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EFNS GUIDELINES

EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders

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Objectives: These EFNS guidelines on the molecular diagnosis of motoneuron disorders, neuropathies and myopathies are designed to summarize the possibilities and limitations of molecular genetic techniques and to provide diagnostic criteria for deciding when a molecular diagnostic work-up is indicated.

Search strategy: To collect data about planning, conditions and performance of molecular diagnosis of these disorders, a literature search in various electronic databases was carried out and original papers, meta-analyses, review papers and guideline recommendations reviewed.

Results: The best level of evidence for genetic testing recommendation (B) can be found for the disorders with specific presentations, including familial amyotrophic lateral sclerosis, spinal and bulbar muscular atrophy, Charcot-Marie-Tooth 1A, myotonic dystrophy and Duchenne muscular dystrophy. For a number of less common disorders, a precise description of the phenotype, including the use of immunologic methods in the case of myopathies, is considered as good clinical practice to guide molecular genetic testing.

Conclusion: These guidelines are provisional and the future availability of molecular-genetic epidemiological data about the neurogenetic disorders under discussion in this article will allow improved recommendation with an increased level of evidence.

Introduction

Since the publication of the first EFNS guidelines on the molecular diagnosis of inherited neurological diseases in 2001v [1,2], rapid progress has been made in this field, necessitating the creation of an updated version of these guidelines, which follows the EFNS Scientific Committee recommendations for guideline papers [3].

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These EFNS guidelines on the molecular diagnosis of motoneuron disorders, polyneuropathies and myopa-

thies are designed to summarize the possibilities and limitations of molecular genetic techniques and to provide diagnostic criteria for deciding when a molecular diagnostic work-up is indicated.

Search strategy

To collect data about planning, conditions and performance of molecular diagnosis of motoneuron disorders, polyneuropathies and myopathies, a literature search in various electronic databases, such as Cochrane library, MEDLINE, OMIM, GENETEST or Embase, was carried out, and original papers, meta-analyses, review papers and guideline recommendations reviewed.

Method for reaching consensus

Consensus about the recommendations was reached by a step-wise approach. First, task force members met at the EFNS congresses in 2007 and 2008 to discuss the preparations of the guidelines. In a second step, experts in the field of genetics of neuromuscular disorders and myopathies wrote a guideline proposal. In a third step, these recommendations were distributed and discussed in detail amongst all task force members until a final consensus had been reached.

Results and recommendations

Recommendations follow the criteria established by the EFNS [3], with some modifications to account for the specific nature of genetic tests. Because genetic testing is by definition the gold standard to diagnose a genetically defined disease, its diagnostic accuracy cannot be tested against another diagnostic method. Therefore, the level of recommendations will be based on the quality of available studies [3], which investigate the proportion of cases of a clinically defined group of patients that are explained by a specific molecular diagnostic test. As nearly all of these studies have a retrospective design and look for a specific mutation in a previously ascertained and clinically diagnosed cohort of patients, the highest achievable recommendation level will be B [3]. If only small case-series studying genotype–phenotype correlations are available, the level of recommendation will be C. If only case reports could be found, but experts still felt that they could give a recommendation, the level of recommendation was assessed as 'good practice point'. The more frequent genes have been included in the article (Tables 1–3), whilst a more comprehensive list of known genes is included in supplementary material online (Appendix 1–3).

Molecular diagnosis of motoneuron diseases

Amyotrophic lateral sclerosis

Familial forms are presented by 5–10% of cases with amyotrophic lateral sclerosis (ALS). ALS-1 is the most common one, represents about 12–23% of familial ALS and is caused by mutations in the gene for superoxide dismutase 1 (*SOD1*) on chromosome 21q21–22 (Table 1). Additionally, about 1–4% of sporadic ALS cases carry *SOD1* mutations. So far, some 158 mutations have been identified in the *SOD1 gene*, of which 142 are believed to be pathogenic. All other forms of monogenetic ALS are rare (Appendix 1) [4]. Juvenile forms of ALS have been characterized as ALS-2, ALS-4, ALS-5 and ALS-X. *SOD1* mutations may be inherited as an autosomal dominant trait with complete or incomplete penetrance, as an autosomal recessive disease or as a *de novo* mutation, with some degree of genotype–phenotype correlation [5]. Hereditary forms of ALS show equal gender distribution, tend to start earlier than sporadic ALS (mean age 46 vs. 60 years) and initially present with bulbar signs in 20–30% of cases but are otherwise clinically indistinguishable from sporadic ALS. ALS may be coincident with frontotemporal dementia (FTD) in 5–15% of cases. Different loci for ALS-FTD including genes involving the tau metabolism have been identified to provide susceptibility to ALS (Table 1 and Appendix 1) [6]. At present, there is no specific therapy for patients with *SOD1* gene mutations. A number of specific phase 1 clinical trials in patients with SOD1 gene mutations are in progress to modulate *SOD1* gene expression.

Proximal spinal muscular atrophy

Proximal spinal muscular atrophy (SMA) is one of the most common and severe autosomal-recessive diseases of children. The frequency is between 1:8000 and 1:10000. The pathology involves dysfunction and loss of anterior horn cells, leading to muscle atrophy and weakness. Four forms of SMA are recognized (Table 2): SMA I (infantile, Werdnig-Hoffmann type), II (intermediate type), III (juvenile, Kugelberg-Welander type) and IV (adult type). Early onset forms (SMA I–III) are frequently caused by a homozygous deletion of exon 7 of the telomeric copy of the survival motor neuron gene (*SMN1*). In the remaining 2–5% of cases, the disease is caused by point mutations or small deletions or insertions in this gene. Most of these cases are compound heterozygotes with the common *SMN1* deletion on one chromosome and another mutation on its homologue. Spinal muscular atrophy with

Table 1 Genetic subtypes amyotrophic lateral sclerosis (ALS) (except rare forms: see Appendix 1)

Disease	Inheritance	Chromosomal position	Gene product	Frequency and ethnicity	Molecular diagnosis	Age at onset (years)	Remarks	OMIM
ALS 1	AD AR	21q	SOD1	Most common autosomal dominant form, 6% of all ALS cases	B	Mean: 46–48 Range: 6–94	Incomplete penetrance with some mutations	105400
ALS 5	AR	15q15	Unknown	Most common autosomal recessive form	D	10–20	Predominant lower motor neuron, late bulbar involvement	602099
ALS 9	AD	14q11	Angiogenin	Most identified in Irish, Italian and Scottish families	C	27–76		611895
ALS-FTD	AD	17q21	*MAPT*		C		Frontotemporal dementia and Parkinsonism more common than ALS	600274
FTLDU	AD	17q21	Progranulin	> 150 families	C	35–87	Prominent frontotemporal dementia, mild parkinsonism, ALS rare	607485

AD, autosomal dominant; AR, autosomal recessive; *MAPT*, microtubule-associated protein tau; *SOD1*, superoxide dismutase 1; FTD, frontotemporal dementia.

Availability of molecular diagnosis:

A: Routine procedure, commercially available, results usually within 4 weeks.

B: Routine procedure but may be time-consuming and expensive, usually because of occurrence of multiple mutations; results may take several months.

C: Usually available only within research setting.

D: Not yet available.

respiratory distress (SMARD1) [7], with mutations in the immunoglobulin mu binding protein 2 gene (*IGHMBP2*) and other forms of SMA significantly overlap with distal hereditary motor neuropathy (see below).

Spinal and bulbar muscular atrophy (SBMA), Kennedy disease

Spinal and bulbar muscular atrophy is an X-linked recessive disorder, affecting males with progressive limb and bulbar weakness, fasciculations (in particular on the chin and periorally, where fasciculations are rarely seen in ALS and SMA type IV) and muscle wasting. Patients have variable involvement of the lower motor and sensory neurons and endocrine systems, including diabetes mellitus, gynecomastia and reduced fertility. Motor deficits mimic those of ALS and dominate the clinical presentation. The main difference is the absence of upper motor neuron involvement, a rather benign course of the disease and the X-linked inheritance in SBMA [8]. SBMA is caused by the expansion of a CAG trinucleotide repeat in the first exon of the androgen receptor (AR) gene (abnormal range ≥35 repeats; normal alleles 9–34 repeats).

Recommendations

Currently, molecular diagnosis mainly has implications for genetic counseling rather than for therapy. However, when more directed causal therapies become available in the future, establishing a correct genetic diagnosis in a given patient will be essential. Despite the rather low prevalence sequencing of the small *SOD1* gene should be considered in patients with ALS with dominant inheritance to offer presymptomatic or prenatal diagnosis, if this is requested by the family (Level B). Screening for *SMN1* deletions is indicated in SMA I-III to confirm the diagnosis and provide genetic counseling (Level B). In patients with spinal muscular atrophies with respiratory distress, starting in the first months of life sequencing of *IGHMBP2* is probably to provide a molecular diagnosis (Level C). In adult-onset SMA, genetic testing for SBMA should be considered in males with bulbar manifestations, gynecomastia and X-linked inheritance (Level B).

Table 2 Genetics of spinal muscular atrophy (SMA)

Disease	Inheritance	Chromosomal position	Gene product	Frequency and ethnicity	Molecular diagnosis	Age at onset (years)	Remarks	OMIM number
Spinal muscular atrophy SMA I (Werdnig-Hoffmann): SMA II: (intermediate form): SMA III (Kugelberg-Welander)	AR	5q11.2–13	Survival motoneuron (SMN1)	Common	A	SMA I: infantile SMA II:: 0–3 SMA III : 3–30	Deletion of the SMN1 gene	253300 253400
SMA IV (adult form)	?	Unknown	Unknown		D	SMA: >30	Rarely deletions of SMN1	271150
Spinal and bulbar muscular atrophy (SBMA), Kennedy disease	X-linked	Xq11-q12	Androgen receptor		A	20–50	CAG repeat expansion	313200
Spinal muscular atrophy with respiratory distress (SMARD1)	AR	11q13	IGHMBP2	>50 families	B	Congenital – 2 months	Allelic with dHMN6	604320

AD, autosomal dominant; AR, autosomal recessive.

Availability of molecular diagnosis:

A: Routine procedure, commercially available, results usually within 4 weeks.

B: Routine procedure but may be time-consuming and expensive, usually because of occurrence of multiple mutations; results may take several months.

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D: Not yet available.

Molecular diagnosis of inherited neuropathies

Introduction

Inherited peripheral neuropathies form a clinically and genetically heterogeneous group of disorders, which together are the most common inherited neuromuscular diseases and has an estimated prevalence of 1 in 2500 [9]. Based on clinical observations, they can be classified into four main categories: the Hereditary Motor and Sensory Neuropathy (HMSN, or CMT after the first describers Charcot, Marie and Tooth), characterized by progressive distal weakness and atrophy, with gait disorder, areflexia and sensory loss with a distal to proximal gradient, distal hereditary motor neuropathy (HMN), hereditary sensory and autonomic neuropathy (HSAN) and the hereditary episodic neuropathies. In total, up to 40 genes have been identified causing the different variants of hereditary neuropathy (Table 3 with the most common forms and Appendix 2. See also http://www.molgen.ua.ac.be/CMTMutations/). In general, AR mutations lead to loss-of-function. However, in AD forms, many of the mutated proteins result in a toxic gain of function that cannot be deduced directly from the normal function of the gene product. Several genes encode ubiquitously expressed proteins raising the question how mutations cause such selective damage to the peripheral nervous system. Nonetheless, some common pathways are emerging: structural myelin proteins, protein synthesis, protein sorting and degradation, transport and cytoskeleton, mitochondrial dynamics, RNA/DNA metabolism and nerve growth regulation [10].

Charcot-Marie-Tooth Disease

Disease onset in CMT is usually in the first two decades of life, and progression is slow resulting in mild to moderate impairment. The motor nerve conduction velocity (NCV) in the median nerve is markedly reduced (<38 m/s) in demyelinating CMT (CMT1) and normal or only slightly decreased in axonal CMT (CMT2) in which decreased amplitudes of the compound muscle action potentials are found. In addition, intermediate forms have been described displaying overlap between CMT1 and CMT2. Inheritance can be autosomal (mostly dominant in non-consanguineous families and outbred populations) and X-linked. *De novo* mutations seem to be frequent, up to one-third of patients depending on the series [11]. In general, recessive is rarer than dominant inheritance and is related to a more severe course of the disease with onset in early infancy, delayed motor milestones, loss of ambulation and variable associated signs [12]. Disease onset and severity shows considerable variability. The most early and severe form is the rare congenital hypomyelinating neuropathy in which disease starts shortly after birth with hypotonia and muscle wasting resulting in feeding and breathing difficulties and sometimes in premature death. Another, severe phenotype known as Déjerine-Sottas Neuropathy has an early infantile onset. Several additional features can be

Table 3 Genetics of the most frequent hereditary neuropathies (rare forms: see Appendix 2)

Gene	Gene product	Locus	Phenotype	Additional features	Alternative phentoypes	OMIM
Charcot-Marie Tooth (CMT)						
Demyelinating forms (CMT1) – autosomal dominant (AD)						
*PMP22 duplication/point mutation**	Peripheral myelin protein 22	17p11.2	CMT1A		HNPP (deletion)	601097
*MPZ**	Myelin protein zero	1q22	CMT1B, CMT1E	Late onset (axonal forms), pupillary abnormalities (CMT2J)	Axonal (CMT2I, CMT2J) and intermediate (CMTDI3)	159440
Axonal forms (CMT2) – autosomal dominant (AD)						
*MFN2**	Mitofusin 2	1p36.2	CMT2A2	Optic atrophy, pyramidal tract signs		608507
X-linked forms (CMTX)						
*GJB1**	Gap junction-associated protein B1	Xq13.1	CMTX1	More severe phenotype in males (demyelinating)		304040
Inherited focal episodic neuropathies						
*PMP22 deletion**	Peripheral myelin protein 22	17p11.2	HNPP		CMT1A (duplication)	162500
SEPT9	Septin-9	17q25	HNA			604061

*Genes offered as routine genetic diagnostics.
HNPP, hereditary neuropathy with liability to pressure palsies; HNA, hereditary neuralgic amyotrophy.

present in certain subforms of CMT that can sometimes help to guide molecular diagnosis e.g., vocal cord paralysis, cranial nerve involvement, upper limb predominance, pyramidal tract signs, optic atrophy etc. [13].

Information on gene and mutation distribution in the different forms of hereditary neuropathy to be used for guideline formulation is based on a limited number of studies. The most common form, CMT1A, is caused by a duplication of the *PMP22* gene on chromosome 17 (Table 3) and accounts for 43% of all CMT cases and up to 70% of AD CMT1 [11]. The high frequency of *de novo* duplication/deletions on chromosome 17 stresses the importance of suspicion of genetic disease in isolated patients with compatible phenotype. The second most common genotype corresponds to mutations in *GJB1* (Table 3) causing X-linked CMT found in approximately 10% of all patients with CMT [14]. Point mutations in *MPZ* and *PMP22* correspond to 5% and 2.5% of patients with CMT1, respectively. CMT2 accounts for at least 1/3 of hereditary neuropathies with CMT2A2 caused by mutations in *MFN2* (Table 3) representing 20–30% in the CMT2 subgroup [15]. In a smaller proportion of patients mutations in *GJB1* and *MPZ* can be found [11]. In the intermediate forms of CMT *GJB1* and *MPZ* are the most likely genes to be involved. Mutations in other genes than those described earlier are only reported in a small minority of patients and reliable population data are lacking (Appendix 2), overall a molecular diagnosis can be made in as much as 65% of adults with a CMT phenotype by performing *PMP22* duplication and *GJB1* mutation analysis. This number rises to 80% in patients with demyelinating CMT [11].

Given the rarity of AR CMT in the European population routine diagnostic screening of the many known genes is currently not feasible (see Appendix 2 for a comprehensive listing). Most patients are isolated because of small size of kinships making the distinction with *de novo* mutations or reduced penetrance in AD CMT very difficult. Molecular diagnosis can be guided by the presence of particular clinical, neuropathological and electrophysiological features [12]. In more selected consanguineous populations, the relative proportion of AR CMT is substantially higher thus potentially increasing the yield of mutation screening in recessive genes, even if data on the relative frequency of each subform are still lacking [12].

Hereditary motor neuropathy

Hereditary motor neuropathy is a mostly AD, rare pure peripheral motor disorder with a distal predominance, accounting for 10% of all hereditary neuropathies. It is sometimes accompanied by pyramidal tract signs, vocal cord paralysis or hand predilection. Nerve conduction studies are indicative of an axonal neuropathy more or less selectively affecting the motor nerves [16].

Two mutations in exon 3 of *BSCL2* (Seipin) have been found in HMN, and this is with 7% the most frequently mutated gene in this disorder (Appendix 2). Mutations are found in 15% of the patients presenting with accompanying pyramidal tract involvement [17].

Hereditary sensory-autonomic neuropathy

HSAN is characterized by variable sensory and autonomic symptoms because of selective degeneration of peripheral sensory and autonomic neurons. Hallmark features are progressive sensory loss with marked insensitivity to pain, skin changes with chronic ulceration and even more severe complications such as osteomyelitis necessitating amputations [18].

Limited information is available on gene and mutations distribution in HSAN (Appendix 2). In a recently performed study, the cumulative mutation frequency in all known genes for a large cohort of patients with HSAN was 19% [19]. Mutations in *NTRK1* (Neurotrophic tyrosine kinase receptor type 1) correspond to a very specific and homogenous phenotype, congenital insensitivity to pain with anhidrosis (CIPA). Mutations in *RAB7* can be found in CMT2B, a motor and sensory neuropathy that is often considered to be part of the spectrum of HSAN because of the pronounced sensory abnormalities and associated ulceromutilations (Appendix 2). *RAB7* (Ras-Associated protein Rab7) and *NTRK1* mutations account each for 7% of patients in selected cohort [19].

Recurrent focal neuropathies

A final subgroup consists of hereditary recurrent focal neuropathies[20], including hereditary neuropathy with liability to pressure palsies (HNPP), related to CMT1 and because of a deletion in the same region of chromosome 17, and hereditary neuralgic amyotrophy (HNA) with recurrent attacks of pain, weakness and sensory disturbances following the distribution of the brachial plexus. Both present with an AD inheritance.

Hereditary neuropathy with liability to pressure palsies is a genetically homogeneous disorder. The overwhelming majority of patients with a clinically established diagnosis of HNPP carry the *PMP22* deletion on chromosome 17 (Table 3). Rare patients with loss-of-function point mutations in *PMP22* can also be found [20]. Mutations in *SEPT9* (Septin 9) are known to cause HNA (Appendix 2). However, this disorder is genetically heterogeneous because several families have been reported that do not map to the locus harboring this gene [20]. No population data are available for HNA.

Recommendations

Diagnosis in hereditary neuropathies is based on patient and family history (including ethnicity) and clinical examination revealing the various hallmarks of neuropathy such as gait disturbance, foot deformities (e.g. *pes cavus* and hammertoes), distal atrophy, weakness and sensory loss in lower and upper limbs and areflexia. It is important to pay special attention to additional and unusual features, since they may point at a specific genetic disorder. Nerve conduction studies differentiating the predominant phenotypes (i.e. motor or sensory, axonal or demyelinating) are essential to orient molecular genetic analyses. Concentric needle EMG recordings are usually indicative of chronic neurogenic changes and may help to distinguish between HMN and distal myopathies. Although the distinction between different disease entities is not always straightforward, most patients can be assigned to one of the categories described earlier.

Currently, molecular genetic testing can be offered for several of the more prevalent CMT genes. There are numerous rare genes (especially for AR forms) for which analysis is unlikely to be offered on a routine basis. Screening of these genes is usually restricted to a handful of research laboratories.

In patients presenting with CMT1, *PMP22* duplication should be examined first followed by sequencing of *GJB1* (in case no male to male transmission is present), *MPZ* and *PMP22* (level B). In the case of CMT2, *MFN2* is the first gene to be screened followed by *MPZ* because a limited number of specific mutations in this gene are known to cause axonal CMT (level B). Mutations in GJB1, especially in women also often present as CMT2. In patients with intermediate CMT, *GJB1* and *MPZ* should be screened (level B).

Hereditary neuropathy with liability to pressure palsies caused by a *PMP22* deletion on chromosome 17 is investigated simultaneously with the screening for *PMP22* duplication (CMT1A) and is thus offered as a routine diagnostic procedure (level B).

Both for HMN and HSAN overall mutation frequencies are too low to make routine diagnostic screening feasible. If screenings are conducted, *BSCL2* is the first candidate to screen in HMN [17], for HSAN, *NTRK1* can be screened in CIPA patients and *RAB7* in patients with CMT2B [19] (level B). The *SEPT9* gene is not part of routine diagnostics but could be screened in the context of HNA (level C).

Molecular diagnosis of myopathies

Introduction

During the last couple of years, a tremendous increase of data on numerous hereditary myopathies has taken place. Besides for the most common hereditary myopathies, prevalence data on the involvement of different genes in different populations are not yet known. In general, the clinical diagnosis can be complemented by

quite precise morphological and protein expression data during muscle biopsy, suggesting a particular gene being involved. Regularly, actualized tables can be found online: http://www.musclegenetable.org/.

Muscle dystrophies

Duchenne/Becker muscular dystrophy (DMD/BMD)
Duchenne/Becker muscular dystrophy is an X-linked recessive condition (Table 4). The frequency of DMD is 1 in 3000 and BMD 1 in 20.000. The age of onset of DMD in most of the cases is below 5 years. Characteristic of the clinical features are progressive muscular weakness – mainly proximal, calf pseudohypertrophy, as well as markedly elevated serum creatine kinase. In BMD, the onset is later, and the course of the disease is generally milder, but there is a remarkable variability of clinical expression. Muscle biopsy demonstrates the typical dystrophic changes, with absence of dystrophin in DMD and variably decreased dystrophin in BMD. The dystrophin gene, which spans 2.4 Mb of DNA, is very large with 85 exons and maps to chromosome Xp21, shows deletions of variable size in approximately 60% of cases, duplications are found in 5–10%, and point mutations are responsible in the remainder.

In a typical case of a young patient with a clinical presentation suggestive of DMD or BMD including X-chromosomal inheritance, a molecular diagnosis can be carried out from blood DNA without the need of a biopsy. If a PCR-based assay for deletions is negative, it is worthwhile to perform dystrophin analysis based on immunohistochemistry and on immunoblot from a muscle biopsy. In the case of abnormal dystrophin expression more complex analysis, including multiplex ligation dependent probe amplification may lead to the diagnosis [21]. As there is a high probability of gonadal mosaicism, prenatal diagnosis is offered not only to the confirmed carriers but also to women who previously gave birth to affected boys (isolated cases), and DNA analysis has shown that they are not the carriers.

Facioscapulohumeral muscular dystrophy (FSHD)
Facioscapulohumeral muscular dystrophy is an autosomal dominant condition. The frequency is 1:20.000 in the Netherland. Distribution of muscle weakness and wasting reveals descending progression involving the face, shoulder girdle, hip girdle and peroneal muscles [22].

The gene for FSHD is located on chromosome 4q35 (Table 4) but is still not known. In affected persons, Southern blots of DNA digested with EcoRI and probed with p13E-11 reveal a decreased fragment between 10 and 38 kb. This is probably because of a deletion of variable size in a 3.3-kb repetitive sequence (D_4Z_4). Interpretation of molecular studies in FSHD is not straightforward, because 30% of the subjects with the deletion are asymptomatic. Furthermore, there is a highly homologous polymorphic repeat on chromosome 10, with observations of exchange between the two chromosomes, and a bi-allelic variation on chromosome 4q35, which stresses the need of the use of more complex molecular methods to diagnose FSH. On the other hand, a deletion has been detected only in 95% of the patients affected with FSHD.

Myotonic dystrophy
Myotonic dystrophy is one of the most frequent muscular dystrophies affecting adults and children. Besides wasting and myotonia in skeletal muscles in a characteristic distribution (facial muscles, mostly temporal, masseter and sternocleidomastoid, as well as distal limb muscles) the disease also affects several other organ systems. Additional features are male baldness, often cataract, cognitive changes, hormonal disturbances, cardiomyopathy and visceral symptoms.

The genetic basis for DM1 is a CTG repeats expansion in the DMPK gene on 19q13 (Table 4). Normal alleles vary from 5 to 37 CTGs, 38–49 is considered as subclinical premutation, expansion over 50 is usually associated with clinical manifestations.

DM2, another autosomal dominant disorder, closely resembles DM1 except that muscle weakness is predominantly proximal and less pronounced whilst hypertrophy of calves is frequent, has been described under the name of proximal myotonic myopathy (DM2). It is caused by an expansion of CCTG repeats in the zinc finger protein-9, which can be directly examined in typical cases, or in DM cases without CTG expansion in the DMPK gene (Table 4).

Emery-Dreifuss type muscular dystrophy.
The clinical features are joint contractures mostly in elbows, knees, ankles, neck; moderate weakness and wasting of muscles, mostly of a proximal distribution in the upper extremities and a distal pattern in the legs; cardiac symptoms also occur. The first symptoms start usually in childhood as contractures. Cardiac symptoms may occur, also in otherwise asymptomatic heterozygous female carriers.

The disease is genetically heterogeneous – the main mode of transmission is X-linked (Table 4 and Appendix 3). In these cases, deletions are found in a small gene on Xq28 (Emerin). Most mutations are private, i.e. different in each affected family and complete sequencing is usually necessary.

Limb-girdle muscular dystrophies
The limb-girdle muscular dystrophies (LGMDs) form a group of genetically determined disorders with the

Table 4 Genetics of the myopathies (except rare forms: see Appendix 3)

Gene	Gene product	Locus	Phenotype	Additional features and/ or alternative phentoypes	OMIM
Muscular dystrophies					
X chromosomal					
DYS	Dystrophin	Xp21.2	Duchenne muscle dystrophy	Cardiomyopathy dilated Becker	310200
EMD	Emerin	Xq28	Emery Dreifuss muscle dystrophy		310300
Autosomal dominant (AD)					
DMPK	Myotonic dystrophy protein kinase	19q13.3	Myotonic dystrophy		160900
FSHD	Facioscapulohumeral muscular dystrophy	4q35	Facio scapulohumeral muscle dystrophy		158900
MYOT	Myotilin	5q31	LGMD1A	Myofibrillar myopathy	159000
CAV3	Caveolin-3	3p25	LGMD1C	Hyper-CK-emia, idiopathic Muscular dystrophy Rippling muscle disease	601253
Autosomal recessive (AR)					
CAPN3	Calpain3	15q15	LGMD2A		253600
DYSG	Dysferlin	2p13	LGMD2B	Miyoshi myopathy. Distal myopathy, with anterior tibial onset	603009
SGCG	γ-sarcoglycan	13q12	LGMD2C		253700
SGCA	α-sarcoglycan	17q12-q21.33	LGMD2D		600119
SGCB	β-sarcoglycan	4q12	LGMD2E		604286
SGCD	δ-sarcoglycan	5q33-q34	LGMD2F		601287
Congenital muscular dystrophies					
Autosomal dominant					
DNM2	Dynamin 2	19p13.2	Congenital muscular dystrophy with dynamin 2 defect	Charcot-Marie-Tooth disease, dominant intermediate B Myopathy, centronuclear, autosomal dominant	NA
Autosomal recessive					
TGA7	Integrin a7	12q	Integrin a7 deficiency		613204
LAMA2	Laminin a2 chain of merosin	6q22–q23	Merosin deficient CMD		607855
FKRP	Fukutin related protein	19q1	CMD + secondary merosin deficiency	Walker-Warburg syndrome	606612
FCMD	Fukutin	9q31-q33	Fukuyama congenital muscular dystrophy	Muscular dystrophy, limb-girdle, type 2L Walker-Warburg syndrome	253800
COL6A1	Alpha 1 type VI collagen	21q22.3	Ullrich Syndrome	Bethlem myopathy (also AD)	254090
Congenital myopathies					
Autosomal recessive					
TPM3	Tropomyosin 3	1q21–q23	Nemaline myopathy 1		609284
ACTA1	Alpha actin	1q42.13–q42.2	Nemaline myopathy 1	Congenital myopathy with excess of thin myofilaments congenital myopathy with fiber-type disproportion	161800
RYR1	Ryanodine receptor 1	19q13.1	Central core disease	Malignant hyperthermia susceptibility 1	117000
MYH7	Myosin, heavy polypeptide 7	14q12	Hyaline body myopathy	Cardiomyopathy, dilated Myopathy, distal 1 Myosin storage myopathy	608358
Autosomal recessive					
NEB	Nebulin	2q22	Nemaline myopathy 2		256030

Table 4 (*Continued*)

Gene	Gene product	Locus	Phenotype	Additional features and/or alternative phentoypes	OMIM
X chromosomal					
MTM1	Myotubularin	Xq28	Myotubular myopathy		310400
Distal myopathies					
Autosomal dominant					
TTN	Titin	2q31	Tibial muscular dystrophy	Cardiomyopathy, dilated, Udd Myopathy LGMD2J	600334
MYOT	Myotilin	5q31	Distal myopathy with myotilin defect	LGMD1A LGMD1	609200
DNM2	Dynamin 2	19p13.2	Dynamin2 related distal myopathy	Charcot-Marie-Tooth disease, dominant intermediate B Myopathy, centronuclear, autosomal dominant	160150
Autosomal recessive					
DYSF	Dysferlin	2p12–14	Distal recessive myopathy	Miyoshi myopathy LGMD2B	254130
Myofibrillar myopathies					
Autosomal dominant					
DES	Desmin	2q35	Myofibrillar myopathy, desmin-related myopathy		601419
PABP2	Poly(A) binding protein 2	14q11.2–q13	Oculopharyngeal muscle dystrohy		164300

LGMD, limb-girdle muscle dystrophy, CMD, congenital muscular dystrophies.

common feature of a progressive proximal muscle weakness. The prevalence is about 1/15000 and varies amongst populations. There is a high variety of clinical phenotypes, with a large number of mutations in different genes described so far (Table 4 and Appendix 3). Four of the autosomal recessive inherited forms result from mutations in the genes coding for dystrophin-associated proteins, sarcoglycans (SG) $\alpha,\beta,\gamma,\delta$, and cardiac involvement is known. The subset of autosomal recessive LGMD without SG involvement is represented by several variants (Table 4 and Appendix 3). One of them is caused by mutations in the calpain 3 (*CANP3*) gene, another variant results from mutations in the dysferlin (*DYSF*) gene. In an autosomal dominant fashion, 5–10% of LGMDs are inherited. The prevalence of mutations in caveolin-3 (*CAV3*), the first gene to be known in this group, and the others is not known. Furthermore, overlap with other phenotypes and cardiac involvement has been well established. The first step in the molecular diagnosis of LGMD is to use a comprehensive panel of immunologic tests in the muscle biopsy. The absence or severe reduction in immunoreactivity using immunohistochemistry or immunoblot of one of the sarcoglycans will point at the most probably mutated gene, whilst a more subtle change may be secondary to the destabilization of the complex. If *SGs* appear normal, the use of antibodies recognizing *CANP3* and *DYSF* in muscles is recommended. Once the candidate has been recognized at the protein level, mutation search can be performed in a selective fashion.

Congenital muscular dystrophies

Several forms of variable muscle dystrophies with an autosomal recessive inheritance, manifesting early in life with a progressive variable phenotype including hypotonia, weakness, contractures, elevated creatine kinase and dystrophic features at muscle biopsy are usually grouped as congenital muscular dystrophies. So far 13 forms of congenital muscular dystrophies (CMD) with overlapping phenotypes have been genetically characterized (Table 4 and Appendix 3). In a typical mixed cohort of patients, less than half could be diagnosed at the molecular level, using immunologic studies of muscle protein and molecular genetic testing [23].

Congenital myopathies

This is a large group of rare diseases having as common clinical denominator congenital floppiness, muscle weakness, slimness, frequent skeletal dysmorphism. The usually slowly progressive clinical phenotype is variable and overlapping amongst the different forms, including central-core disease, multi minicore disease, congenital fiber type disproportion and newly described entities like actin aggregate myopathy or desmin myopathy (Table 4 and Appendix 3). The diagnosis is based on specific morphological abnormalities found in the muscle biopsy.

Central core disease (CCD) (Table 4) is transmitted as autosomal dominant trait. The characteristic feature of muscle histopathology is an amorphous area in the

center of the fiber. CCD is caused by mutations in the ryanodine receptor on chromosome 19q13 and is allelic (different mutations in a single gene) to one form of malignant hyperthermia susceptibility (MHS). Patients with CCD are at risk for malignant hyperthermia and both conditions may appear in the same family. MHS is genetically heterogeneous. It has been estimated that approximately 50% of cases are due to mutations in the ryanodine receptor. Identification of a particular mutation in a family with an individual known to be susceptible to malignant hyperthermia may be helpful to counsel family members and obviate a muscle biopsy.

The characteristic histopathological feature of nemaline myopathy (Table 4) is the presence of small rods, originating from the Z-band of the muscle fiber, staining red by the Gomori technique. The disease is transmitted as an autosomal recessive (maps to 2q21.2–2q22) or autosomal dominant trait (maps to 1q 21–23). The gene product is α-tropomyosin. The course is quite variable with very severe, usually lethal neonatal, childhood and adult forms.

In myotubular or centronuclear myopathy (Table 4), the nuclei are situated centrally, surrounded by a pale halo. The muscle fibers show signs of immaturity. There are several different forms of myotubular myopathy, including X-linked (mapped to Xq28), recessive and autosomal dominant forms. Actin or desmin aggregates are demonstrated in the muscle biopsy.

Other myopathies

Distal myopathies form a group of mainly muscular dystrophies with dorsal or ventral involvement of distal upper and lower extremities. The incidence is regionally variable, and the age of onset is typically in adulthood. The phenotype may overlap with other myopathies, and vacuoles are commonly found at muscle biopsy. Myofibrillar myopathies are characterized by specific cytoplasmatic inclusions. Similar to other hereditary myopathies, morphological features complement clinical phenotype description to guide molecular diagnostics (Table 4 and Appendix 3).

Recommendations

In patients with certain distinctive phenotypes, and a suggestive family history, a molecular diagnosis can be made without additional investigations, this includes a male patient with muscular dystrophy, whose uncle had a similar phenotype, a patient with the typical presentation of a myotonic dystrophy or of a facio-scapulohumeral dystrophy. In such cases, an analysis of the respective gene should be performed without a muscle biopsy (level B). In limb-girdle dystrophies, in congenital dystrophies and in congenital myopathies, a biopsy is needed to collect data on the morphological and molecular phenotype through microscopical and protein expression analysis. This data will then guide the choice of the appropriate gene testing (level B).

Conflicts of interest

Member of this Task Force have no conflicts of interest related to the recommendations given in this article.

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Appendix 1 Genetic subtypes of amyotrophic lateral sclerosis (ALS)

Disease	Inheritance	Chromosomal position	Gene product	Frequency and ethnicity	Molecular diagnosis	Age at onset [years]	Remarks	OMIM number
ALS 1	AD AR	21q	SOD1	Most common autosomal dominant form, 6% of all ALS cases	B	Mean: 46–48 Range: 6–94	Incomplete penetrance with some mutations	105400
ALS 2	AR	2q33	Alsin	Very rare.	B	Mostly < 10; rarely up to 60	Predominant spasticity with a PLS/HSP phenotype, rarely ALS; long survival	205100
ALS 3	AD	18q21	Unknown	1 French family	D	Mean : 45		606640
ALS 4	AD	9q34	Senataxin		B	6–21	Allelic with ataxia with ocular apraxia type 2	602433
ALS 5	AR	15q15	Unknown	Most common autosomal recessive form	D	10–20	Predominant lower motor neuron, late bulbar involvement	602099
ALS 6	AD	16q12	Unknown	4 families in Europe and US	D	29 – 70	Variable penetrance	608030
ALS 7	AD	20p13	Unknown	1 family	D	Mean: 57		608031
ALS 8	AD	20q13	VAPB	7 Brasilian families	B	25 – 55	Allelic with proximal SMA of adult onset	608627
ALS 9	AD	14q11	Angiogenin	Most identified in Irish, Italian and Scottish families	C	27 – 76		611895
ALS10	AD	1p36	TDP-43/ TARDBP	Rare (< 1%?). Caucasian and Chinese families	C	41 – 72		612069
ALS X	X-linked	Xp11–q12	Unknown	1 unreported family	D	10 – 50	Prominent bulbar and pseudobulbar dysfunction	
ALS-FTD 1	AD	9q21–q22	Unknown	2 families	D	40 – 62	Frontotemporal dementia	105550
ALS-FTD 2	AD	9p21–p13	Unknown	Canadian, Dutch and Scandinavian families	D	39 – 72	Frontotemporal dementia mixed with ALS	611454
ALS-FTD 3	?	3p11	CHMP2B	single large Danish family		46 – 65	Frontotemporal dementia	600795
ALS-FTD	AD	17q21	MAPT				Frontotemporal dementia and Parkinsonism more common than ALS	600274
FTLDU	AD	17q21	Progranulin	> 150 families		35 – 87	Prominent frontotemporal dementia, mild parkinsonism, ALS rare	607485
ALS susceptibility	?	15q21	TRPM7	Guam			ALS-Parkinsonism-Dementia Complex	105500
ALS susceptibility	?	2p13	Dynactin-1					601143
ALS susceptibility	?	22q12	Neurofilament heavy chain					162230
ALS susceptibility	?	12q12	Peripherin					170710

AD, autosomal dominant; AR, autosomal recessive.

Availability of molecular diagnosis:

A: Routine procedure, commercially available, results usually within 4 weeks.

B: Routine procedure, but may be time-consuming and expensive, usually due to occurrence of multiple mutations; results may take several months.

C: Usually available only within research setting.

D: Not yet available.

Appendix 2 Genetics of neuropathies

Gene	Gene product	Locus	Phenotype	Additional features	Alternative phentoypes	OMIM
Charcot-Marie Tooth (CMT)						
Demyelinating forms (CMT1) – autosomal dominant (AD)						
*PMP22 duplication/ point mutation**	Peripheral myelin protein 22	17p11.2	CMT1A		HNPP (deletion)	601097
*MPZ**	Myelin Protein Zero	1q22	CMT1B, CMT1E	Late onset (axonal forms), pupillary abnormalities (CMT2J)	Axonal (CMT2I, CMT2J) and intermediate (CMTDI3)	159440
LITAF	LPS-induced TNFα factor	16p13.3–p12	CMT1C			603795
EGR2	Early Growth Response 2	10q21.1–q22.1	CMT1D	Early onset	AR (CMT4E)	129010
NEFL	Neurofilament Light chain	8p21	CMT1F		Axonal (CMT2E)	162280
ARHGEF10	Rho Guanine-Nucleotide Exchange Factor 10	8p23		Asymptomatic Hypo-myelination		608136
Demyelinating forms (CMT1) – autosomal recessive (AR)						
GDAP1	Ganglioside-Induced Differentiation Associated Protein 1	8q13–q21.1	CMT4A	Early onset, diaphragm and vocal cord paralysis	Axonal (CMT2K), intermediate (CMT RIA)	606598
MTMR2	Myotubularine-Related Protein 2	11q22	CMT4B	Myelin outfoldings, early onset		603557
MTMR13	Myotubularine-Related Protein 13	11p15	CMT4B2	Myelin outfoldings		607697
SH3TC2	SH3 and tetratricopeptide repeat domain 2	5q32	CMT4C	Severe scoliosis		608206
NDRG1	*N*-myc Downstream-Regulated Gene 1	8q24.3	CMT4D	Sensorineural deafness		605262
PRX	Periaxin	19q13.1–q13.2	CMT4F	Early onset, sensory ataxia		605725
HK1	Hexokinase 1	10q22	CMT4G (Russe)			142600
FGD4	FGD1-related F-actin binding protein	12p11.2	CMT4H	Early onset		611104
FIG4	SAC domain-containing inositol phosphatase 3	6q21	CMT4J	Early onset		609390
Axonal forms (CMT2) – autosomal dominant (AD)						
KIF1B	Kinesin Family Member 1B	1p36.2	CMT2A1	Single family		605995
*MFN2**	Mitofusin 2	1p36.2	CMT2A2	Optic atrophy, pyramidal tract signs		608507
RAB7	Ras-Associated protein Rab7	3q21	CMT2B	Severe sensory loss, ulcerations		602298

Appendix 2 (*Continued*)

Gene	Gene product	Locus	Phenotype	Additional features	Alternative phentoypes	OMIM
TRPV4	Transient Receptor Potential Vanilloid subfamily V, member 4	12q24	CMT2C	Vocal cord paralysis	SPSMA, congenital distal SMA	605427
GARS	glycyl-tRNA synthetase	7p15	CMT2D	Upper limb predominance	HMN V	600287
HSPB1	Small heat-shock protein B1	7q11.23	CMT2F		HMN II	602195
HSPB8	Small heat-shock protein B8	12q24	CMT2L		HMN II	608014
AARS	Alanyl-tRNA Synthetase	16q22	CMT2M			601065
Axonal forms (CMT2) – autosomal recessive (AR)						
LMNA	Lamin A/C	1q21.2	CMT2A		Laminopathies	150330
GAN	Gigaxonin	16q24.1	Giant axonal neuropathy	Early onset, mental retardation		605379
Intermediate forms – autosomal dominant (AD)						
DNM2	Dynamin 2	19p1219p13.2	CMT DIB		Centronuclear myopathy	602378
YARS	Tyrosyl-tRNA synthetase	1p35	CMT DIC			603623
X-linked forms (CMTX)						
*GJB1**	Gap Junction associated protein B1	Xq13.1	CMTX1	more severe phenotype in males (demyelinating)		304040
PRPS1	Phosphoribosylpyrophosphate synthetase I	Xq22–q24	CMTX5	Severe axonal phenotype with deafness and optic neuropathy		311850
HMN						
Autosomal dominant (AD)						
HSPB1	Small heat-shock protein B1	7q11.23	HMN II		CMT2F	602195
HSPB8	Small heat-shock protein B8	12q24	HMN II		CMT2L	608014
GARS	Glycyl-tRNA synthetase	7p15	HMN V	Upper limb predominance	CMT2D	600287
BSCL2	Seipin	11q13	HMN V	Pyramidal tract signs, upper limb predominance	Lipodystrophy, Silver syndrome	606158
DCTN1	Dynactin 1	2p13	HMN VII	Vocal cord paralysis		601143
SETX	Senataxin	9q34	HMN	Pyramidal tract signs	ALS4	608465
X-linked forms						
ATP7A	ATPase, Cu(2+)-transporting alpha polypeptide	Xq12–q13	SMAX3			300011

Appendix 2 (*Continued*)

Gene	Gene product	Locus	Phenotype	Additional features	Alternative phentoypes	OMIM
Autosomal recessive (AR)						
IGHMBP2	Immunoglobulin μ-binding protein 2	11q13.2–q13.4	HMN VI SMARD1	Early onset, respiratory distress		600502
PLEKHG5	Pleckstrin homology domain-containing family G member 5	1p36	DSMA4	Early onset		611101
HSAN						
Autosomal dominant (AD)						
SPTLC1	Serine palmitoyltransferase, long-chain base subunit 1	9q22.1–q22.3	HSN I	Lancinating pain, variable motor involvement		605712
Autosomal recessive (AR)						
HSN2	HSN2	12p13.3	HSN II	Early onset		608620
FAM134B	Family with sequence similarity 134, member B	5p15.1	HSN IIB	Early onset, mutilating ulcerations		613114
FAM134B	Family with sequence similarity 134, member B	5p15.1	HSN IIB	Early onset, mutilating ulcerations		613114
IKBKAP	Inhibitor of κ light polypeptide gene enhancer in B cells, kinase complex-associated protein	9q31	HSN III (Riley-Day syndrome)	Severe autonomic dysfunction, congenital onset		603722
NTRK1	Neurotrophic tyrosine kinase receptor type 1	1q21–q22	HSN IV	Congenital insensitivity to pain and anhydrosis		191315
NGFB	Nerve growth factor-β	1p13.1	HSN V	Congenital insensitivity to pain, fractures		162030
Inherited focal episodic neuropathies						
*PMP22 deletion**	Peripheral myelin protein 22	17p11.2	HNPP		CMT1A (duplication)	162500
SEPT9	Septin-9	17q25	HNA			604061

CMT RIA, recessive intermediate CMT type A; ALS 4, amyotrophic lateral sclerosis 4; SMARD, spinal muscular atrophy with respiratory distress; DSMA4, distal spinal muscular atrophy 4; *genes offered as routine genetic diagnostics.

Appendix 3 Genetics of myopathies

Gene	Gene product	Locus	Phenotype	Additional features and/or Alternative phentoypes	OMIM
Muscular dystrophies					
X chromosomal					
DYS	dystrophin	Xp21.2	Duchenne muscle dystrophy	Cardiomyopathy, dilated Becker	310200
EMD	emerin	Xq28	Emery Dreifuss muscle dystrophy		310300
FHL1	four and a half LIM domain 1	Xq26.3	Emery Dreifuss muscle dystrophy 6		300696
Autosomal dominant					
DMPK	myotonic dystrophy protein kinase	19q13.3	Myotonic dystrophy		160900
ZNF9	zinc finger protein 9	3q21	Myotonic dystrophy 2		602668
SYNE1	spectrin repeat containing nuclear envelope 1	6q25	Emery Dreifuss muscle dysrophy 4	Cerebellar ataxia, autosomal recessive, type 1 Spinocerebellar ataxia, autosomal recessive 8	612998
SYNE2	spectrin repeat containing nuclear envelope 2	14q23.2	Emery Dreifuss muscle dysrophy 5		612999
LMNA	lamin A/C	1q11.q23	Emery Dreifuss muscle dysrophy 2	Cardiomyopathy, dilated, 1A Charcot-Marie-Tooth disease, axonal, type 2B1 Muscular dystrophy, limb-girdle, type 1B	181350
FSHD	FSHD	4q35	Facio scapulohumeral muscle dystrophy		158900
MYOT	myotilin	5q31	LGMD1A	Myopathy myofibrillar	159000
LMNA	lamin A/C	1q21.2-q21.3	LGMD1B	cf EDMD2	159001
CAV3	caveolin-3	3p25	LGMD1C	Hyperckemia, idiopathic Muscular dystrophy Rippling muscle disease	607801
	Unknown	7q	LGMD1D		603511
	Unknown	6q23	LGMD1E	Cardiomyopathy, dilated, 1F	602067
	Unknown	7q32	LGMD1F		608423
	Unknown	4q21	LGMD1G		609115
Autosomal recessive					
LMNA	lamin A/C	1q21.2–q21.3	Emery Dreifuss muscle dystrophy 3	cf EDMD2	181350
CAPN3	calpain3	15q15	LGMD2A		253600
DYSG	dysferlin	2p13	LGMD2B	Miyoshi myopathy Myopathy, distal, with anterior tibial onset	603009
SGCG	γ-sarcoglycan	13q12	LGMD2C		253700
SGCA	α-sarcoglycan	17q12–q21.33	LGMD2D		600119
SGCB	β-sarcoglycan	4q12	LGMD2E		604286
SGCD	δ-sarcoglycan	5q33–q34	LGMD2F		601287
TCAP	Telethonin	17q11–q12	LGMD2G		601954
TRIM32	Tripartite motif-containing 32	9q31–q34.1	LGMD2H		254110
FKRP	Fukutin related protein	19q31–q34.1	LGMD2I	Muscle-eye-brain disease Muscular dystrophy, congenital, 1C Walker-Warburg syndrome	607155
TTN	titin	2q31	LGMD2J	Cardiomyopathy, dilated, Tibial muscular dystrophy, tardive	608807
POMT1	protein-*O*-mannosyltransferase 1	9q34.1	LGMD2K	Walker-Warburg syndrome	609308

Appendix 3 (*Continued*)

Gene	Gene product	Locus	Phenotype	Additional features and/or Alternative phentoypes	OMIM
ANO5	anoctamin 5	11p13–p12	LGMD2L		611307
FKTN	fukutin	9q31–q33	LGMD2M	Fukuyama congenital muscular dystrophy Walker-Warburg syndrome	611588
POMT2	protein-*O*-mannosyltransferase 2	14q24.3	LGMD2N		NA
POMGNT1	*O*-linked mannose beta1,2-*N*-acetylglucosaminyltransferase	1p34.1	LGMD2O	Muscle-eye-brain disease Walker-Warburg syndrome	NA
Congenital muscular dystrophies					
Autosomal dominant					
COL6A1	alpha 1 type VI collagen	21q22.3	Bethlem myopathy	Bethlem myopathy	158810
COL6A2	alpha 2 type VI collagen	21q22.3	Bethlem myopathy		158810
COL6A3	alpha 3 type VI collagen	2q37	Bethlem myopathy		158810
DNM2	dynamin 2	19p13.2	Congenital muscular dystrophy with dynamin 2 defect	Charcot-Marie-Tooth disease, dominant intermediate B Myopathy, centronuclear, autosomal dominant	NA
Autosomal recessive					
TGA7	integrin a7	12q	Integrin α7 deficiency		613204
LAMA2	laminin a2 chain of merosin	6q22–q23	MDC1A Merosin deficient CMD		607855
	Unknown	1q42	MDC1B CMD + secondary merosin deficiency		604801
FKRP	fukutin related protein	19q13.3	MDC1C CMD + secondary merosin deficiency	Walker-Warburg Syndrome	606612
LARGE	like-glycosyltransferase	9q31–q33	MDC1D Congenital muscular dystrophy with severe mental retardation		608840
FCMD	fukutin	9q31–q33	Fukuyama congenital muscular dystrophy	Muscular dystrophy, limb-girdle, type 2L Walker-Warburg syndrome	253800
POMT1	protein-*O*-mannosyltransferase 1	9q34.1	Walker-Warburg syndrome		236670
POMT2	protein-*O*-mannosyltransferase 2	14q24.3	Walker-Warburg syndrome		236670
POMGGnT	*O*-linked mannose beta1,2-*N*-acetylglucosaminyltransferase	1p34.1	Muscle-eye-brain disease	Walker-Warburg Syndrome	253280
SEPN1	Selenoprotein N1	1p36.13	Rigid spine syndrome	Desmin-related myopathy with Mallory bodies Minicore myopathy with external ophthalmoplegia - Minicore myopathy, severe classic form myopathy, congenital, with fiber-type disproportion	602771
COL6A1	alpha 1 type VI collagen	21q22.3	Ullrich Syndrome	Bethlem myopathy	254090
COL6A2	alpha 2 type VI collagen	21q22.3	Ullrich Syndrome		254090
COL6A3	alpha 3 type VI collagen	2q37	Ullrich Syndrome		254090
Congenital myopathies					
Autosomal dominant					
TPM3	tropomyosin 3	1q21–q23	NEM1 Nemaline myopathy 1		609284
ACTA1	alpha actin, skeletal muscle	1q42.13–q42.2	NEM3 Nemaline myopathy 3	congenital myopathy with excess of thin myofilaments congenital Myopathy with fiber-type disproportion	161800
TPM2	tropomyosin 2 (beta)	9p13.2–p13.1	NEM 4 Nemaline myopathy 4	arthrogryposis multiplex congenita,distal,type IA	

Appendix 3 (*Continued*)

Gene	Gene product	Locus	Phenotype	Additional features and/or Alternative phentoypes	OMIM
CAP disease	609285				
	Unknown	15q15–q25	NEM6 Nemaline myopathy 6		609273
DNM2	dynamin 2	19p13.2	Centronuclear myopathy	Charcot-Marie-Tooth disease, dominant intermediate B dynamin2 related distal myopathy	160150
RYR1	ryanodine receptor 1	19q13.1	Central core disease	Malignant hyperthermia susceptibility 1	117000
MYH7	myosin, heavy polypeptide 7, cardiac muscle, beta	14q12	Hyaline body myopathy	Cardiomyopathy, dilated Myopathy, distal 1 Myosin storage myopathy	608358
Autosomal recessive					
NEB	nebulin	2q22	NEM2 Nemaline myopathy 2		256030
TNNT1	slow troponin T	19q13.4	NEM5 Nemaline myopathy, Amish type		605355
CFL2	cofilin 2	14q12	NEM7 Nemaline myopathy 7		610687
SEPN1	selenoprotein N1	1p36.13	Myopathy, congenital, with fiber-type disproportion	Desmin-related myopathy with Mallory bodies Minicore myopathy with external ophthalmoplegia Minicore myopathy Rigid spine syndrome	255310
BIN1	amphiphysin	2q14	Centronuclear myopathy		601248
RYR1	ryanodine receptor 1	19q13.1	Central core disease	Malignant hyperthermia susceptibility 1	117000
	Unknown	3p22.2-p21.32	Hyalin body myopathy		255160
MYH7	myosin, heavy polypeptide 7, cardiac muscle, beta	14q12	Hyaline body myopathy	Cardiomyopathy, dilated Myopathy, distal 1 Myosin storage myopathy	608358
TRIM32	tripartite motif-containing 32	9q33.2	Sarcotubular myopathy	LGMD2H	
X chromosomal					
MTM1	myotubularin	Xq28	Myotubular myopathy		310400
Distal myopathies					
Autosomal dominant					
TTN	titin	2q31	Tibial muscular dystrophy	Cardiomyopathy, dilated, Udd Myopathy LGMD2J	600334
MYOT	myotilin	5q31	Distal myopathy with myotilin defect	LGMD1A LGMD1	609200
CAV3	caveolin 3	3p25	Distal myopathy with caveolin defect	cardiomyopathy, familial hypertrophic LGMD1C Rippling muscle disease	
LDB3	LIM domain binding 3	10q22	Late onset distal myopathy	cardiomyopathy, dilated myofibrillar myopathy ZASP-related	
DNM2	dynamin 2	19p13.2	Dynamin2 related distal myopathy	Charcot-Marie-Tooth disease, dominant intermediate B Myopathy, centronuclear, autosomal dominant	160150
Autosomal recessive					
DYSF	dysferlin	2p12–14	Distal recessive myopathy	Miyoshi myopathy LGMD2B	254130
GNE	UDP-N-acetylglucosamine-2- epimerase/*N*-acetylmannosamine kinase	9p13.3	IBM2 Hereditary inclusion body myopathy	Nonaka myopathy	600737

Appendix 3 (*Continued*)

Gene	Gene product	Locus	Phenotype	Additional features and/or Alternative phentoypes	OMIM
NEB	nebulin	2q22	Distal myopathy with nebulin defect		
Myofibrillar and other myopathies					
Autosomal dominant					
CRYAB	crystallin, alpha B	11q22.3–q23.1	Myofibrillar myopathy, alpha-B crystallin related		608810
DES	desmin	2q35	Myofibrillar myopathy, desmin-related myopathy		601419
SEPN1	selenoprotein N1	1p36.13	Desmin-related myopathy with Mallory bodies		602771
BAG3	BCL2-associated athanogene 3	10q25.2–q26.2	Myofibrillar myopathy with BAG3 defec		612954
PABP2	Poly(A) binding protein 2	14q11.2–q13	Oculopharyngeal muscle dystrohy		164300
TTN	titin	2q31	Edstrom myopathy		603689
X chromosomal					
FHL1	four and a half LIM domain 1	Xq26.3	Scapuloperoneal myopathy	x-linked myopathy with postural muscle atrophy Emery-Dreifuss muscular dystrophy, x-linked , type 2	300695

LGMD, limb-girdle muscle dystrophy.