Hereditary Neuropathies
Clinical Presentation and Genetic Panel Diagnosis

Katja Eggermann, Burkhard Gess, Martin Häusler, Joachim Weis, Andreas Hahn, Ingo Kurth

Summary

Background: Hereditary peripheral neuropathies constitute a large group of genetic diseases, with an overall prevalence of 1:2500. In recent years, the use of so-called next-generation sequencing (NGS) has led to the identification of many previously unknown involved genes and genetic defects that cause neuropathy. In this article, we review the procedures and utility of genetic evaluation for hereditary neuropathies, while also considering the implications of the fact that causally directed treatment of these disorders is generally unavailable.

Methods: This review is based on pertinent publications retrieved by a PubMed search employing the search terms “hereditary neuropathy,” “Charcot-Marie-Tooth disease,” “hereditary sensory neuropathy,” and “hereditary motor neuropathy.”

Results: With rare exceptions, the diagnostic evaluation for hereditary neuropathies proceeds in a stepwise fashion, beginning with the study of individual genes. If this fails to detect any abnormality, NGS analysis, which involves the sequencing of many different genes in parallel and has now become available for routine work-up. Exome and genome analyses are currently performed only when considered to be indicated in the individual case. Whenever a hereditary neuropathy is suspected, other (including potentially treatable) causes of neuropathy should be ruled out. Mutations in neuropathy-associated genes may also be associated with other clinical entities such as spastic paraplegia or myopathy. Thus, interdisciplinary assessment is necessary.

Conclusion: The molecular diagnosis of neuropathies has become much more successful through the use of NGS. Although causally directed treatment approaches still need to be developed, the correct diagnosis puts an end to the often highly stressful search for a cause and enables determination of the risk of neuropathy in other members of the patient’s family.

Cite this as:

The clinical presentation of CMT is characterized by progressive muscle weakness, muscular atrophy, and sensory disturbances. Compared with the acquired neuropathies, which are mainly characterized by...

Clinical presentation

Symptoms and disease course

The clinical presentation of CMT is characterized by progressive muscle weakness, muscular atrophy, and sensory disturbances. Compared with the acquired neuropathies, which are mainly characterized by...
sensory features, CMT is often characterized by motor deficits with a loss of proprioceptive reflexes, peroneal nerve paralysis or palsy, pes cavus, and claw toes. The disorder may also be accompanied by neuropathic pain, scoliosis, skeletal deformities, deafness, cognitive deficits, tremor, impaired speech and dysphagia, breathing difficulties, or structural changes of the central nervous system (4). The long nerves in the leg are often affected earlier and in a more pronounced way than the nerves in the arms. Especially in severe autosomal-recessive forms of CMT, the disorder often starts in childhood.

In HSN and HSAN, a loss of the sensation of pain may be the main clinical symptom, with subsequent/ consequent injuries and painless fractures. Depending on the subtype, autonomic symptoms such as cardiac arrhythmias, indigestion, or hypo/anhidrosis may complicate the disease (5). Reported frequencies for the individual comorbid symptoms are incomplete because this form of the disorder is rare. By contrast, small fiber neuropathy (SFN), with what is mostly degeneration of the small unmyelinated pain fibers (C fibers) and myelinated Aδ fibers, manifests with burning and occasionally periodic pain. In hereditary neuropathies without much sensory involvement, reference is usually made to distal HMN or distal small fiber neuropathy (SFN), with what is mostly a loss of intraepidermal nerve fiber density in a skin biopsy specimen can confirm the diagnosis of SFN (6).

**Further diagnostic evaluation**

Young age at manifestation and a positive familial history should give rise to the suspicion of a hereditary neuropathy, but thorough diagnostic evaluation is still required to rule out metabolic, nutritive-toxic, infectious, and inflammatory or autoimmunological causes. In addition to analyzing cerebrospinal fluid (7), laboratory tests should include measuring the erythrocyte sedimentation rate, creatinine, glycated hemoglobin (HbA1c), carbohydrate deficient transferrin, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and vitamin B12. Furthermore, immunofixation and protein electrophoresis should be undertaken. Nerve sonography will show a thickening of the nerves in some neuropathies (8, 9). MRI of the muscle can be used to expose distal muscular atrophy as a sensitive and objective parameter over the disease course (10).

**Nerve biopsy**

The indication for a nerve biopsy (sural nerve) should be discussed especially if non-hereditary neuropathies are considered as a potentially treatable differential diagnosis. These include inflammations such as vasculitis and perineuritis as well as atypical cases of neuritis (chronic inflammatory demyelinating or axonal neuropathy, CIDP or CIAP), a lymphoma affecting the nerves, and amyloid neuropathy. Preparation of nerve and skin biopsy specimens is laborious and includes—in addition to conventional paraffin section histology—special immunohistochemical and electron microscopic methods. The investigation should therefore be undertaken in specialized centers (11, 12).

**Particular characteristics of childhood disease**

Autosomal recessive hereditary disorders of early onset are often subsumed under the term CMT4. In childhood, symptoms are, however, often less characteristic and electrophysiological diagnostic evaluation not conclusive (13, 14).

As a neuropathy that manifests early in life can also be a partial symptom of a syndromic disorder, comprehensive differential diagnostic evaluation is required. In some cases, however, characteristic additional symptoms are detected that make the diagnosis
Deletions of the PMP22 gene are occasionally found in patients with CMT2 (16); for this reason, it makes sense first to undertake the relevant examination in axonal neuropathy too. If indications are found of X-linked inheritance in a family (CMTX)—for example, in the absence of father–son inheritance and more severely affected male patients—the GJB1 gene including its regulatory sequences should be examined first (17). If primarily smaller fibers are affected in the sense of SFN and a reduced intraepidermal density of nerve fibers has been histologically confirmed, a causal mutation can be confirmed in 10–30% on analyzing the genes

For CMT2 (16); for this reason, it makes sense first to undertake the relevant examination in axonal neuropathy too. If indications are found of X-linked inheritance in a family (CMTX)—for example, in the absence of father–son inheritance and more severely affected male patients—the GJB1 gene including its regulatory sequences should be examined first (17). If primarily smaller fibers are affected in the sense of SFN and a reduced intraepidermal density of nerve fibers has been histologically confirmed, a causal mutation can be confirmed in 10–30% on analyzing the genes SCN9A, SCN10A, and SCN11A, which encode voltage-gated sodium channels (18). In other forms of CMT or HSAN or HMN, the overall detection rate by usual gene account for only a small proportion of the exceptions mentioned above—mutations in the individual gene account for only a small proportion of the overall mutation rate and for this reason, analyzing genes in a temporal sequence is not expedient (25).

**Analyzing individual genes**

If demyelinating CMT is suspected, the first diagnostic step should consist of determining the number of copies of the PMP22 gene (15, 16). Up to 70% of patients with familial CMT have a duplication of the PMP22 gene. Conversely, patients with hereditary neuropathy with liability to pressure palsies (HNPP) often have a deletion in the respective genomic region. Deletions of the

### Table: Charcot-Marie-Tooth disease with onset in childhood and adolescence

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene</th>
<th>Onset</th>
<th>Clinical characteristics</th>
<th>Typical nerve biopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT4A</td>
<td>GDAP1</td>
<td>&lt;2 years</td>
<td>Severe CMT, paralysis of vocal cords and diaphragm</td>
<td>Segmental demyelination, onion bulb formations</td>
</tr>
<tr>
<td>CMT4B1</td>
<td>MTMR2</td>
<td>3 years</td>
<td>Severe CMT, facial/bulbar weakness, scoliosis</td>
<td>Myelin outflowing, loss of myelinated fibers</td>
</tr>
<tr>
<td>CMT4B2</td>
<td>SBF3</td>
<td>4–13 years</td>
<td>Severe CMT, glaucoma, kyphoscoliosis</td>
<td>Myelin outflowing, loss of myelinated fibers</td>
</tr>
<tr>
<td>CMT4B3</td>
<td>SBF2</td>
<td>1st decade</td>
<td>Severe CMT, possible microcephaly, cranial neuropathy</td>
<td>Focal disruption of myelin outgrowth</td>
</tr>
<tr>
<td>CMT4C</td>
<td>SH3TC2</td>
<td>1st–2nd decade</td>
<td>Severe CMT, kyphoscoliosis, deafness, tongue fasciculations</td>
<td>Long cytoplasmic protrusions of unmyelinated fibers, onion bulb formations</td>
</tr>
<tr>
<td>CMT4D</td>
<td>NDRG1</td>
<td>1–10 years</td>
<td>Severe CMT, deafness</td>
<td>Demyelination, axon loss, onion bulb formations, axonal inclusions</td>
</tr>
<tr>
<td>CMT4E</td>
<td>EGR2</td>
<td>Birth</td>
<td>Congenital hypotension, respiratory failure, arthrogryposis</td>
<td>Pronounced loss of myelinated and unmyelinated fibers, onion bulb formations</td>
</tr>
<tr>
<td>CMT4F</td>
<td>PRX</td>
<td>Birth</td>
<td>CMT1, primarily sensory symptoms</td>
<td>Pronounced loss of myelinated fibers, congenital hypomyelination</td>
</tr>
<tr>
<td>CMT4G</td>
<td>HK1</td>
<td>8–16 years</td>
<td>Relatively severe CMT1</td>
<td>Hypomyelination, regenerating clusters</td>
</tr>
<tr>
<td>CMT4H</td>
<td>FDG4</td>
<td>&lt;2 years</td>
<td>Severe CMT, scoliosis</td>
<td>Hypomyelination, small onion bulb formations</td>
</tr>
<tr>
<td>CMT4J</td>
<td>FIG4</td>
<td>≤6th decade of life</td>
<td>Severe CMT, similarities to motor neuron diseases</td>
<td>Pronounced axon loss, thin myelinated fibers</td>
</tr>
</tbody>
</table>

* CMT4 (modified from Tazir et al. 2013 [14]); CMT, Charcot-Marie-Tooth disease

Complex clinical presentations with neuropathy as a partial symptom are found in Anderman syndrome, for example (agenesis of the corpus callosum and mental retardation) or giant axonal neuropathy (extremely kinky hair and substantial mental retardation). Further autosomal recessive hereditary neuropathies with childhood onset include mitochondrial disorders—for example, mutations in COX6A1 (a component of complex IV in the mitochondrial respiratory chain) or SURF1 (cerebral lactacidosis and diffusion disorders on MRI/Leigh syndrome as a result of combined defectiveness of the mitochondrial respiratory chain). The following metabolic and neurodegenerative disorders go hand in hand with involvement of the peripheral nervous system:

- Refsum disease
- Metachromatic leukodystrophy
- Krabbe disease
- Adrenomyeloneuropathy
- Pelizaeus–Merzbacher disease (PMD)
- Lowe syndrome
- Hereditary ataxias (for example, Friedreich’s ataxia).

**Next generation sequencing–based testing**

Next generation sequencing–based testing to diagnose a peripheral neuropathy has become part of routine clinical practice in the meantime (Figure 2) (5, 21, 22). Panel diagnostics for neuropathies is used to sequence and assess a multitude of causative genes in parallel (23, 24) (eTable). The simultaneous analysis of many neuropathy genes makes sense in that—except for the exceptions mentioned above—mutations in the individual gene account for only a small proportion of the overall mutation rate and for this reason, analyzing genes in a temporal sequence is not expedient (25).
Suggested diagnostic algorithm in suspected hereditary neuropathy. As common causes for Charcot-Marie-Tooth disease (CMT), few individual genes should be analyzed initially. In small fiber neuropathies (SFN), an initial restricted search for mutations may also be useful. Peripheral neuropathies should always be evaluated by using next generation sequencing (NGS) panels at an early stage. Clinical overlaps may usefully prompt an extension of the panel by including genes from the disorders of the amyotrophic lateral sclerosis (ALS) spectrum, hereditary spastic paraplegias (HSP), or myopathies. Alternatively, exome or genome sequencing can be used to comprehensively investigate causal genetic variants. Del, deletion; dup, duplication; demyelin., demyelinating; HMN, hereditary motor neuropathy; HS(A)/N, hereditary sensory (and autonomic) neuropathy; X-chrom., X-chromosomal.

Including NGS-based diagnostics in the Uniform Value Scale (Einheitlicher Bewertungsmaßstab, EBM) currently allows its restricted use in routine diagnostic evaluation in Germany (25 kilobases of coding sequence per case). This is an important first step for the extraordinarily high number of genes that are potentially responsible, but from a medical perspective this is not sufficient. The same is true for the diagnostic evaluation of neuropathies in childhood, even though mutations in the SH3TC2, MPZ, or PRX gene are more common in this setting (26, 27).

In view of the rapidly rising number of new, disease-associated genes and considerations regarding other disorders, after patients have been given extensive and detailed information and on the background of falling costs, from a diagnostic perspective it is increasingly exome sequencing—that is, parallel sequencing of all 23 000 human genes—that holds promise as a diagnostic step. However, this measure is currently down to individual decisions on the part of the German healthcare insurers and is very rarely granted. Genetic counseling needs to include—before a comprehensive molecular analysis is undertaken—information especially on the possible additional findings of NGS diagnostics, which may relate to inherited tumor risks or predispositions to other disorders of a late manifestation. How to deal with additional findings, and the obligation to share these that such findings might necessitate, is currently the subject of intensive debate. To this end, we wish to mention the opinion expressed by the German Society of Human Genetics (e2) or the policy statement of the American College of Medical Genetics and Genomics (28).

Dealing with genetic variants of unclear significance

Each human genome includes some 30 million genetic variants (single nucleotide polymorphism, SNP). Most of these are common in the population and are not of any clinical significance. Other variants are clearly pathogenic (mutations), whereas yet others have to be classified as so-called variants of unknown clinical significance (VUS [29]). The class of the VUS are of central importance, because often, several variants of potential relevance—but whose significance is initially not clear—are detected among the analyzed neuropathy genes. These will then have to be assessed with regard to their potential pathogenicity. These variants may include the causal mutation. However, it is equally possible that only non-pathogenic variants are found. In order to assess a variant, bioinformatic prediction programs are used in addition to literature searches. Furthermore, the rate with which the variant occurs in the general population is checked by searching databases. Similarly, discussions with clinicians and nerve biopsy findings can help to classify the pathogenic mutation (29). In some cases, testing other family members for the variant can provide unequivocal clarification. Only in individual cases, however, should the corresponding variants initially be used to test non-affected family members predictively. In summary, NGS diagnostics is an instrument that improves the chance to secure an unequivocal finding that confirms the diagnosis.

The importance of genetic testing

The criticism that is leveled at the indication for genetic testing of neuropathies and the wider use of NGS panel diagnostics is usually the argument that these disorders cannot be treated. Even though the treatment of neuropathies is—except for very few exceptions—symptomatic, it is important to make a clear distinction from treatable hereditary forms, such as transthyretin amyloidosis or Fabry disease (26). Another increasingly common finding is that typical neurophysiological signs of inflammatory neuropathy are also found in patients with hereditary neuropathies—for example, in mutations in GJB1, SH3TC2, FIG4, or SPTLC1—and that a hereditary form does not always present with symmetrical distribution patterns. In the case of a treatment refractory neuropathy that is presumed to be inflammatory, genetic testing should therefore be considered on the basis of differential diagnostic deliberations too.

One fact that is often ignored is that molecular diagnostic confirmation puts an end to a search for the
cause of the clinical symptoms that is mostly lengthy, costly, and burdensome for the patient. Many patients experience the latter as very helpful in dealing with their illness. By confirming the diagnosis, a clear conclusion can be drawn about inheritance, which in turn enables assumptions regarding the likelihood of repetition within a family. This knowledge can be very important for the purposes of family planning and enables clarification especially in more severe disease courses by means of predictive or prenatal tests. In this context and in the diagnostic evaluation and explanation of the results, the aspect of human genetic counseling is of central importance.

Genetic overlaps in neuropathies

It is increasingly becoming obvious that mutations in the same gene can lead to clinically distinct entities. In the MPZ gene, mutations were initially described as the cause of a demyelinating CMT (CMT1) (30). Subsequently, however, axonal and intermediate forms caused by MPZ mutations have also been reported (31, 32). Furthermore, overlaps have been found in the inheritance patterns: mutations in EGR2, GDAP1, NEFL, and further CMT-associated genes can follow a recessive as well as a dominant inheritance pattern. Not only electrophysiological classifications and inheritance modi can overlap, but different neuromuscular disorders are caused by variants in the same gene. This is becoming ever more obvious, in particular thanks to the wider use of NGS diagnostics. Genetic variants that are associated with CMT can clinically also lead to HSAN or HMN or distal spinal muscular atrophy (Figure 3). Furthermore, the central nervous system may be affected. Finally, completely contrary clinical presentations have been observed for mutations in the same gene. Mutations in the ATL1 gene are an important cause of HSP, but they can also lead to HSAN without any indication of involvement of the central nervous system (33, 34). Further overlaps exist for neuropathies and myopathies—for example, in mutations in the DNM1 gene (35)—or neuropathies or motor neuron diseases—for example, in variants in the FIG4 gene (36, 37) (Figure 3). What this makes abundantly clear is that genetic diagnostic evaluation and the classification of the neuropathies should not adhere to rigid categorization principles. Additional arguments speak in favor of exome sequencing in order to widen the search for mutations. Symptoms that were deemed atypical can probably be detected better and earlier on the basis of the genetic result, and clinical results can be re-evaluated on the basis of the mutation. The medical history and nerve biopsy often show that a neuropathy has several causes. Accordingly, in addition to genetic variants, it is possible to identify vascular—often prediabetic—lesions and inflammatory alterations. All this underlines a need for intensive cooperation of different medical specialties, such as neurology, neuropediatrics, neuropathology, and human genetics—for example, in the setting of neuromuscular centers. The symptomatic treatment of often severe clinical courses further requires multidisciplinary care delivered by neurologists, neuropsychiatrists, orthopedic surgeons, pulmonologists, psychologists, and physiotherapists/occupational therapists, all of whom should be specialists in neuromuscular disorders.

Outlook

NGS-based genetic testing contributes vitally to our understanding of neuropathies and has contributed to the identification of many new disease-associated genes. This forms the basis for understanding pathomechanisms that are crucial for the development of targeted therapies. One such example are preclinical models, such as the application of HDAC6 inhibitors, which improved some disease parameters, or serine therapy in HSAN1, which is already being studied in clinical trials. The latter reduced neurotoxic metabolic products, in some case reports (SPTLC1 mutations) (38, 39). The study registry clinicaltrials.gov currently includes 232 studies under the search term Charcot-Marie-Tooth. However, 168 of these studies have an interventional study design, mostly using medications with a symptomatic effect. Only very few have studied the causes. However, it is to be expected that the importance of genetic characterization will increase further subsequent to further studies, and that the classification of neuropathies will increasingly be using molecular classifications. A huge challenge for the coming years is dealing with genetic variants of unclear clinical significance, some of which may have a modifying effect on the clinical course (so-called
Key messages

- Patients with an autosomal dominant or sporadic demyelinating neuropathy should be tested using the PMP22 duplication test.
- Genetic testing for demyelinating Charcot-Marie-Tooth disease is recommended in therapy refractory chronic inflammatory demyelinating neuropathy (CIDP). Genetic testing for transthyretin amyloidosis is recommended in rapidly progressive sensorimotor neuropathy of unknown origin.
- To find further explanations for hereditary neuropathies, a multitude of genes will have to be considered because of genetic heterogeneity.
- Next generation sequencing (NGS) is an effective testing method for peripheral neuropathies and should be used early on in the stepwise diagnostic evaluation.
- Integrating the results of NGS into the overall clinical picture requires close collaboration between clinicians, neuropathologists, and human geneticists.

modifier genes). Conceivably it is the combined mechanisms of action of several of such variants that holds the key to understanding why a genetic variant causes a peripheral neuropathy in one patient but affects primarily the upper motor neurons in other cases. A pathogenesis on the basis of different genetic variants with a combined effect is increasingly being reported (40). It may be assumed that in future, in addition to improved bioinformatic approaches, advances in the area of artificial intelligence will help us understand the complex combined workings of genetic variants.

Conflict of interest statement

Dr. Gess has received conference delegate fees and travel expenses from Grifols. He has received speaker honoraria from Bayer. He has received study funding (third party funding) from Grifols and Pharmnext.

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References

CLINICAL SNAPSHOT

Oxygen-Resistant “Cyanosis” After Sun Exposure

A 63-year-old man (1.75 m, 98 kg) was taken to the hospital by the emergency medical services because of acute dyspnea and the clinical picture of severe cyanosis. He had returned the previous day by airplane from a holiday in the sun in the Canary Islands. The pre-hospital suspected diagnosis of pulmonary embolism was not confirmed. The patient was found to have left-heart decompensation in the setting of a hypertensive crisis. He had taken amiodarone (200 mg/day) for five years because of a recurrent tachyarrhythmia. His ostensible cyanosis despite adequate oxygen saturation had come about as a phototoxic hyperpigmenting effect of amiodarone. This effect is due to lysosomal storage of lipids and amiodarone metabolites in dermal histiocytes. Efflorescence arises in dose-dependent fashion, with a long latency after the patient starts taking the drug, in light-exposed areas such as the forehead, nose, and cheeks. Skin folds (e.g. in the eyelids) are spared. Transient erythema is frequent, arising in as many as 10% of patients taking amiodarone. The full picture of the disorder has been very rarely described. Slate-gray hyperpigmentation can persist for years after amiodarone has been discontinued and can be reactivated by renewed sunlight exposure, as in the present case. The treatment consists of permanent avoidance of amiodarone and protection from sunlight exposure.

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Supplementary material to:

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eReferences


eTABLE

Overview of genes in which mutations may be responsible for neuropathies

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Responsible genes</th>
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</thead>
<tbody>
<tr>
<td>HMSN</td>
<td>AARS, ABCA1, ABHD12, AIFM1, ALS2, ANG, ARHGEF10, BAG3, BSC1L2, C100RF2, C100RF65, CCT5, COX6A1, COX10, CTD1, CYP27A1, DCAF8, DCTN1, DGAT2, DHTK1, DNAJB2, DNMT2, DRP2, DYNC1H1, EGR2, FAM126A, FBLN5, FGD4, FGF4, FUS, FXN, GALT, GAN, GARS, GDAP1, GJB1, GJB3, GNB4, GSN, HADHA, HADHB, HARS, HINT1, HK1, HOXD10, HSPB1, HSPB3, HSPB8, IFRD1, IGHMBP2, INF2, KARS, KIF1B, KIF5A, KLHL13, LITAF, LMNA, LRSAM1, MARS, MED25, MFV2, MME, MICAL1, MOC2, MVIT, MPV17, MTP2, MTHFR, NDRG1, NDUFAS, NEFH, NEFL, NIPA1, OPTN, PDHA1, PDK3, PEX12, PLEKHG5, PLP1, PMP2, PMP22, PKP2, POLG, PRPS1, PRX, RAB7A, REEP1, SAC3, SBP1, SBP2, SEP79, SHOC1C2, SHOC1B, SLCA4, SLCA5, SLCA15, SOX10, SPG11, SURF1, SYT2, TARDBP, TDP1, TFI, TNR1, TRM2, TRPV4, TUBB3, TYP, VCP, YARS, ZNF106</td>
</tr>
<tr>
<td>HSAN/SFN</td>
<td>AAAS, ARL6IP1, AT1L, AT1L2, AT1L3, CLTCL1, DNMT1, DST, FAM134B, FLVCR1, GLA, GLPPA, IKBAP, KIF14, NAGLU, NIF, NTRK1, PRDM12, RAB7A, RNF170, SCN10A, SCN11A, SCN1A, SP2LC1, SPTLC2, ECPR2, TMEM173, TRPA1, TTR, WNK1</td>
</tr>
<tr>
<td>dHMSN/dSMA</td>
<td>AARS, ASAH1, ASCC1, APT1A, BICD2, BSC1L2, CHC1D10, CLP1, DCTN1, DNAJB2, DYNCE1H1, EXOSC3, EXOSC6, FBXO38, GARS, HEXA, HINT1, HMBS, HSPB1, HSPB3, HSPB6, IGHMBP2, LASS1L, PLEKHG5, RBM7, REEP1, SOC2, SETX, SIGMAR1, SLCA4, TFG, TRIP4, TRPV4, UBA1, VAP8, VRK1</td>
</tr>
</tbody>
</table>

In the context of an analysis of next generation sequencing panels, these genes (and subgroups) can be examined in parallel. This table is not intended to give the complete picture. The rapid growth in knowledge in the area of neuropathies requires continuous adjustment of the panels or even wider-ranging testing methods, such as exome or genome sequencing.