most prevalent hereditary neurological condition and during the last two decades many causative genes and loci associated with CMT have been identified. CMT

diseases are the clinical manifestations of peripheral nerve dysfunction resulting from abnormalities in Schwann cells and their myelin sheath, with an intimate contribution of the axon-glia communication. In this chapter we have focused on the autosomal recessive forms (AR-CMT). The list of AR-CMT loci and genes is predicted to be higher in the forthcoming years, since the number of patients is increasing and the relationship between phenotypes and genotypes is difficult to be established. For better finding of this relationship and improve the diagnostic criteria, histological aspects may be indicative of which is the disease-causative gene (i.e.,abnormal organization of nodes of Ranvier in CMT4C patients). Thus, after the recording of clinical and electrophysiological data, an examination of one nerve biopsy per family may determine which gene is most likely mutated. This screening step would facilitate and accelerate diagnosis by molecular biological analysis, which may be impossible in non-specialised laboratories. However, this screening criteria cannot be sufficient because some phenomena previously reserved exclusively for one form of CMT disease, have later been observed for other ones. Some clinical features firstly considered hallmarks for some CMT forms, as hoarseness for CMT4A or early glaucoma for CMT4B2, have rarely been described in some patients. To date, several AR-CMT forms are related to mutation with founder effect and are group-specific, as in the case of the Gypsy population (HMSN-Russe, HMSN-Lom). Nowadays, the pathogenic roles of AR-CMT genes are only partially known. Although the functions of several proteins, in particular GDAP1, PRX, LMNA, MTMR2, MTMR13 and to certain extent SH3TC2, have been investigated extensively, it is still unknown the relationship between their respective genes coding and the phenotypes. To answer why and how the axonal degeneration occurs it is necessary to understand the mechanism underlying the Schwann cells/axons interactions. When the molecular biology of peripheral nerves will be better understood, the development of novel therapeutic strategies that would result in effective treatment for these diseases and the discovery of more specific markers for diagnosis will become apparent.

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