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PRACTICAL GENETICS

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Charcot–Marie–Tooth disease

Charcot-Marie-Tooth (CMT) disease is a heterogeneous group of genetic disorders presenting with the phenotype of a chronic progressive neuropathy affecting both the motor and sensory nerves. During the last decade over two dozen genes have been identified in which mutations cause CMT. The disease illustrates a multitude of genetic principles, including diverse mutational mechanisms from point mutations to copy number variation (CNV), allelic heterogeneity, age-dependent penetrance and variable expressivity. Population based studies have determined the contributions of the various genes to disease burden enabling evidence-based approaches to genetic testing.

In brief

- The cardinal clinical feature is peripheral neuropathy: lower motor neuron-type motor deficits and sensory signs and symptoms. As neuropathy can be associated with many multisytemic disorders, it is required to be the predominant manifestation.
- Clinical phenotypes are established by age of onset, neurophysiological findings and in some cases by neuropathology.
- Clinical phenotypes include Charcot–Marie–Tooth disease type 1 (CMT1), Charcot–Marie–Tooth disease type 2 (CMT2), Dejerine–Sottas neuropathy (DSN), congenital hypomyelinating neuropathy (CHN) and Roussy–Levy syndrome (RLS).
- Genetic heterogeneity, age-dependent penetrance and variable expressivity are key characteristics of CMT and related peripheral neuropathies.
- Thirty-six loci and more than two dozen genes are involved in CMT, implicating pathways in myelination, radial and axonal transport, Schwann cell differentiation, signal transduction, mitochondrial function, endosome, protein translation and single-stranded DNA break repair.
- The plethora of genetic information necessitates a rational approach to genetic testing.
- CMT is one of the genetic conditions in which molecular-based therapies are progressing to the clinical trial phase.

Introduction

The prevalence of Charcot–Marie–Tooth disease (CMT) is 1 per 2500 population, which results in 125 000 patients in the United States alone, making it the most common inherited neurological disease. Over the last 15 years, molecular genetics research identified over two dozen genes in which mutations cause the CMT phenotype. *In vitro* functional assays and experiments in animal models of specific genetic alterations elucidated the pathomechanisms by which mutations in certain genes cause disease and delineated pathways involved in peripheral nerve biology. Some of these genes/mutations contribute to a significant fraction of inherited peripheral neuropathy cases and thus molecular analysis can have a substantial function in establishing a precise molecular diagnosis. Population-based cohorts established the contribution of the individual genes to disease burden, allowing evidence-based prioritization of genetic testing. Compounds have been shown to ameliorate symptoms in animal models progressing the field toward clinical trials. This in turn stimulated clinical research to establish the natural history of the disease and to develop tools to assess outcome in prospective clinical trials.

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Clinical overview

Cardinal features of CMT

The main features of CMT are a combination of lower motor neuron-type motor deficits and sensory signs

and symptoms, reflecting the sensory-motor neuropathy. Length-dependent paresis and muscle atrophy develops, with areflexia, although a subset of patients will retain deep tendon reflexes, especially in the axonal forms. The chronic nature of the motor neuropathy will result in foot deformity (eg, *pes cavus*), hammertoes and high-arched feet. Involvement of the hands may follow as the disease progresses. Sensory symptoms are less frequent than in acquired chronic neuropathies, but may point to specific gene involvement. Signs of sensory system dysfunction are common (70%) and include loss of vibration and joint position sense followed by decreased pain and temperature sensation in stocking and glove distribution. Clinical features do not distinguish between the demyelinating or axonal forms.

Ancillary diagnostic tests include electrophysiological studies and sural nerve biopsy. Recently, peripheral nerve MRI and skin biopsy have emerged as potential diagnostic aids in certain types of hereditary neuropathies, though further research studies are needed. EMG and nerve conduction studies (NCS) are extremely helpful in the clinical classification of hereditary peripheral neuropathies and in guiding genetic testing. Electrophysiological studies distinguish two major types – the demyelinating form, which is characterized by symmetrically slowed nerve conduction velocity (NCV; usually <38 m/s), and the axonal form, which is associated with normal or subnormal NCV and reduced compound muscle action potential. The term intermediate CMT is used without consensus in the literature. It identifies the group of patients who cannot be classified readily as either CMT1 or CMT2, as they tend to have features of both demyelination and axonopathy. The NCV falls in the 30–45 m range, with overlap with both the demyelinating and the axonal form.[1] If this pattern is recognized, certain genes are more likely to be involved than others (eg, *GJB1* and *MPZ*).

Sural nerve biopsies from patients with the demyelinating type reveal segmental demyelination and onion bulb formation, whereas the nerve biopsies from patients with the axonal form show axonal loss, absent or few onion bulbs and no evidence of demyelination. With the advent of genetic testing, invasive diagnostic tests such as nerve biopsy are reserved for patients in whom genetic testing does not yield to a molecular diagnosis, patients with atypical presentation or patients in whom inflammatory neuropathy is suspected.

Depending on age of onset and neurophysiological findings, several clinical phenotypes have been described historically. As molecular characterization of phenotypes became available, genetic and clinical heterogeneity of the hereditary motor and sensory neuropathies (HMSNs) became apparent.

Disease phenotypes

Charcot–Marie–Tooth Disease (MIM 118200, 118220) As CMT1 and CMT2 present with similar clinical features, distinction on the basis of the neurological exam is often impossible. The onset of clinical symptoms is in the first or second decade of life. Weakness starts distally in the feet and progresses proximally in an ascending pattern. Neuropathic bony deformities develop including *pes cavus* (high-arched feet) and hammer toes. With further progression the hands become weak. Muscle stretch reflexes disappear early in the ankles and later in the patella and upper limbs. Mild sensory loss to pain, temperature or vibration sensation in the legs is consistent with the phenotype. Patients also complain of numbness and tingling in their feet and hands, but paresthesias are not as common as in acquired neuropathies. Restless leg syndrome occurs in nearly 40% of patients with the axonal form.[2]

Hereditary neuropathy with liability to pressure palsies (MIM 162500) The clinical phenotype is characterized by recurrent nerve dysfunction at compression sites. Asymmetric palsies occur after relatively minor compression or trauma. Repeated attacks result in the inability of full reversal. Thus with ageing the patients with hereditary neuropathy with liability to pressure palsies (HNPP) can have significant clinical overlap with CMT1. Electrophysiological findings include mildly slowed NCV, increased distal motor latencies and conduction blocks.[3] The neuropathological hallmark is sausage-like thickening of myelin sheaths (tomacula).

Dejerine–Sottas neuropathy (MIM 145900) Dejerine–Sottas neuropathy (DSN) is a clinically distinct entity defined by delayed motor milestones. Signs of lower motor neuron-type lesion accompany the delayed motor milestones. Neurophysiological studies reveal severe slowing of NCV (<10 m/s). Neuropathology reveals pronounced demyelination, and a greater number of onion bulbs are present compared to CMT. Cerebrospinal fluid proteins may be elevated. Most patients have significant disability.

Congentital hypomyelinating neuropathy (MIM 605253) Congentital hypomyelinating neuropathy (CHN) is usually present at birth, although frequently the delayed motor development draws the first attention to the peripheral neuropathy. The distinction between DSN and CHN is often difficult by clinical examination as they both may present as a hypotonic infant. The differentiation of CHN and DSN is based on pathology: the presence of onion bulbs suggest DSN whereas their absence indicate CHN. CHN may present as arthrogryposis multiplex congenita.[4]

Roussy–Levy syndrome (MIM 180800) Roussy–Levy syndrome (RLS) was originally described as demyelinating CMT associated with sensory ataxia and tremor. As molecular data became available, it was shown that these

patients have the same molecular abnormalities as observed in patients clinically classified as demyelinating CMT. RLS represents the spectrum of CMT.

Differential diagnosis of CMT

Peripheral neuropathy has a broad differential diagnosis: it can be the only manifestation, part of a complex neurological phenotype or part of a multisystemic disorder. Careful search for other affected organ systems or central nervous system (CNS) involvement during the history and physical examination is of utmost importance. Laboratory screening for correctable causes should always be performed, including screening for diabetes, vitamin B deficiency and serum immunofixation electrophoresis, especially in the adult population. Marked CNS involvement makes CMT less likely; in these cases leukodystrophies, mitochondrial disorders, the hereditary ataxias with neuropathy (Friedreich ataxia, abetalipoproteinemia), Refsum disease, Pelizeaus–Merzbacher disease and amyloid neuropathies should be considered. Hereditary sensory neuropathies lack motor symptoms and are associated with autonomic dysfunction. The lower motor neuron-type weakness may mimic a distal myopathy; however, electrophysiology is useful in differentiating between the two.

CMT is predominantly a peripheral neuropathy phenotype; however, certain features are consistent with the disease and in fact may even help guide the molecular genetic testing. Sensorineuronal hearing loss is present in 5% of the patients. Adie's pupil is almost pathognomic for the Thr124Met mutation in *MPZ*.[5] Ophthalmoparesis, facial weakness, vocal cord paralysis and bulbar signs reflect cranial nerve involvement; these are common in *EGR2* mutations.[6] Hyperkeratosis and juvenile glaucoma are associated with mutations in *NEFL*[7] and *MTMR13*[8] genes, respectively. Scoliosis is present in 20% of the cases and is a secondary phenomenon caused by the neuromuscular weakness.

Inheritance pattern

All forms of Mendelian inheritance – autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL) – can be seen in CMT families. The AD demyelinating form is the most frequent pattern observed.[9] Out of the 36 linked loci, 14 are AD, 13 AR and 3 XL. HNPP and RLS show AD inheritance whereas CHN is AR or sporadic. DSN has both AD and AR forms. Genotype–phenotype correlation studies suggest that genetic heterogeneity, age-dependent penetrance and variable expressivity significantly contribute to the genetics of CMT. It is estimated that about one-third of the point mutations and 5–24% of the duplication mutation may occur *de novo*;[10–12] thus, the absence of family history does not preclude genetic testing.

Classification

The classification system for CMT and related peripheral neuropathies was initially developed on the basis of the clinical phenotype, electrophysiological and inheritance patterns (Table 1). This classification was derived from clinical data on large pedigrees and served as an invaluable tool in identifying genes responsible for certain types of CMT. The molecular classification added further refinement and introduced ambiguities. Genes identified as a specific locus-associated and type-associated gene were found to be responsible for other types of CMT, or with a different inheritance pattern depending on the specific mutant allele.

Genetics

The more than two dozen genes (Table 1) implicated in the HMSNs belong to various functional classes, all involved in the biology of peripheral nerve development and function. They include structural proteins that are important in myelination (eg, *PMP22*, *MPZ*), radial transport proteins (eg, *Cx32*), proteins of axonal transport (eg, *NEFL*), transcription factors involved in Schwann cell differentiation (*EGR2*), members of signal transduction pathways (eg, *PRX*, *MTMR2*, *SBF2*, *NDGR1*), proteins related to mitochondrial function (eg, *MFN2*, *GDAP1*), proteins related to the endosome (*RAB7*, *SIMPLE*) and molecular chaperones (*HSP22*, *HSP27*), a gene involved in DNA single-stranded break repair (*TDP1*), and genes involved in protein translation (*GARS*, *YARS*), in nuclear envelope function (LMNA) and in the actin cytoskeleton (*DNM2*). A detailed summary of all the contributing genes is beyond the scope of this clinical review and has been summarized.[13,14] Table 2 summarizes the genes, their functions and the associated phenotypes.

Genetic testing

The genetic complexity of CMT necessitates a rational approach for clinical genetic testing. Factors to consider when initiating genetic testing should include careful evaluation of (1) the availability of clinical testing, (2) the yield of a specific molecular test, (3) the aim of establishing a molecular diagnosis and (4) the frequency of *de novo* mutations.

Evidence-based data from 12 population-based studies from various ethnic backgrounds[10,11,15–25] established the contribution of 5 genes/genomic rearrangements to disease burden: *PMP22* duplication/deletion; *MPZ*, *Cx32* and *PMP22* point mutations. Electrophysiological classification (demyelinating versus axonal neuropathy) markedly improves the diagnostic yield (Table 3). In families, with informative pedigrees to determine the inheritance pattern, further targeting of the diagnostic testing can be achieved.[19,25]

Table 1 Genetic classification of Charcot–Marie–Tooth disease and related peripheral neuropathies

CMT	*Locus*	*Gene*	*Product*	*OMIM*
CMT1A	17p11.2	*PMP22*	Peripheral myelin protein 22	118220
CMT1B	1q22	*MPZ*	Myelin protein zero	118200
CMT1C	16p13.1–p12.3	*SIMPLE/LITAF*	SIMPLE	601098
CMT1D	10q21.1–q22.1	*EGR2*	Early growth response protein 2	607678
CMT1E	17p11.2	*PMP22*	Peripheral myelin protein 22	118220
CMT1F	8p21	*NEFL*	Neurofilament triplet L protein	607684
CMT2A	1p36	*MFN2*	Mitofusin 2	118210
CMT2B	3q21	*RAB7*	Ras-related protein Rab-7	600882
CMT2B1	1q21.2	*LMNA*	Lamin A/C	605588
CMT2B2	19q13.3	*Unknown*	Unknown	605589
CMT2C	12q23–q24	*Unknown*	Unknown	606071
CMT2D	7p15	*GARS*	Glycyl-tRNA synthetase	601472
CMT2E/F1	8p21	*NEFL*	Neurofilament triplet L protein	607684
CMT2F	7q11–q21	*HSPB1*	Heat-shock protein B1	606595
CMT2G	12q12–q13	*Unknown*	Unknown	608591
CMT2H	8q21.3	*Unknown*	Unknown	607731
CMT2I	1q22	*MPZ*	Myelin protein zero	118200
CMT2J	1q22	*MPZ*	Myelin protein zero	118200
CMT2K	8q13–q21.1	*GDAP1*	Ganglioside-induced differentiation protein 1	214400
CMT2L	12q24	*HSPB8*	Heat shock protein B8	608673
CMT4A	8q13–q21.1	*GDAP1*	Ganglioside-induced differentiation protein 1	214400
CMT4B1	11q22	*MTMR2*	Myotubularin-related protein 2	601382
CMT4B2	11p15	*SBF2/MTMR13*	SET binding factor 2	604563
CMT4C	5q32	*SH3TC2*	SH3TC2	601596
CMT4D	8q24.3	*NDRG1*	NDRG1 protein	601455
CMT4E	10q21.1–q22.1	*EGR2*	Early growth response protein 2	607678
CMT4F	19q13.1–q13.2	*PRX*	Periaxin	145900
CMT4G	10q23.3	*Unknown*	Unknown	605285
CMT4H	12p11.21–q13.11	*FGD4*	FRABIN	609311
CMT4J	6q21	*FIG4*	FIG4	611228
DI-CMTA	10q24.1–q25.1	*Unknown*	Unknown	606483
DI-CMTB	19p12–13.2	*DNM2*	Dynamin 2	606482
DI-CMTC	1p35	*YARS*	Tyrosyl-tRNA synthetase	608323
DI-CMTD	1q22	*MPZ*	Myelin protein zero	607791
CMTX	Xq13.1	*GJB1*	Gap junction β-1 protein, connexin 32	302800

Duplication of a chromosomal segment harboring *PMP22* (ie, the CMT1A duplication)[26] represents 43% of the total CMT cases, whereas the yield of duplication detection rises to 70% in CMT1. The deletion of the same chromosomal segment results in HNPP.[27] Although the deletion has not been reported in any other phenotype, the yield of deletion testing is over 90% in this distinctive phenotype.

Cx32 mutations are the next most common culprits in inherited neuropathy. In informative pedigrees a dominant inheritance pattern and lack of male-to-male transmission points to this gene on the X chromosome. Because electrophysiology frequently suggests the intermediate form, molecular testing for *Cx32* is appropriate in both CMT1 (after duplication testing) and CMT2. In the CMT1 group, *MPZ* and *PMP22* mutations are the next most common, followed by the rare genes.[25] In the CMT2 group, *Cx32* mutations are followed by *MPZ* mutations in frequency; however, recent data, though not population based, suggest that *MFN2* mutations may be one of the most common causes of CMT2.[28–30]

The high frequency of *de novo* mutations in duplication/deletion (37–90%)[10,12] and in point mutations[11] illustrates that genetic disease is commonly sporadic in presentation. The absence of a family history does not exclude CMT and related peripheral neuropathies. In fact, in a patient presenting with chronic polyneuropathy in the absence of other signs and symptoms, after the most common systemic and treatable causes, such as diabetes, uremia and nutritional deficiency, genetic causes are more common than autoimmune or paraneoplastic neuropathy. A rational diagnostic approach is presented in Figure 1. In pediatric cases, which are more severe and when reproductive plans may depend on the genetic information, complete evaluation with panel testing is warranted.

Management

Treatment approaches to the HMSNs can be supportive or etiologic. As CMT is a slowly progressive neurodegenerative disease, patients require periodic assessments. Physiotherapy and occupational therapy aid in maintaining

Table 2 Genotype–phenotype correlation

Gene	*Protein*	*Protein domain(s)*	*Function (s)*	*Disorder(s)*
Cx32/GJB1	Connexin 32	Connexin	Gap-junction formation	CMTX
DNM2	Dynamin 2	GTPase	Cellular fusion–fission	DI-CMT
EGR2	Early growth response protein 2	C_2H_2-type zinc finger	Transcription factor, cell proliferation	CMT1, CHN, DSN
FGD4	FRABIN	RhoGEF	Rho GDP/GTP exchange factor, actin cytoskeleton	CMT, DSN
FIG4	FIG4	PtdIns(3,5)P_2 5-phosphatase	Late endosome–lysosome	CMT, DSN
GARS	Glycyl-tRNA synthetase	WHEP-TRS, core catalytic domain, anticodon-binding domain	Aminoacyl-tRNA synthesis	CMT2, dSMA V
GDAP1	Ganglioside-induced differentiation protein 1	Glutathione *S*-transferase	Mitochondrial fission	CMT2, CMT4A
HSPB1/HSP27	Heat-shock protein B1	α-Crystallin	ATP-independent chaperone, prevents aggregation, role in refolding	CMT2F Distal motor neuropathy
HSPB8/HSP22	Heat-shock protein B8	α-Crystallin	Protein kinase/chaperone	Distal motor neuropathy, CMT1
SH3TC2	SH3TC2	Src homology 3 domains, tetratricopeptide repeat domain	Adapter/docking protein	CMT4C
LMNA	Lamin A	Intermediate filament, type-V ATPase	Nuclear envelope structure	CMT2
MFN2	Mitofusin		Mitochondrial fusion	CMT2
MPZ	Myelin protein zero	Immunoglobulin V-type, immunoglobulin C-type	Myelin structural protein, homophilic adhesion	CMT1, DSN, CMT2, CHN, RLS
MTMR2	Myotubularin-related protein 2	GRAM, protein tyrosine phosphatase (catalytic), domain in glycosyltransferase, myotubularin and membrane-associated protein	Protein tyrosine phosphatase, dual specificity phosphatase (PI3 phosphatase)	CMT4B, CHN
NDRG1	NDRG1 protein	α/β Hydrolase fold	Growth arrest/cell differentiation	HMSN-L
NEFL	Neurofilament triplet L protein	Neurofilament, intermediate filament, myosin, hemagglutinin	Neurofilament organization and regulation	CMT2, CMT1, DSN
PMP22	Peripheral myelin protein 22	PMP-22/EMP/MP20/Claudin	Myelin structure/growth arrest	CMT1, HNPP, DSN, CHN, RLS
PRX	Periaxin	*P*SD-95, *D*lg, *Z*O-1/2 (PDZ)	Cytoskeletal, extracellular signaling	DSN, CMT4F
RAB7	Ras-related protein Rab-7	GTPase	Vesicle transport	CMT2
SBF2/MTMR13	SET binding factor 2	GRAM, SID, PH	Signaling	CMT4B2
SIMPLE/LITAF	SIMPLE	RING-finger motif	Transcription factor, ubiquitin ligase?	CMT1, CMT2
TDP1	Tyrosyl-DNA phosphodiesterase 1	α-Amylase	DNA replication, hydrolysis of DNA–protein bond	CMT2
YARS	Tyrosyl-tRNA synthetase	Tyrosinyl-tRNA synthetase (TyrRS) catalytic core and tRNA-binding domains	Protein synthesis	DI-CMT

Table 3 Mutation frequencies for CMT and related neuropathies

CMT1A duplication Total	*CMT1A duplication CMT1*	*HNPP deletion Total/HNPP*	*PMP22 mutation Total*	*Cx32 mutation Total*	*MPZ mutation Total*
43%	70%	11%/*92%*	2.5%	12%	5%

Abbreviations: CMT1A, Charcot–Marie–Tooth disease type 1A; HNPP, hereditary neuropathy with liability to pressure palsies.

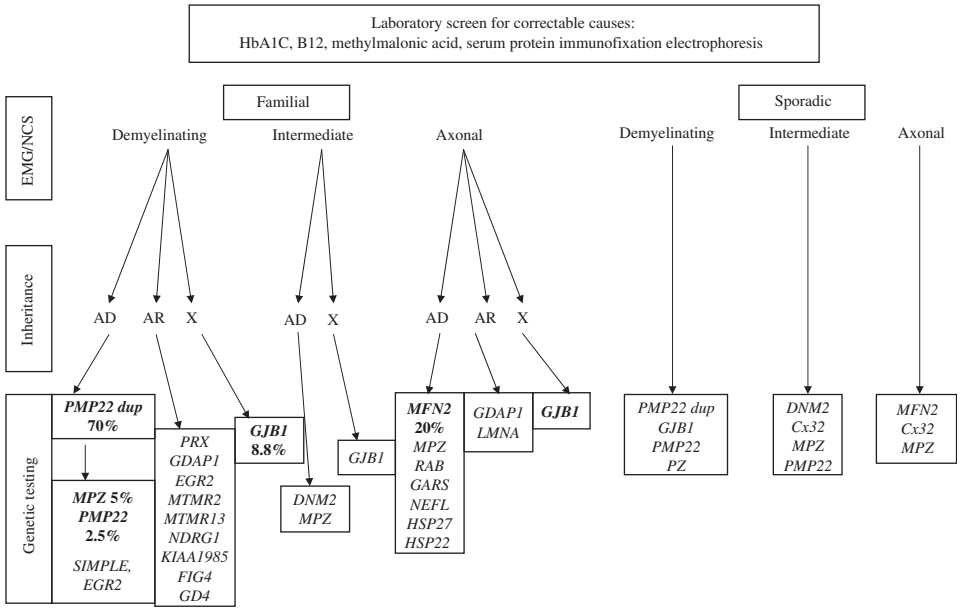

Figure 1 Suggested testing scheme in hereditary sensory and motor polyneuropathy for patients with and without a family history of CMT based on the genotype–phenotype correlations and frequency data in 12 population-based studies.

range of motion and thus help in functioning appropriately.[31,32] The application of orthotic devices and assistive equipment can be made if safety or function requires them. In some instances, surgical interventions for the hands and feet are necessary.[33,34]

Symptomatic treatment may have a substantial impact on the quality of life. Nonsteroidal anti-inflammatory drugs may help to relieve lower back or leg pain. Neuropathic pain can be treated with antiepileptic drugs (gabapentin, pregabalin, topiramate) or tricyclic antidepressants (amitriptyline).[35,36] The tremor may respond to β-blockers or primidone.[37] Caffeine and nicotine can aggravate the fine intentional tremor, thus avoidance of these substances is recommended. Neurotoxic drugs (http://www.charcot-marie-tooth.org/) and excessive alcohol should be avoided. A small dose of vincristine can produce a devastating effect in patients with CMT, thus early detection of HMSN can avoid life-threatening vincristine neurotoxicity.[38]

Potential therapeutic approaches aiming at normalizing dosage by small molecules in the CMT1A duplication models include vitamin C and onapristone, a progesterone antagonist.[39–41] An alternate molecular mechanism, point mutations in *Pmp22* in the *Trembler* and *Trembler J* mouse models cause peripheral neuropathy; the disease was modified by the administration of curcumin likely by alleviating the unfolded protein response.[42] These treatments have been shown to be effective only in animal models thus far; however, vitamin C has progressed to a phase 2 clinical trial.

Genetic counseling

Because CMT follows the principles of Mendelian inheritance, genetic counseling for recurrence of CMT1 and CMT2 is relatively straightforward if the family history for an affected individual is defined. Because of intrafamilial variability in disease expression, definition of parental disease status requires either testing for a mutation defined in the propositus or, if the mutation is not identifiable, a thorough neurological exam with objective NCS.

An affected parent with AD or XL-dominant CMT1 or CMT2 has a 50% risk of having a child with the same mutation. At what age a child with a mutation will be

clinically affected is not known because the penetrance has not been determined prospectively for genetically well-defined patient populations. In general only a few patients with AD CMT1 or CMT2 have substantial difficulty walking before age 50 years, and almost all patients express some symptoms by the sixth decade of life.[43] For fathers with XL-dominant CMT, the risk of having an affected son is negligible but the risk of having an affected daughter is 100%, whereas for mothers with XL-dominant CMT, the risk of having an affected son or daughter is 50%.

In the absence of a molecular diagnosis in AD CMT1, NCV slowing is detectable by age 2–5 years;[44,45] therefore, if a young adult has normal NCVs, their risk of developing AD CMT1 is negligible, whereas if the NCVs are abnormal, the patient has at least a 90% lifetime risk of developing symptoms. Electrophysiological changes associated with AD CMT2 develop with disease progression, thus only about half of patients can be identified by age 20 years.[43] In one study performed before the molecular era in 15 unrelated families, the average age of onset was 12.2 years. The penetrance was 28% in the first decade, but almost complete by the third decade.[46]

When unaffected parents have a child affected with CMT1 or CMT2, four possibilities exist: a *de novo* dominant mutation in the affected child, AR inheritance, XL inheritance or nonpaternity. Distinction between these possibilities requires either the identification of the causative mutation(s) or the identification of affected siblings. The identification of a *de novo* heterozygous presumed dominant mutation suggests a low recurrence risk for the parents; however, the risk is higher than that for the general population because of the possibility of germ-line mosaicism.[47] A proband with a heterozygous presumed dominant mutation has a 50% risk of having affected children. For AR inheritance, the parental risk of an affected child is 25% because penetrance is nearly complete.

Summary

CMT is one of the most prevalent neurogenetic conditions, with a plethora of accumulated knowledge of the genes and pathways implicated in peripheral nerve function and dysfunction. Although a lot remains to be learnt, clinical research has aided the estimation of the contribution of specific genes to disease burden. Animal models provide the basis for preclinical treatment trials in which small compounds modifying gene expression to normalize gene dosage and potentially modulating protein misfolding have been identified. Clinical research has developed tools to assess outcome in clinical trials[48] and data on disease progression are accumulating. Thus, we have all the tools to move to the exciting translational research phase, where patients can potentially benefit from the translation of laboratory discoveries at the bedside.

Disclosure

JRL is a co-inventor of patented molecular diagnostic test for CMT (US patents 5 306 616; 5 599 920; 5 780 223; 7 273 698) and a consultant for Athena Diagnostics.

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