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Charcot-Marie-Tooth disease: Frequency of genetic subtypes in a German neuromuscular center population

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Abstract

Charcot-Marie-Tooth (CMT) neuropathies belong to the most common neurogenetic disorders. To date, mutations in more than 40 genes are known to be able to cause CMT. This genetic heterogeneity is a challenge for genetic diagnostics. Data on frequencies of mutations in CMT genes from large patient cohorts are needed to develop strategies for efficient genetic testing. In this study we have analysed patient histories, electrophysiological and genetic testing data in our cohort of 776 patients. In electrophysiologically demyelinating CMT, *PMP22* duplication was the most common genetic cause, followed by mutations in *GJB1* and *MPZ*. In axonal CMT, *GJB1* was the most commonly affected gene, followed by *MFN2* and *MPZ*. In CMT1, the clearance rate was 66%, in CMT2 it was 35%. Overall, the genetic clearance rate in our patient cohort was 58%. We found a higher rate of genetic diagnosis in patients seen in our neuromuscular center compared to out-of-clinic patients whose DNA was tested in our laboratory.

This study provides further data on frequencies of CMT genes and subtypes and points to the importance of a thorough clinical and electrophysiological work-up for the direction of genetic testing.

Keywords: Charcot-Marie-Tooth; Hereditary neuropathy; Peripheral neuropathy; Genetics; Neuromuscular

1. Introduction

Hereditary motor and sensory neuropathies, also called Charcot-Marie-Tooth (CMT) neuropathies, are the most common group among the hereditary neuropathies and belong to the most common forms of genetic disorders overall. Patients with CMT usually present with distal muscle wasting, sensory loss and foot deformities [1]. The severity shows great variability, as does the age of onset, depending on the CMT subtype. CMT subtypes are grouped by axonal, demyelinating or intermediate phenotype, autosomal-dominant, autosomal-recessive or X-chromosomal inheritance [2,3]. CMT-1 is considered to be demyelinating, CMT-2 is considered to be axonal. Both CMT-1 and -2 are autosomal-dominant. Autosomal-recessive forms of CMT are grouped as CMT-4. X-chromosomal forms of CMT are termed CMT-X. In recent years, molecular genetic research has revealed a multitude of genes responsible for different subtypes of CMT. Currently, more than 40 CMT genes are known [2]. This represents a challenge for neuromuscular centers as genetic testing strategies have to be defined in order to cost-effectively achieve a genetic diagnosis of CMT patients. In this light, data on the relative abundance of genetic changes in CMT patients are of interest. Previous studies have shown that the four most commonly affected genes can account for up to 90% of positively diagnosed CMT patients [4–6]. The four most common genes in previous studies were: *Peripheral Myelin Protein 22 kDa* (PMP22), *Connexin-32* (Cx32), *Myelin-Protein-Zero* (MPZ) and *Mitofusin-2* (Mfn2) [4,5]. As frequencies of gene mutations can vary considerably between different populations, data on patient cohorts from different countries are also useful in directing genetic diagnostics [7]. In our neuromuscular center we

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had the opportunity to perform the genetic diagnostics of 776 patients with a suspected diagnosis of CMT. Of these 776 patients 624 patients were treated in our neuromuscular center. From the remaining 152 patients, we received only blood probes for genetic diagnosis. For patients that were treated in our neuromuscular center, patient histories were followed up and several patients were identified, in which an etiology of the initial clinical symptoms other than hereditary neuropathy was found during the course of treatment. Furthermore, we retrospectively analysed the results of the genetic diagnostic workup of patients. Apart from the results of genetic testing, we also reviewed the nerve conduction studies of patients to divide them into axonal and demyelinating phenotypes and calculate the gene frequency separately for each phenotype.

The data presented here provide an overview of frequencies of genetic subtypes of CMT patients in a large German neuromuscular center.

2. Materials and methods

2.1. Clinical characterization of patients and CMT subtypes

All patients evaluated at our clinic from 2004 to 2012 were included in our study. Patients of whom blood probes for genetic testing were received between 2004 and 2012 were also included. Patients evaluated in our clinic were considered to have CMT if a sensorimotor neuropathy was present and the family history was positive for a similar condition. Patients without a positive family history were considered to have CMT if their neurological and neurophysiological examination was typical for CMT and no cause for an acquired neuropathy such as toxic (e.g. medication-related), metabolic (e.g. diabetic), inflammatory (e.g. CIDP), infectious (e.g. HIV) or critical-illness neuropathy could be found. First or second degree relatives were considered to carry the same mutation if a similar clinical phenotype was present. Patients were classified as axonal or demyelinating CMT by nerve conduction velocity of the median or ulnar nerve ($<$38 m/s: demyelinating, CMT1, $\geqslant$38 m/s: axonal, CMT2) [3]. Patients with a medical history of transient pareses and/or sensory loss related to typical nerve compression points (pressure palsies), conduction blocks and mild demyelinating neuropathy were considered for a clinical phenotype of hereditary neuropathy with liability to pressure palsies (HNPP) [8,9].

2.2. Genetic testing

Patients with CMT1 were tested for duplications of chromosome 17p11.2 first. If negative, patients were then tested for *GJB1* mutations (unless male–male transmission occurred in the family history), *PMP22* point mutations or *MPZ* mutations. Patients with CMT1 were also screened for *EGR2*, *NEFL*, *GDAP1*, *LITAF*, *SH3TC2*, *MTMR2* or *PRX* mutations where appropriate.

Patients with CMT2 were tested for *MFN2* mutations first. Then, *GJB*1 (unless male–male transmission was reported in the family) and *MPZ* were screened for mutations. Further CMT2 patients were tested for *EGR2*, *NEFL*, *GARS*, *GDAP1*, *TRPV4*, *HSPB1*, *HSPB8* and *GAN1* mutations where appropriate.

Patients with HNPP were tested for deletions of chromosome 17p11.2. If negative, patients were screened for point mutations in *PMP22*.

3. Results

3.1. Patients

In the study period 776 patients received genetic testing for a suspected diagnosis of CMT. Of these 776 patients, 624 were treated in our neuromuscular center. For the remaining 152 patients, we only received blood probes for genetic testing. Patients treated in our center were followed up and those patients, in which an etiology for peripheral neuropathy other than a hereditary genetic cause was found, were excluded. This occurred in 35 of the 624 patients treated in our neuromuscular center. The most common non-hereditary etiologies that came up in the follow-up were diabetic neuropathy, ethanol-toxic neuropathy, CIDP, medication-related neuropathy and multiple sclerosis.

For all patients, nerve conduction studies were analysed. In the 152 patients, whose probes we received for testing, only in five cases nerve conduction study results were available. In the 589 patients that were treated for CMT in our center, we could obtain sufficient nerve conduction study results in 572 patients. Taken together, we could analyse the genetic results of 577 patients with sufficient nerve conduction study data. In these patients, we were able to stratify the results of genetic testing by the electrophysiological phenotype (axonal or demyelinating). In 164 patients, insufficient or no data on nerve conduction studies were available. Hence, in these patients genetic diagnostics could not be related to the electrophysiological phenotype. Mostly, these were patients that were not treated in our center, but only blood probes were received for genetic testing. Some patients treated in our clinic also lacked sufficient electrophysiological data, for example because no electrophysiological response could be measured in any nerve tested, which can be the case in severe neuropathies.

3.2. Results of genetic testing – by electrophysiological phenotype

Of the 589 patients with sufficient nerve conduction studies, 355 were classified as CMT1, 151 as CMT2 and 83 as HNPP. In CMT1 patients, 66% could be genetically confirmed. In CMT2 patients, 35% received a positive