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Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing

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Abstract

Background—Charcot-Marie-Tooth disease (CMT) is a clinically and genetically heterogeneous group of diseases with approximately 45 different causative genes described. The aims of this study were to determine the frequency of different genes in a large cohort of patients with CMT and devise guidelines for genetic testing in practice.

Methods—The genes known to cause CMT were sequenced in 1607 patients with CMT (425 patients attending an inherited neuropathy clinic and 1182 patients whose DNA was sent to the authors for genetic testing) to determine the proportion of different subtypes in a UK population.

Results—A molecular diagnosis was achieved in 62.6% of patients with CMT attending the inherited neuropathy clinic; in 80.4% of patients with CMT1 (demyelinating CMT) and in 25.2% of those with CMT2 (axonal CMT). Mutations or rearrangements in *PMP22*, *GJB1*, *MPZ* and *MFN2* accounted for over 90% of the molecular diagnoses while mutations in all other genes tested were rare.

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Contributors

SMM wrote the first draft, and collected and analysed the data. ML, KF, AP, Y-TL, GLD, AMR, JMP, VC, HM, MPTL, KB and GR collected and analysed the data, and edited drafts of the manuscript. MD was involved in study conception, analysed the data and edited drafts of the manuscript. JCB, HH and MMR were involved in study conception, collected and analysed the data, and edited drafts of the manuscript.

Competing interests

None.

Ethics approval

Ethics approval was provided by the National Hospital for Neurology and Neurosurgery Research Ethics Committee.

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Conclusion—Four commonly available genes account for over 90% of all CMT molecular diagnoses; a diagnostic algorithm is proposed based on these results for use in clinical practice. Any patient with CMT without a mutation in these four genes or with an unusual phenotype should be considered for referral for an expert opinion to maximize the chance of reaching a molecular diagnosis.

INTRODUCTION

The inherited neuropathies are a genetically and clinically heterogeneous group of disorders encom- passing Charcot-Marie-Tooth disease (CMT), hereditary neuropathy with liability to pressure palsy (HNPP), hereditary motor neuropathy (HMN) and hereditary sensory and autonomic neuropathy (HSAN, also known as hereditary sensory neuropathy). Mutations in over 45 distinct genes have been implicated in causing the inherited neuropathies, and many more remain unknown.[1] CMT is the most common inherited neuromuscular disorder, affecting 1 in 2500.[2] Inheritance may be autosomal dominant, autosomal recessive or X linked; however, de novo dominant cases occur relatively frequently in CMT and thus some patients may not have a family history of CMT. Neurophysiology differentiates CMT into demyelinating CMT1 (upper limb motor nerve conduction velocity (MNCV) <38 m/s), axonal CMT2 (MNCV >38 m/s) and intermediate CMT (ICMT, MNCV 25e45 m/s). CMT1 occurs more frequently than CMT2; this may be partially explained by the fact that the majority of causative genes for CMT2 remain undetermined.[3, 4]

The classical CMT phenotype is of onset within the first two decades with difficulty walking, sensory loss, foot deformities and signs of a length dependent sensorimotor neuropathy. However, some patients present early with much more severe disease while others remain asymptomatic until adulthood. To some extent the underlying genetic cause explains the variable phenotypes seen in CMT although there is significant overlap; mutations in many different genes cause a similar phenotype and, conversely, mutations in the same gene may cause different phenotypes.1 This clinical and genetic heterogeneity makes diagnosis and genetic counselling difficult for clinicians. A molecular diagnosis is also useful in order to guide prognosis. More importantly, now that clinical trials of treatment have commenced for some types of CMT (eg, ascorbic acid for CMT1A),[5] an accurate genetic diagnosis is essential.

As part of our peripheral nerve service in the National Hospital for Neurology and Neurosurgery, we run an inherited neuropathy clinic. We also run a diagnostic laboratory for some of the common CMT genes (chromosome 17 dosage analysis, sequencing of *PMP22, GJB1, MFN2, MPZ, GDAP1, BSCL2* and *SPTLC1*) and, in addition, are sent many DNA samples from patients with CMT for research testing of the less common CMT genes from throughout the UK. As a result, we are well placed to determine the frequency of the different genetic subtypes of CMT in our patient cohort and devise a strategy to guide genetic testing for clinicians.

Patient cohort

Since 2006, a detailed database has been kept documenting all patients seen in our inherited neuropathy clinic. In addition, the database includes details of external patients whose DNA samples were sent to us for diagnostic and/or research testing. We included isolated patients as well as those with a family history. Details recorded include patient age, type of inherited neuropathy (CMT1, CMT2, ICMT, HNPP, HMN, HSAN), family history and other clinical features, including neurophysiology and the CMT neuropathy score (CMTNS)[6] or the CMTNS2,[7] where available.

For patients seen in our inherited neuropathy clinic, detailed information regarding phenotype was available. Clinical diagnosis was based on symptoms, signs, family history (including assessment of family members when possible) and neurophysiology, and patients were classified into subgroups (eg, CMT1, CMT2, ICMT) as previously defined by us.[8, 9] For external patients, more limited information was available and diagnosis was based on the information received. In order to distinguish CMT from HMN, both clinical and neurophysiological evidence of sensory involvement was taken into account. Patients with a predominantly sensory neuropathy (sensory axonal neuropathy characterised by loss of sensation, including pain and temperature with or without positive sensory symptoms, such as pain and paraesthesiae and ulceromutilating complications) were classified as HSAN.[10] Patients with complex neurological diseases who had neuropathy as part of the phenotype (eg, ataxia with oculomotor apraxia) were classified as having a complex neuropathy. The molecular part of this study concerns those patients we classified as having a primary inherited neuropathy (CMT, HNPP, HMN and HSAN) with a more detailed analysis of those patients classified as having CMT. We excluded patients with a complex neuropathy from the molecular study.

We determined the frequency of each subtype of CMT based on the number of patients with a particular subtype out of the total number of index patients. As we perform genetic testing sequentially, all patients have not had all possible genes tested and this should be kept in mind when interpreting the results. We also determined ‘hit rates’ for mutations in specific rare genes by calculating the number of positive results found out of the total number of patients for whom testing was performed. study.

Molecular genetic analysis

For this study, as well as the genes screened in our diagnostic laboratory (chromosome 17 dosage analysis, *PMP22, GJB1, MFN2, MPZ, GDAP1, BSCL2 and SPTLC1*) we also screened *LITAF, SH3TC2, MTMR2, EGR2, NEFL, TRPV4, HSPB1, HSPB8 and GAN1* where appropriate. *LITAF* and *SH3TC2* were screened in patients with CMT1 who were negative for *PMP22* rearrangements; *TRPV4, HSPB1* and *HSPB8* were screened in patients with CMT2 who were negative for mutations in *MFN2* as well as in patients with HMN; *MTMR2* was screened in a select group of patients with early onset severe autosomal recessive CMT1 negative for *PMP22* rearrangements; and *EGR2* and *NEFL* were screened in patients with CMT1 negative for rearrangements of *PMP22* or in patients with CMT2 negative for mutations in *MFN2*. Dosage analysis of the 17p region, including *PMP22*, was performed by semiquantitative fluorescent PCR or multiplex ligation dependent probe amplification. For sequencing, coding exons and flanking intronic regions were amplified using primer oligonucleotides and Roche (Mannheim, Germany), Applied Biosystems (Foster City, California, USA) or Qiagen (Hilden, Germany) PCR kits, according to the manufacturers’ instructions. Primers and PCR conditions are available on request. Sequence reactions were performed using Big Dye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems), and products were cleaned using Dye Terminator removal plates (Abgene, Vilnius, Lithuania). Sequencing products were resolved on an AB 3730xl Sequencer. The resulting sequences were aligned and analysed with SeqScape (Applied Biosystems) or Sequencher (Gene Codes Corporation) software. Variations were confirmed by repeat sequencing. Segregation of mutations within families was performed where possible. Where novel variations were found, control groups of UK or Asian chromosomes were screened according to the ethnicity of the patient. Mutations were considered potentially pathogenic if they were absent from controls and segregated with disease in the family. We also considered conservation of amino acids among species and used three commonly used prediction programs, PolyPhen (http://genetics.bwh.harvard.edu/pph/), SIFT (http://

blocks.fhcrc.org/sift/SIFT.html) and aGVGD (http://agvgd.iarc.fr/) to help decide on the pathogenicity of the mutations.

Results

A total of 2732 patients are included in our neuropathy database, 2094 of whom have a diagnosis of a primary inherited neuropathy (76.6%) (CMT, HNPP, HMN, HSAN). The remaining 638 individuals include unaffected family members and patients with more complex neurological conditions (complex neuropathy) who have neuropathy as part of their syndrome (eg, autosomal recessive spastic ataxia of Charlevoix-Saguenay, ataxia with oculomotor apraxia, etc). A total of 916/2732 (33.5%) patients were seen in our inherited neuropathy clinic between 2006 and 2011 and more detailed phenotype information is available for this subgroup.

Inherited neuropathy clinic cohort

Of the 916 patients seen in our inherited neuropathy clinic, 601 (65.6%) had a primary inherited neuropathy (425 CMT, 46 HNPP, 61 HMN, 69 HSAN). Of the 425 patients with CMT, 240 had CMT1 (56.5%), 115 had CMT2 (27.1%), 62 had ICMT (15.6%) and eight (1.9%) were unclassified (usually because the patient refused nerve conduction studies or had unrecordable responses on nerve conduction studies). Overall, 266/425 (62.6%) patients with CMT received a molecular diagnosis: 193/240 (80.4%) patients with CMT1, 29/115 (25.2%) patients with CMT2 and 37/62 (59.7%) patients with ICMT (see table 1 for the breakdown of genetic diagnoses). Two hundred and forty-five of the 266 molecular diagnoses (92%) were accounted for by mutations or rearrangements of *PMP22, GJB1, MFN2* or *MPZ.*

Of the 46 patients with a clinical diagnosis of HNPP, 27 (58.7%) had the *PMP22* deletion and four (8.7%) had a point mutation in *PMP22*. Of the 61 patients with HMN, [10] (16.4%) had a molecular diagnosis; five *HSPB1*, two *SMN1*, one *GARS*, one *HSPB8* and one *BSCL2*. Of the 69 patients with HSAN, 14 (20.3%) had mutations in *SPTLC*1, five (7.2%) *SPTLC2*, one (1.4%) heterozygous *NGFB* and one *FAM134B* (1.4%).10 The CMT subtype associated with each gene was in keeping with published data (table 2). Analysing the common genes, patients with the *PMP22* duplication all had CMT1, those with *MFN2* mutations all had CMT2 and patients with *GJB1* or *MPZ* mutations had a range of phenotypes, including CMT1, CMT2 or ICMT. The phenotypes of the rarer forms of CMT are summarised in table 2.

Patients not attending inherited neuropathy clinic

Of the 1816 patients not attending the inherited neuropathy clinic, 1493 (82.2%) had a primary inherited neuropathy: 1182 (65.1%) CMT, 56 (3.1%) HNPP, 126 (6.9%) HMN and 129 (7.1%) HSAN.

Of the 1182 patients with CMT, 446 had CMT1 (37.7%), 335 had CMT2 (28.3%), 23 had ICMT (0.4%) and 378 were unclassified (32%) (type of CMT not documented on genetic request form). Overall, 446/1182 (37.7%) patients with CMT received a genetic diagnosis: 269/446 (60.3%) with CMT1, 44/335 (13.1%) with CMT2, 5/23 (21.7%) with ICMT and 128/378 (33.9%) of the unclassified group. Four hundred and nineteen of the 446 patients who achieved a molecular diagnosis (94%) were accounted for by mutations or rearrangements of *PMP22, GJB1, MFN2* or *MPZ* (table 3).

When the molecular diagnosis rate was compared in patients attending the inherited neuropathy clinic with those that did not attend our clinic, the diagnosis rates were significantly different for all groups (table 4). Overall, a molecular diagnosis was achieved

in 62.6% of patients attending the inherited neuropathy clinic versus 37.7% in those not attending this clinic (p<0.003).

Hit rates for specific genes

We determined hit rates for the genes not available in the diagnostic laboratory. Mutations in these genes are thought to be rare which is why a diagnostic test is not widely available. Large numbers of patients (see table 5 for numbers) with CMT1 were screened for *LITAF, EGR2* and *SH3TC2*; patients with CMT1 or CMT2 were screened for *NEFL*; and patients with CMT2 or HMN were screened for *TRPV4, HSPB1* and *HSPB8*. A select group of patients with early onset severe CMT1 were screened for *MTMR2*. We found mutations in all genes tested (table 5); each (other than *MTMR2* for which only nine patients were tested) accounted for <3% of patients who did not have mutations in the genes that most commonly cause CMT (*PMP22* duplication in CMT1 and *MFN2* in CMT2).

Discussion

In this study, we detailed the frequency of different primary inherited neuropathies (CMT, HNPP, HMN and HSAN) in both a cohort of patients attending a specialised inherited neuropathy clinic and in a large cohort of patients whose DNA was sent to us for molecular testing. Furthermore, we determined the molecular diagnosis rate in patients attending a specialist inherited neuropathy clinic and in those in the larger cohort, and also determined the hit rate for specific rare CMT genes.

We found that CMT1 was more common than CMT2 (56.5% vs 27.1%) in the inherited neuropathy cohort; this is similar to the distribution found in a recent epidemiological study from Northern England that found that 56.7% of their CMT cohort had CMT1 and 17.6% had CMT2.[3] A Norwegian study found roughly equal distributions of CMT1 and CMT2 (48.2% vs 49.4%)[11]; however, Norway has a higher prevalence of CMT than other European countries[3, 12] and has a relatively isolated genetic population which might explain the differing results.

A molecular diagnosis was achieved in 62.6% of patients with CMT attending our inherited neuropathy clinic. Saporta *et al* performed a similar study in 2011 of 787 patients with CMT attending an inherited neuropathy clinic in Detroit where a molecular diagnosis was made in 67% of cases.[4] This study included HNPP within the CMT cohort, which accounted for 6.1% of all of their CMT patients, thus the molecular diagnosis rate in CMT alone was 60.9%, very similar to our findings. The majority of molecular diagnoses in our study were accounted for by rearrangements or mutations in four genes: *PMP22, GJB1, MFN2* and *MPZ*. These four genes accounted for 92% of the molecular diagnoses in patients attending our inherited neuropathy clinic and 94% of the molecular diagnoses in other patients. Similarly, the same four genes accounted for 91% of genetically determined CMT in the Detroit cohort.[4]

Greater than 80% of patients with CMT1 received a molecular diagnosis, mostly accounted for by the *PMP22* duplication (70%). This is in keeping with other European estimates which found that 70.7% of CMT1 patients had the *PMP22* duplication. [13] In fact, the *PMP22* duplication accounted for 39.5% of all CMT, similar to the 36.9% in Detroit4 and 42.8% in Northern England.[3] In contrast, only 25.2% of patients with CMT2 received a molecular diagnosis, the majority caused by either *MFN2* or *GJB1* mutations. Although a lower proportion of CMT2 (10.4%) was accounted for by *MFN2* mutations than suggested by other studies,[14] overall, *MFN2* mutations accounted for 2.8% of CMT, similar to that found by Saporta *et al* (2.7%). This may reflect a referral bias, as many patients with CMT2 referred to our clinic have had *MFN2* excluded prior to referral. Given that most known

CMT2 genes each account for a small proportion of CMT2 families, next generation sequencing technology is likely to lead to increasing numbers of genes for CMT2.[15]

All other genes tested accounted for less than 3% of CMT each in a large cohort of patients who were negative for either the *PMP22* duplication (in patients with CMT1) or *MFN2* mutations (in patients with CMT2). This suggests that mutations in these genes are rare causes of CMT in the general CMT population. This is in keeping with the literature which suggests that *LITAF* mutations are found in 0.6e3.75% of CMT1,[16, 17] *SH3TC2* mutations in 21.7% of recessive CMT1 and 0.4% of all CMT,[4, 18, 19] *EGR2* mutations in 0.1e2% of CMT1,[16, 20] *NEFL* mutations in 0.5e3% of CMT1[16, 21] and 2% of all CMT,[21] *HSPB1* mutations in 1.4e4.8% of CMT2/HMN[22, 23] and *HSPB8* mutations in 0e2.6% of CMT2/HMN.[23–25] Patients with CMT due to mutations in these rare genes often have specific phenotypic clues to the diagnosis; for example, CMT4C due to recessive mutations in *SH3TC2* usually presents early with a demyelinating neuropathy and associated scoliosis and has characteristic features of elongated Schwann cell processes on nerve biopsy,[19] thus the diagnosis may be more likely to be reached in a specialist inherited neuropathy clinic.

The molecular diagnosis rate was significantly lower in patients who were not seen in the inherited neuropathy clinic (37.7%). This is partly due to the high proportion of DNA samples sent for genetic testing without specifying the subtype of CMT (32%). The practice in our diagnostic laboratory is to screen the genetic test requested; that is, if a DNA sample is sent requesting *PMP22* duplication, this test is performed even if the type of CMT is not specified. In this situation, we cannot ensure that the appropriate genetic test is performed, or give advice on further genetic testing. We receive some requests for *PMP22* duplication testing in patients documented to have CMT2 although no patient with a *PMP22* duplication has ever been documented to have an axonal phenotype; thus it is possible that many of the unclassified DNA samples that we receive requesting specific genetic tests are inappropriate, which may explain the lower molecular diagnosis rate in this cohort.

Although our clinic receives referrals from neurologists throughout the UK, we also receive referrals directly from general practitioners. The fact that approximately 40% of all CMT patients seen in our clinic have CMT1A indicates that our data are not significantly biased by referral pattern, as this is comparable with population based studies in the UK[3] and other clinic based studies.[4]

Currently, only a limited number of genes can be routinely tested in the UK (http://www.ukgtn.nhs.uk); however, *PMP22*, *GJB1*, *MPZ* and *MFN2* testing is widely available. Given that mutations or rearrangements in these four genes account for the vast majority of molecular diagnoses in patients with CMT, with other known genes causing CMT much less commonly, we have suggested an algorithm for genetic testing in the UK based on these results (figure 1).We have kept this algorithm simple by only including the four genes which account for >90% of genetically confirmed CMT. More detailed algorithms are available which include some of the rarer genes (eg, see Saporta and colleagues[4]); however, since mutations in these rarer genes account for a small proportion of CMT and since there are so many different rare genes known, some having specific phenotypic clues, it may be simpler and more cost effective to refer patients negative for mutations in these four genes for an expert opinion. It is important to emphasise that many patients present without a family history, and this does not necessarily exclude autosomal dominant inheritance. As a molecular diagnosis is significantly more likely to be achieved in patients attending a specialist inherited neuropathy clinic, we suggest that if screening of these four genes does not reveal a causative mutation, the patient should be considered for referral to an inherited neuropathy clinic where a detailed phenotype may give additional clues to guide further genetic testing.

Conclusion

This study demonstrates that a molecular diagnosis can currently be achieved in over 60% of patients with CMT. A molecular diagnosis is much more likely in patients with CMT1 rather than CMT2, confirming that many genes for CMT2 remain unknown. Four commonly available genes account for over 90% of all CMT molecular diagnoses and we have proposed a diagnostic algorithm based on these results for use in clinical practice. Any patient with CMT without mutations in these four genes or with an unusual phenotype should be considered for referral for an expert opinion to maximise the chance of reaching a molecular diagnosis.

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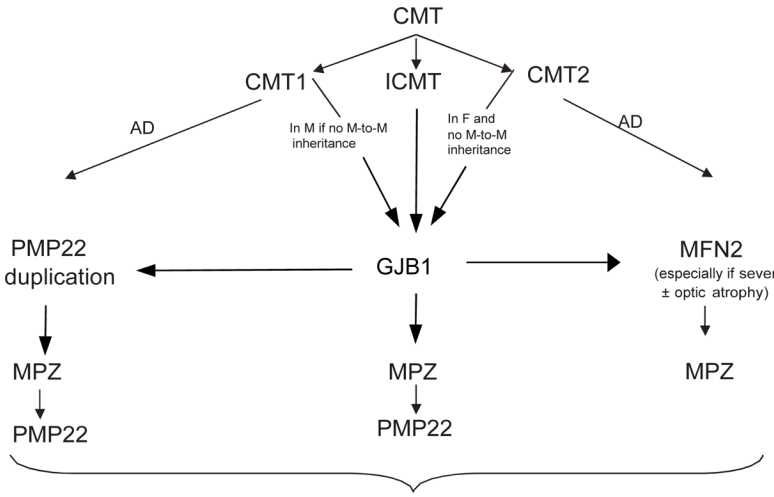

Figure 1.

Suggested algorithm for genetic testing of patients with Charcot-Marie-Tooth disease. AD, autosomal dominant; CMT, Charcot-Marie-Tooth disease; CMT1, demyelinating CMT; CMT2, axonal CMT; GJB1, gap junction β1; ICMT, intermediate CMT; F, female; M, male; MFN2, mitofusin 2; MPZ, myelin protein zero; PMP22, peripheral myelin protein 22. If negative or unusual phenotype consider specialist referral

Table 1

Molecular diagnoses in patients with Charcot-Marie-Tooth disease attending an inherited neuropathy clinic

Genetic mutation	n	%
PMP22 duplication	168	39.5
PMP22 point mutation	6	1.4
GJB1	46	10.8
MFN2	12	2.8
MPZ	13	3.1
BSCL2	1	0.2
GDAP1	2	0.5
HSPB1	2	0.5
SH3TC2	5	1.2
LITAF	4	0.9
MTMR2	1	0.2
NEFL	2	0.5
TRPV4	3	0.7
GAN1	1	0.2

BSCL2, Berardinelli-Seip congenital lipodystrophy 2; GAN1, gigaxonin; GDAP1, ganglioside induced differentiation associated protein 1; GJB1, gap junction β1; HSPB1, heat shock 27 kDa protein 1; LITAF, lipopolysaccharide induced TNF factor; MFN2, mitofusin 2; MPZ, myelin protein zero; MTMR2, myotubularin related protein 2; NEFL, neurofilament, light polypeptide; PMP22, peripheral myelin protein 22; SH3TC2, SH3 domain and tetratricopeptide repeats 2; TRPV4, transient receptor potential cation channel, subfamily V, member 4.

Table 2

Charcot-Marie-Tooth disease subtype associated with individual genes in patients attending an inherited neuropathy clinic

	CMT1	CMT2	ICMT
PMP22 duplication	168		
PMP22 point mutation	5		1
GJB1	1	8	33
MPZ	9	1	1
MFN2		12	
LITAF	4		
NEFL	2		
SH3TC2	3		2
MTMR2	1		
BSCL2		1	
GDAP1	1	1	
HSPB1		2	
TRPV4		3	
GAN1		1	

BSCL2, Berardinelli-Seip congenital lipodystrophy 2; CMT, Charcot-Marie-Tooth disease; CMT1, demyelinating CMT; CMT2, axonal CMT; GAN1, gigaxonin; GDAP1, ganglioside induced differentiation associated protein 1; GJB1, gap junction β1; HSPB1, heat shock 27 kDa protein 1; ICMT, intermediate CMT; LITAF, lipopolysaccharide induced TNF factor; MFN2, mitofusin 2; MPZ, myelin protein zero; MTMR2, myotubularin related protein 2; NEFL, neurofilament, light polypeptide; PMP22, peripheral myelin protein 22; SH3TC2, SH3 domain and tetratricopeptide repeats 2; TRPV4, transient receptor potential cation channel, subfamily V, member 4.

Table 3

Genetic diagnoses in patients with Charcot-Marie-Tooth disease not attending an inherited neuropathy clinic

Genetic mutation	n	%
PMP22 duplication	247	20.9
PMP22 point mutation	5	0.4
GJB1	101	8.5
MFN2	48	4.1
MPZ	18	1.5
BSCL2	1	0.1
GDAP1	10	0.8
HSPB1	1	0.1
SH3TC2	4	0.3
LITAF	2	0.2
MTMR2	1	0.1
NEFL	2	0.2
TRPV4	1	0.1
EGR2	4	0.4

BSCL2, Berardinelli-Seip congenital lipodystrophy 2; EGR2, early growth response 2; GAN1, gigaxonin; GDAP1, ganglioside induced differentiation associated protein 1; GJB1, gap junction β1; HSPB1, heat shock 27 kDa protein 1; LITAF, lipopolysaccharide induced TNF factor; MFN2, mitofusin 2; MPZ, myelin protein zero; MTMR2, myotubularin related protein 2; NEFL, neurofilament, light polypeptide; PMP22, peripheral myelin protein 22; SH3TC2, SH3 domain and tetratricopeptide repeats 2; TRPV4, transient receptor potential cation channel, subfamily V, member 4.

Table 4

Molecular diagnosis rate

	Inherited neuropathy Clinic (n (%))	Others (n (%))	p Value
CMT1	193/240 (80.4%)	269/446 (60.3%)	<0.0001 *
CMT2	29/115 (25.2%)	44/335 (13.1%)	0.0015 *
ICMT	37/62 (59.7%)	5/23 (21.7%)	0.001 *
Overall CMT	266/425 (62.6%)	446/1182 (37.7%)	0.003 *

* Fisher's exact test used; all p values significant at <0.05.

CMT, Charcot-Marie-Tooth disease; CMT1, demyelinating CMT; CMT2, axonal CMT; ICMT, intermediate CMT.

Table 5

Hit rates for rare Charcot-Marie-Tooth genes

Gene	Mutations found (n)	Patients screened (n)	% Hit rate of No screened
LITAF	4	185	2.2
SH3TC2[1]	9	329	2.7
NEFL	3	183	1.6
EGR2	4	135	3
TRPV4[*]	5	353	1.4
HSPB1[*]	9	411	2.2
HSPB8[*]	1	406	0.2
MTMR2[2]	2	9	22.2

All patients in this cohort were negative for PMP22 duplication or MFN2 mutations depending on whether they had CMT1 or CMT2.

[*] Patients with CMT2 and distal hereditary motor neuropathy screened.

[1] An additional 11 patients had heterozygous mutations but only had the hot spot (exon 11) screened.

[2] Only nine selected patients screened hence the higher hit rate.

CMT, Charcot-Marie-Tooth disease; CMT1, demyelinating CMT; CMT2, axonal CMT; EGR2, early growth response 2; HSPB1, heat shock 27 kDa protein 1; HSPB1, heat shock protein 8; LITAF, lipopolysaccharide induced TNF factor; MTMR2, myotubularin related protein 2; NEFL, neurofilament, light polypeptide; PMP22, peripheral myelin protein 22; SH3TC2, SH3 domain and tetratricopeptide repeats 2; TRPV4, transient receptor potential cation channel, subfamily V, member 4.