Pathogenic variants in three families with distal muscle involvement

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Three families suspected of distal hereditary motor neuropathy underwent genetic screening with the aim to identify the molecular defect underlying the disease. The description of the identification reflects the shift in molecular diagnostics that was made during the last decades. Our candidate gene approach yielded a known pathogenic variant in BSCL2 (p.Asn88Ser) in one family, and via a CMT-capture, in HSPB1 (p.Arg127Trp), in addition to five other variations in Charcot-Marie-Tooth-related genes in the proband of the second family. In the third family, using whole exome sequencing, followed by linkage-by-location, a three base pair deletion in exon 33 of MYH7 (p.Glu1508del) was found, a reported pathogenic allele albeit for a myopathy. After identification of the causative molecular defect, cardiac examination was performed for patients of the third family and this demonstrated abnormalities in three out of five affected family members. Heterogeneity and expansion of clinical phenotypes beyond known characteristics requires a wider set of genes to be screened. Whole exome/genome analysis with limited prior clinical information may therefore be used to preclude a detailed clinical evaluation in cases of large families, preventing screening of a too narrow set of genes, and enabling the identification of novel disease-associated genes. In our cases, the variants had been reported, and co-segregation analysis confirmed the molecular diagnosis.

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1. Introduction

Distal hereditary motor neuropathies (dHMsNs) are a clinically and genetically heterogeneous group of disorders that primarily affect motor neurons, without sensory involvement. Although many gene mutations and loci linked to the disease are known, the genetic defect has been identified in only one third of the cases [1,2]. In this study we present three large families of which the proband had been diagnosed with dHMN with an autosomal dominant mode of inheritance. Due to the inheritance pattern, similarity in phenotype and the fact that pathogenic variants in some genes can cause both Charcot-Marie-Tooth disease (CMT)/hereditary motor and sensory neuropathies (HMSN) and dHMN, we decided to perform a genetic screening with obvious candidate genes. When unsuccessful, our approach was to proceed to targeted sequencing using a custom-made capture containing the coding exons of 44 CMT-associated genes. Finally, we performed whole exome analysis, in the third family followed by linkage-by-location. Our study shows that co-segregation analysis in combination with (targeted) exome sequencing is a powerful tool to identify the pathogenic mutation within large families where standard gene panels do not suffice. It also underlines the significance of screening a wide(r) set of genes to cover all possible underlying defects. In our case, the molecular analysis led to

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cardiac examination and identification of the cardiac abnormalities in the third family.

2. Patients, materials and methods

2.1. Patients and families

Three five generation-families that presented with slowly progressing weakness of the lower limbs and absent sensory abnormalities were carefully examined. Pedigrees of the families are given in Fig. 1. Blood samples from affected and non-affected family members of two to three generations were available for research. Written consent was obtained for all individuals.

2.2. Sequencing of candidate genes

Genomic DNA was isolated from blood using standard procedures. For amplification of the exons of the candidate genes, M13 tagged specific exon-primers were used (sequences available upon request) with 20 ng of template DNA and Hotfire polymerase (Solis Biodyne). PCR was performed according to a touchdown PCR program, with a final annealing temperature at 55 °C. Prior to Sanger sequencing using the Big Dye Terminator kit (ABI), samples were treated with shrimp alkaline phosphatase and exonuclease I. Sequences were run on an ABI3730xl sequencer and analyzed using the Codon Code Aligner software.

2.3. Targeted sequencing of CMT-associated genes

A CMT-specific custom-made capture (Nimblegen, Roche) was developed for routine screening. The capture contained the coding exons of the following CMT-associated genes: SEPT9 AARS ARHGEF10 ATL1 BSC12 CCT5 CTDP1 DCTN1 DNM2 EGR2 FAM134B FGD4 FIG4 GARS GDAP1 GJB1 HSN2 HSPB1 HSPB8 IGHMBP2 IKBKP LITAF LMNA LRSAM1 MFB2 MP2 MTMR2 NDRG1 NEFL NGFB NTRK1 PLEKHG5 PMMP2 PRPS1 RAB7A SBF2 SH3TC2 SLC12A6 SOX10 SPTLC1 SPTLC2 TRPV4 YARS. DNA of the index persons was fragmented (Covaris), tagged with specific MIDs and used for library preparation. For the capture, the DNA of three libraries was combined, after which a sequencing library was prepared according to the manufacturer’s protocol (Nimblegen, Roche) prior to sequencing on a Titanium FLX pyrosequencer (Roche).

2.4. Whole exome sequencing and linkage-by-location

After library preparation a pilot run was performed on the Solid Wildfire sequencer with an average coverage of 5x. To obtain a higher coverage, the same libraries were used on a Solid 5500 sequencer, (75 bp forward and 35 bp reverse). Rare variations were used to construct a haplotype. Assuming that all affected persons would carry identical variants in the region linked with the disease, we confined the linkage region by identification of two regions in which variations were no longer present in all affected persons, as the result of a crossing-over event.

2.5. Muscle pathology

Routine stains (including haematoxylin and eosin (HE), ATPase preincubated at pH 9.4, and NADH were performed on 7-μm cryostat sections according to standard procedures [3].

3. Results

3.1. Clinical description of families

Family 1 Nine affected patients were examined. Disease onset occurred during puberty slowly progressing into adulthood, with atrophy and paresis of the tibialis anterior and peroneal muscles, pes cavus, hammer toes, and claw hands. There was slight paresis of the hand musculature, and flexor contractures of the fingers, specifically of flexor V. Upper motor neuron involvement, i.e., brisk knee and ankle jerks (including clonus) was found in half of the patients, extensor plantar responses in 40%. Nerve conduction studies showed normal or minimally reduced motor conduction velocities, and normal sensory conduction and SNAPs.

Family 2: Five affected patients were examined. Onset of disease occurred in adolescence with muscle cramping and overt weakness of the leg musculature in the third to fourth decade of
life. Paresis of the tibialis anterior, peroneal muscles, pes cavus and, in 4 out of 5 patients weakness of the calf muscles was observed. In due course the proximal leg muscles and hands became involved as well, leading to wheelchair dependency in two patients. Tendon reflexes were diminished (knee) or absent (ankle). Nerve conduction studies demonstrated prolonged distal latencies of the motor nerves and low CMAPs, and normal conduction velocities.

Family 3: Clinical details are given in Table 1. Disease onset occurred in early childhood with atrophy and moderate paresis of the tibialis anterior and peroneal muscles. The oldest patient had to be artificially ventilated since age 60. Muscle biopsies of patients of the first two generations (II1, II2 and III4) demonstrated a peculiar picture of fiber type disproportion including atrophic type 1 fiber predominance and scattered large type 2 fibers in all three (Fig. 2) and a neurogenic appearance showing fascicles composed only of atrophic fibers. The muscle biopsy of a 35-year-old male (III4) was only performed after the genetic analysis showing a variability in the size of muscle fibers, scattered atrophic type 1 fibers with nuclear clumps, fiber splitting and numerous fibers with internal nuclei consistent with a myopathy (not shown).

EMG studies showed both myopathic (short-duration, polyphasic motor unit action potentials (MUAPs)), and neurogenic abnormalities (long-duration, high-amplitude MUAPs, fibrillations, myotonic discharges, and positive sharp waves). Motor and sensory conduction was normal. Following the (genetic) diagnosis, cardiac examination including cardiac MRI was performed, showing slight dilatation of the left ventricle in 3 out of 5 examined and non-compaction in 2 out of these 3. In two (middle-aged) patients cardiac examination was normal.

3.2. Identification of a Silver disease pathogenic variant in family 1

Based on the clinical phenotype with purely motor abnormalities, signs of upper motor neuron development in a proportion of the patients and mode of inheritance in family 1, we
focused on the GARS, TRPV4 and BSCL2 genes, after having excluded mutations in the coding parts of PMP22, MPZ, HSPB1, HSPB8, and MFN2. A known pathogenic variant (c.263A>G, p.Asn88Ser (NM_032667.6)) [4] was found in the BSCL2 gene. Consequently, all other affected and non-affected available individuals of this family were screened showing the presence of the pathogenic variant in ten affected patients (10), and additionally, in two healthy individuals, one of whom was an obligate carrier. In 11 non-affected family members, the mutation was not found thus showing a near perfect co-segregation with the disease.

3.3. Identification of a HSPB1 pathogenic variant in family 2

Targeted sequencing of the exons of 44 CMT-associated genes demonstrated the presence of a known pathogenic variant in HSPB1: c.379C>T; p.Arg127Trp (NM_001540.5) [5] in the proband of the family who was severely affected (i.e., wheelchair-bound at age 48 years). In addition, five other variants in CMT-associated genes were detected and confirmed by Sanger sequencing. These variants were located in SOX10 (c.781C>T; p.Arg261Cys; NM_006941.4), HSPB8 (c.50G>T; p.Arg17Leu; NM_014365.3), GAN (c.1445C>T; p.Ala482Val; NM_022041.4), PMP22 (c.353C>T; p.Thr118Met; NM_000304.4) and SETX (c.4096T>C; p.Ser1366Pro; NM_015046.6). Of the observed changes, only the variant in HSPB1 was found in all affected family members. Remarkably, the person with no additional variations showed a much milder phenotype (Fig. 3). The other three patients carried an additional variant in PMP22 (Fig. 3). The patients who were more moderately affected, carried two additional variations both including the PMP22 variation, while the most affected patient carried five additional variations including the PMP22 variation.

3.4. Identification of a pathogenic mutation in a muscle specific gene, MYH7, in family 3

Since our targeted CMT-capture did not identify the pathogenic variant, we proceeded to a low-coverage WES approach in six affected and four non-affected family members and used Ingenuity Analysis to identify rare variants shared by the majority of patients. This yielded 19 variants, 6 of which mapped to chromosomal part 14q11.2. Of note, previous 2-point linkage analysis with CA repeats in this family had indicated a possible linkage to the very same region, between TCRD and D14S50 although the LOD score did not reach significance (2.11, theta = 0; results not shown). The same ten family members were sequenced at a higher coverage and all variants within this region were examined for heterozygosity or homozygosity of the wildtype or alternative allele and reliability of the genotype in IGV. Assuming that no recombination would yet have occurred (linkage-by-location) when we were close to the site of the pathogenic variant, and comparing all variants found in two affected children, their parents one of whom was affected, their non-affected grandmother and 3 affected and 2 non-affected siblings of their affected parent, we could construct a haplotype of 10.2 Mb (between rs4550696, and rs7142098; Fig. 4) shared by all affected family members. Within this region, we identified a change that was reported a pathogenic allele, although not for a neurogenic disorder. In MYH7, a heterozygous 3 bp deletion was found near the 3′-end of the gene (NM_000257.4; c.4522_4524delGAG, p.Glu1508del). Consequently, this change was confirmed by Sanger sequencing and was found to be present in all affected and absent in all non-affected family members.

4. Discussion

This study describes the different approaches in molecular diagnostics. As a result of our sequencing efforts we could identify the pathogenic mutations in the three families with suspected dHMN. In family 1, using a candidate gene approach, we identified a pathogenic variant in the BSCL2 gene. Heterozygous mutations affecting the glycosylation site of BSCL2/seipin are known to cause Silver syndrome, a rare autosomal dominant disease with amyotrophy of the hands, sometimes the lower limbs and spasticity of the distal limbs (spastic paraplegia SPG17) or lead to a motor neuropathy due to defects in autophagy [4,6,7]. Patients carrying the Silver mutation may exhibit a spectrum of phenotypes [8–11] which fits the description of the phenotype in our family.

Targeted exome sequencing in the second family identified a pathogenic HSPB1 variant encoding a molecular chaperone also described to be involved in the pathogenesis of ALS [12]. HSPB1/HSP27 is linked to both recessive and dominantly inherited axonal Charcot-Marie-Tooth disease with minimal sensory involvement and dHMN [13]. Clearly, the clinical phenotype is highly variable which suggests that several modifiers of the disease may exist. In our family, several other variants in CMT-associated genes were found. However, their association with the phenotype is unclear. An additional variant in PMP22 (c.353C>T) was present in all patients who were moderately or severely affected. This variation was originally reported as a cause for CMT1A, but its pathogenicity was questioned later on [14], and the variant was described as a partial loss-of-function in a HNPP-like neuropathy.

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**Table 1:** Presence of additional variations in members of family 2. Severity of the phenotype per patient is indicated by a darker color as indicated by the arrow.

| Gene  | Variant | Phenotype | Frequency |
|-------|---------|-----------|-----------|
| HSPB1 | c.379C>T; p.Arg127Trp | + | + | + | - |
| SOX10 | c.781C>T; p.Arg261Cys | unknown change | unknown frequency |
| HSPB8 | c.50G>T; p.Arg17Leu | unknown change | unknown frequency |
| G4N  | c.1445C>T; p.Ala482Val | MAF 0.002-0.004 |
| PMP22 | c.353C>T; p.Thr118Met | MAF 0.002 |
| SETX | c.4096T>C; p.Ser1366Pro | unknown frequency |

**Fig. 3.** Presence of additional variations in members of family 2. Severity of the phenotype per patient is indicated by a darker color as indicated by the arrow.
[15]. Of note, the person with the most severe phenotype carried five additional variants in CMT-associated genes, while the person who was mildly affected had no additional variants in these genes. Possibly, the presence of these additional changes may modulate the phenotype although they are not sufficiently pathogenic to cause the disease as they were also found in the unaffected mother and sibling of the index patient.

The third family carries a mutation in a muscle-specific gene, MYH7, which is often associated with cardiomyopathy. However, mutations in the C-terminal tail (exons 32–36) have been described in Liang distal myopathy [16–23]. The found mutation in family 3 has been reported as a pathogenic allele in several countries, in some cases as a de novo occurring variant leaving little doubt regarding its pathogenicity [24–29]. The clinical phenotype in these families ranged from being mildly affected to being wheelchair- and respirator-dependent, which also fits the description in our family. This variability has been reported for other MYH7 variants as well, including asymptomatic carriers and severe cases with early onset, respiratory insufficiency and dilated cardiomyopathy [20,24,30]. Remarkably, in 1968, the disease in the family in this study had been classified as a distal myopathy [31].

Later, the diagnosis was changed to dHMN based on the large clusters of atrophic muscle fibers in the biopsies of three affected individuals and dominance of neurogenic abnormalities on EMG. Muscle pathology and EMG may be misleading as was the case in our family. Muscle membrane irritability, in the form of fibrillation potentials, positive sharp waves and myotonic discharges, often referred to as derivering potentials, may be found on needle EMG in chronic myopathies [32] while short, small, polyphasic APs, usually found in myopathies, may also rarely be observed in neurogenic disorders. The interpretation as neurogenic led to a misdiagnosis of dHMN which was also reported for other MYH7 variants [33,34]. Due to the presence of mild sensory symptoms, one family was even diagnosed with axonal CMT [17]. Vooi et al. reported an accompanying peripheral neuropathy in the oldest member of one family [35], and another case of motor neuropathy was described in an Italian family albeit that this patient carried two mutations, p.Lys1617del and p.Glu1619lys, the latter one of which was also present in the non-affected mother of the patient [36]. When examining publicly available databases on the expression of the MYH7 gene, it was also reported to be expressed in brain and nerves albeit at a much lower level than in heart

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**Fig. 4.** Confinement of the linkage region and construction of a disease-haplotypen body 3. In the left side of the figure different alleles are indicated by an arbitrary number, in the right side of the figure is specified whether the respective position was wildtype (WT), heterozygous (Het) or homozygous for the alternative nucleotide (Alt), gray regions at the top and bottom of the figure represent the parts where the linkage with a specific allele was lost marked by rs4550069 and rs7142098. Boxed and shaded positions indicate the presence of the found SNPs that were shared between all patients in our first screen. The first column represents the haplotype linked to the disease, the genotype of the grandfather (1) was derived from his (grand)rowd children.
and muscle which triggers the question as to the nature of the function this gene may have in neuronal cells and whether this may contribute to misinterpretation of the phenotype. After the genetic diagnosis had been made, the patients were subjected to cardiac examination and three out of five patients appeared to have a dilated left ventricle and/or non-compaction of the left ventricle. Cardiac abnormalities have been reported to occur in a minority of the patients carrying MYH7 tail mutations (exon 32–36) other than the p.Glu1508del mutation [20,23,37]. The majority of patients with the p.Glu1508del mutation was reported to be accompanied by cardiac abnormalities [24,27]. We report the first Dutch family with the p.E1508del mutation and a fifth family in which cardiac abnormalities are present warranting cardiac examination for all patients carrying MYH7 tail mutations.

Next generation sequencing has considerably contributed to identification of the genetic cause of dHMN albeit the detection rate ranges from only 14% in cohorts from London, UK and Iowa, USA [1] to 35.6% in a cohort from North England [38]. Exome sequencing of isolated cases yields many variants even when confining the analysis to CMT-associated genes as was the case for family 2. Whole exome analysis may lead to the identification of novel disease-associated genes or be helpful in identifying modulatory variants. Our results emphasize both the importance of a careful and detailed clinical examination and the inclusion of a wide(r) set of genes to be screened. In our cases, the causal variants were reported pathogenic alleles that co-segregated with the disease. Only in family 2, two asymptomatic individuals were found to carry the pathogenic variant in BSCL2. One was an obligate carrier and the other person may still develop the disease. Alternatively, it may be the result of incomplete penetrance that was reported for this mutation before [4] indicative of other factors that influence the development or severity of the disease. For large families, segregation analysis in combination with exome sequencing has proven the most powerful tool to find the causative pathogenic variant, even with limited clinical information. It resulted in the third family in the correction of the diagnosis, and prompted cardiac screening and identification of cardiac abnormalities in several patients of this family. When dealing with previously unreported variants or isolated cases, the interpretation of whole exome analysis becomes increasingly difficult [39]. Since whole exome analysis probably yields many likely pathogenic variants, a detailed clinical evaluation of the phenotype is in this cases essential. Additionally, there is a growing need of functional assays and even more data sharing to enable us to correctly categorize found variants into pathogenic and non-pathogenic classes.

Author’s statement

All authors have materially participated in the research and/or article preparation. MAJW wrote the manuscript and conducted the experiments, DK did part of the experiments, MB, JEH, GJG, KY van S, HHG examined the described families, EA performed muscle pathology, AJ performed the bio-informatical analysis, FvR was responsible for the molecular diagnostics, and MdeV and FB supervised the research. All authors have approved the final article.

Declaration of Competing Interest

None.

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