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Phenotypes, genotypes, and prevalence of congenital myopathies older than 5 years in Denmark

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ABSTRACT

Objective: Congenital myopathy as a nosologic entity has long been recognized, but knowledge of overall and subtype prevalence and phenotype-genotype relationship is scarce, especially in the adult population.

Methods: A national cohort of 107 patients ≥5 years diagnosed with congenital myopathy were prospectively assessed clinically, histologically, and genetically.

Results: Twenty-five patients were excluded because of atypical features or alternative etiologies. The remaining 82 were on average 28 years old. Histologic examination revealed 14 (17%) with core disease, 15 (18%) centronuclear myopathy, 12 (15%) nemaline rods, 27 (33%) congenital fiber-type disproportion or type I predominance, and 14 (17%) nonspecific myopathic changes. Genetic etiology was identified in 46 patients (56.1%); 22.0% were heterozygous or compound heterozygous for mutations in *RYR1*, 7.3% had *DNM2* mutations, and 7.3% *NEB* mutations. Less than 5% had mutations in *ACTA1*, *TPM2/3*, *MTM1*, *TTN*, *SEPN1*, or *SC4NA*. A genetic cause was established in 83% with specific histology (cores/rods/centronuclear myopathy) vs 29% with unspecific histology. The detailed clinical examination found gene-dependent discrepancies in the pattern of muscle affection and walking ability. Although walking ability was delayed in patients with *ACTA1*, *TPM2/3*, and *RYR1* mutations, it was within normal limits in patients with *NEB* and *DNM2* mutations.

Conclusions: We found that overall, genetic and histologic prevalence of congenital myopathy in Denmark differs from previous retrospective reports. Less *RYR1* and more *DNM2* and *NEB* mutations and less core histology were present in our cohort. These differences may be explained by our prospective design, the older cohort of patients, and by differences in genetic background.

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GLOSSARY

CCD = central core disease; **CFTD** = congenital fiber-type disproportion; **CM** = congenital myopathy; **CMS** = congenital myasthenic syndrome; **CNM** = centronuclear myopathy; **DNM2** = dynamin 2; **HGMD** = Human Gene Mutation Database; **LGMD** = limb-girdle muscular dystrophy; **MRC** = Medical Research Council; **MTM1** = myotubularin 1; **NM** = nemaline myopathy; **RYR1** = ryanodine receptor 1; **SEPN1** = selenoprotein 1; **WES** = whole-exome sequencing.

Congenital myopathy (CM) has been recognized for decades, but the genetic cause is only established in about half of cases[1,2] and the knowledge of the distribution of genetic and histologic subtypes is insufficient. Data concerning CM have been collected retrospectively and mainly in pediatric patients.

The low genetic identification rate can partly be explained by undefined genes and by that some of the genes associated with CM[3–6] are very large, making analyses challenging. An uncertain relationship between the genotype and the clinical/histologic phenotype also hampers the identification of genetic etiology. CM is traditionally classified according to muscle histology into nemaline, core, or centronuclear myopathies (CNMs). It has become increasingly clear,

See editorial

From the Copenhagen Neuromuscular Center (N.W., J.V.), Department of Neurology, and Department of Clinical Genetics (U.W.), Rigshospitalet, University of Copenhagen; and The Danish National Rehabilitation Centre for Neuromuscular Diseases (M.D.), Aarhus, Denmark.

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however, that not only can CMs be associated with unspecific pathologies but the pathology and genotype are not mutually specific.[7] A better understanding of prevalence and relationship between phenotypes and genotypes is a prerequisite for patient care, corroboration genetic findings, and ultimately development of treatment. In Denmark, patients with CM are registered at 2 centers. We made use of this opportunity to prospectively evaluate phenotypes and genotypes in a national cohort with a diagnosis of CM.

METHODS

The study was conducted at the Copenhagen Neuromuscular Center, Rigshospitalet, Denmark, in collaboration with the Danish National Rehabilitation Centre for Neuromuscular Diseases. One hundred nineteen patients registered with a diagnosis of CM aged older than 5 years were invited. Two patients were not invited because of severe psychiatric comorbidity. The age limit of 5 years was chosen, as the functional tests used were not validated for younger patients and because we wanted to focus on older CMs. All participants completed questionnaires concerning symptoms and medical history. A neurologist (N.W.) and a physiotherapist (U.W.) examined all patients. Muscle strength was evaluated using a transformed 11-point Medical Research Council (MRC) scale (0–10).[8] Creatine kinase was assessed and DNA was isolated. After initial evaluation, participants with phenotypic characteristics atypical for CM (adult onset, fast progression, creatine kinase ≥600 U/L, dystrophy as the main histologic finding, or alternative disease explanation) were excluded. Participants with a CM phenotype, but other genetic etiology, were excluded in the course of the genetic evaluation.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethics committee (protocol H-C-2009-017), and all participants or their parents provided informed consent.

Genetic test strategy. All participants were tested sequentially for mutations in skeletal muscle alpha actin 1 (*ACTA1*) and tropomyosin 2+3 (*TPM2+3*) genes, as no definite histologic or clinical phenotypes are established for these genes, and the tests were readily available. Second-line analyses were directed by specific histologic or phenotypic findings. Core histology (central core disease [CCD]) elicited testing of the ryanodine receptor 1 (*RYR1*) gene and the selenoprotein 1 (*SEPN1*) gene. CNM or pronounced ophthalmoplegia leads to assessment of the genes dynamin 2 (*DNM2*), myotubularin 1 (*MTM1*), amphiphysin (*BIN1*), and *RYR1*. Rigid spine patients went through *SEPN1* testing. Pronounced contractures led to the investigation of collagen VI genes (not considered CM by the authors). The remaining unclassified patients were examined for aberrations in *NEB* and *RYR1*, and if no mutations were found, exome sequencing was performed in the majority (Broad Institute, Boston or Nijmegen University, Holland) with subsequent assessment of genes involved in myopathy.

Genetic analyses. DNA was isolated from blood. The exons and flanking sequences of *ACTA* (NM_001100.3), *TPM2* (NM_003289.3), and *TPM3* (NM_152263.2) were PCR amplified and Sanger sequenced using BigDye v1.1 on an ABI3130 sequencer. Analysis of *DNM2* is described elsewhere.[7] The *NEB* (NM_004543.4) and *RYR1* (NM_000540.2) genes were sequenced using a custom AmpliSeq targeting approach on an Ion PGM (Thermo Fisher). Areas with low (<30X) or missing coverage were Sanger sequenced. Data analysis was performed on the Torrent Suite v.3.6 or higher. All variants were confirmed by Sanger sequencing.

RESULTS

Participants. One hundred seven of the 119 invited participants were included (figure 1). Twenty-five were excluded, leaving a total of 82 in the study. Of the excluded, 14 displayed a phenotype inconsistent with CM; 3 of these were subsequently confirmed with limb-girdle muscular dystrophy, type 1C (LGMD1C), LGMD2L, and LGMD2A. Eleven had a phenotype compatible with CM, but an alternative genetic etiology was identified in 10, and DNA was missing in 1 (figure 1).

Prevalence and distribution of histology. Denmark has 5.4 million inhabitants older than 5 years. With 82 CM cases, prevalence is estimated to 2:100,000 in persons older than 5 years.

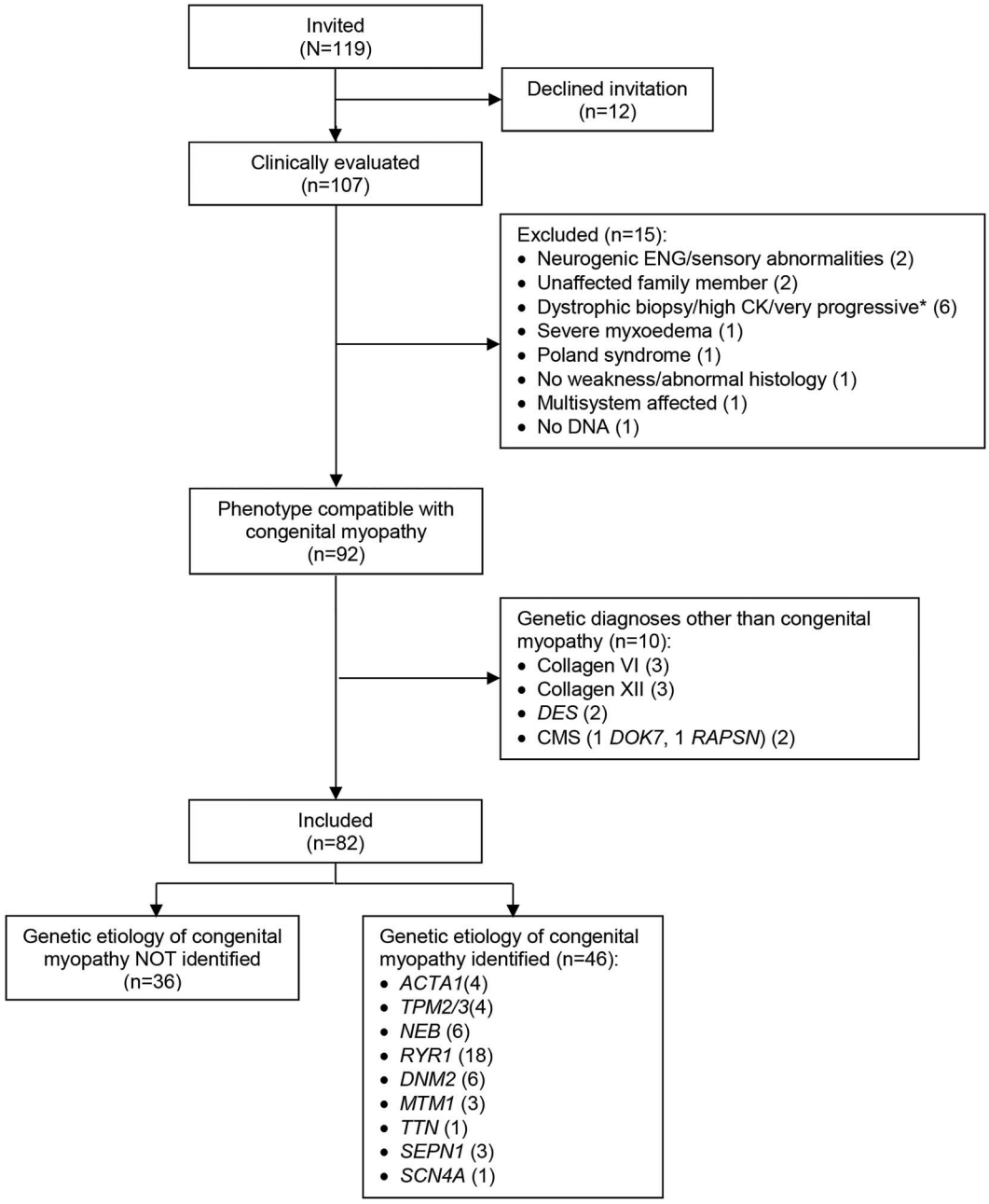
Forty-one had specific histology; 14 (17%) had cores (3 multimini core disease), 15 (18%) had CNM, and 12 (15%) nemaline myopathy (NM). The remaining 41 had more unspecific histology; 27 (33%) had congenital fiber-type disproportion (CFTD) or type I predominance (T1), and 14 (17%) had unspecific myopathic biopsies. In 2, biopsy material was unavailable (table 1).

Genetics. A genetic diagnosis was reached in 46 (56.1%) (tables 1 and 2). Eighteen had mutations in *RYR1* (22.0%) (13 heterozygous and 5 compound heterozygous), 6 had mutations in *DNM2*, and 6 in *NEB*. Three or less had mutations in *ACTA1*, *TPM2*, *TPM 3*, *MTM1*, *SEPN1*, *SCN4A*, or *TTN* genes (tables 1 and 3). Twenty-one participants had a particular clinical/histologic phenotype leading to a genetic diagnosis. Twenty-five patients had no clinical or histologic clues, and genetic etiology was identified by single gene testing in 20 and by whole-exome sequencing (WES) in 5; 3 with recessive *RYR1* mutations, 1 with mutation in *TTN*, and 1 with mutation in *SCN4A*.

The diagnostic yield was highly dependent on histologic findings (table 2); if only participants with cores, CNM, or NM were evaluated, a genetic etiology was identified in 83%. If CFTD/T1 were included, the number decreased to 63%.

A genetic etiology was identified in 3/14 (21%) with unspecific histology, 9/27 (33%) with CFTD/T1, 12/12 (100%) with NM, 9/14 (64%) with cores, and 13/15 (87%) of participants with CNM. CFTD and T1 were pooled, as these histologies coexisted in the same families.

Figure 1 Patient flow



ACTA1 = skeletal muscle α-actin 1; AD = autosomal dominant; AR = autosomal recessive; CK = creatine kinase; CMS = congenital myasthenic syndrome; *DES* = desmin; *DNM2* = dynamin 2; *DOK7* = downstream-of-kinase 7 myasthenic syndrome; LGMD = limb-girdle muscular dystrophy; *MTM1* = myotubularin 1; *NEB* = nebulin; *RAPSN* = receptor-associated protein of the synapse myasthenic syndrome; *RYR1* = ryanodine receptor 1; *SCN4A* = sodium channel 4A; *SEPN1* = selenoprotein 1; *TPM2/3* = tropomyosin 2/3; *TTN* = titin. *Of these 6, 1 had LGMD2L, 1 LGMD2A, and 1 LGMD1C.

The 10 participants with a phenotype compatible with CM, but alternative genetic etiology had collagen myopathy, desminopathy, or congenital myasthenic syndrome (CMS) (figure 1). Seven of 10 had unspecific or CFTD histology, whereas the remaining 3 had more specific histology: one with desminopathy had cores, another with desminopathy had rods, and one collagen VI had centronuclear changes (table 2).

The age of genetically unresolved (27.8 ± 16.7) and resolved (28.0 ± 14.6) patients was identical. The genetically unresolved had generally more unspecific histology and were less severely affected (tables 2 and 3).

Mutations. A total of 48 different mutations were identified of which 31 were listed in the Human Gene Mutation Database (HGMD) or ClinVar as pathogenic. The remaining 17 were absent from the

Table 1 Histologic findings vs genotype

	Proportion of histology		Proportion of gene identification		Genes										
	N	%	N	%	*ACTA1*	*TPM2*	*TPM3*	*NEB*	*ADRYR1*	*ARRYR1*	*DNM2*	*MTM1*	*SCN4A*	*TTN*	*SEPN1*
Unspecific histology (CFTD/T1/myopathy/fibrosis)	41	50	12	29											
Specific histology (ex CFTD)	41	50	34	83											
NM	12	15	12	100	3	2		6							1
Cores	14	17	9	64					8						1
CNM	15	18	13	87						3	6	3		1	
CFTD/T1	2	33	9	33	1		2		4	2					
Myopathy/fibrosis/NO	14	17	3	21					1				1		1
Sum/%	82	100	46		4.8	2.4	2.4	7.1	15.5	6.0	7.1	3.6	1.2	1.2	3.6

Abbreviations: *ACTA1* = skeletal muscle α-actin 1; AD = autosomal dominant; AR = autosomal recessive; CFTD = congenital fiber-type disproportion; CNM = centronuclear myopathy; *DNM2* = dynamin 2; *MTM1* = myotubularin 1; *NEB* = nebulin; NM = nemaline myopathy; NO = no report; *RYR1* = ryanodine receptor 1; *SCN4A* = sodium channel 4A; *SEPN1* = selenoprotein 1; TI = type I dominance; *TPM2/3* = tropomyosin 2/3; *TTN* = titin.
Congenital myopathy phenotype with noncongenital myopathy genetic etiology was excluded.

HGMD or ClinVar and to our knowledge have not been associated with disease before. Twelve of these were identified in recessively inherited disorder; 8 were predicted to result in premature stop codons or frameshifts and 4 were missense mutations. The 4 missense mutations were identified in SEPN1, RYR1, and SCN4A, respectively, where mutations very often are missense and were predicted to be potentially pathogenic by SIFT, PolyPhen2, AlignGVGD, and MutationTaster in silico prediction softwares and were absent from the ExAC database compiling information of more than 120,000 alleles (exac.broadinstitute.org), and from a Danish control cohort of 2000 WES.[9] Of the 4 variants, 2 were identified along with a known pathogenic mutation, whereas the remaining 2 were identified in SEPN1 in a patient with a clear clinical presentation of a selenoprotein deficiency. Where family members were available, segregation analyses were performed to conform a compound heterozygous state.

The remaining 5 novel variants were all missense variants in RYR1 located in the well-known hotspot region for the dominantly inherited *RYR1* disorder.[10]

Phenotypes. From the detailed muscle examination, some patterns of weakness could be recognized for particular genotypes (table 3, figure 2). The *ACTA1* patients were generally very weak in proximal, distal, and respiratory muscles, although 1 adult patient did not follow this pattern. By contrast, the *TPM2*/3 patients had few MRC measurements below 7, but despite this had the same decrease in respiratory function as the *ACTA1* patients. *NEB* patients typically had preferential affection of the shoulder girdle and pronounced ankle dorsiflexor weakness with MRC of just 1–2, but comparatively mild respiratory involvement. As expected, dominant and recessive *RYR1* patients differed in severity, with recessive patients being more severely affected. The *DNM2* patients had a relatively nonselective profile except a marked ankle weakness. The *MTM1* patients were more severely affected than the others, but hand function was relatively better than that in the *ACTA1* patients. The respiratory involvement in the *MTM1* and *SEPN1* patients exceeded that in all other groups. Finally, scoliosis was noted in the *SEPN1* patients, but otherwise only occasionally. Contractures were not prevalent, but were noted in some *NEB*, *RYR1*, *DNM2*, *MTM1*, *TTN*, and *SEPN1* patients (table 3). Ophthalmoplegia was confined to *DNM2* and *MTM1* and recessive *RYR1*. Ptosis was mostly seen in *DNM2* patients. Average time of walking ability was calculated in groups with more than 3 patients and exceeded the World Health Organization–defined normal limit of 18 months in patients with

Table 2 Chance of identifying genetic etiology according to histology

	Proportion of histology		Proportion of gene identification				
			CM gene		Non-CM gene		
	N	%	N	%	N	%	Genes
Unspecific histology (CFTD/T1/myopathy/fibrosis)	49		12	25	7	15	
Specific histology (ex CFTD)	44		34	77	3	7	
NM	13	14	12	92	1	8	*DES*
Cores	15	16	9	60	1	7	*DES*
CNM	16	17	13	81	1	6	*ColVI*
CFTD/T1	32	35	9	28	5	16	*2 ColVI, 3 ColXII*
Myopathy/fibrosis/NO	16	17	3	19	2	13	*1 DOK7, 1 RAPS*
Sum/%	92	100					

Abbreviations: CFTD = congenital fiber-type disproportion; CM = congenital myopathy; CNM = centronuclear myopathy; NM = nemaline myopathy; NO = no report; TI = type I dominance.
CM phenotype with noncongenital genetic etiology was included.

mutations in *ACTA1* (30 months), *TPM2/3* (20 months), and *RYR1* (21 months, 2 never walked), whereas patients with mutations in *NEB* (15 months) and *DNM2* (14 months) fell within normal development. Four patients (a genetically unresolved participant aged 26 years, 1 *DNM2* patient aged 69, an *RYR1* patient aged 55 years, and a *TTN* patients aged 13 years) died during the study period from 2009 until now.

Information on work history was available in 42 of the 46 genetically verified cases; 36 attended school or worked part or full time. The remaining 6 received pension. No participant had clinical evidence of cardiac involvement, and ECG performed in nearly all participants was unremarkable.

DISCUSSION The present study investigated patients with CM older than 5 years. As only survivors from the early childhood were included, the information gathered is helpful for health care personal caring for older children and adults because existing knowledge has been obtained preferentially from pediatric cohorts. The study is also a prospective, national study of phenotypes and genotypes in CM. Therefore, unlike previous retrospective studies, the study is less affected by selection bias and strengthened by a systematic data collection by just 1 neurologist and physiotherapist. The report presents new data on national prevalence, distribution of histologic subtypes and genotypes, and expands the description of phenotypic characteristics. Because of the relatively low number of participants, the data need confirmation.

We estimated a prevalence of 2:100,000. This is lower than most previous studies, which determined the prevalence by chart reviews or databases to about 4:100,000 and focused on the pediatric population.[11–13] The exclusion of children not surviving to 5 years in our study could account for some of the discrepancy. A previous study reported that 12% of their patients with CM died before the age of 6 years. Those patients had mutations in *ACTA1*, *MTM1*, or *KLHL40*.[2] Patients with mutations in those genes may therefore be underrepresented in our material if extrapolated to a general population. The total prevalence, however, is probably not much influenced by this, as we, compared to previous studies, have included more elderly persons and in that way "compensate" for the lack of young children. Another explanation for our lower prevalence estimate could be that the prospective evaluation in our study may have eliminated more wrongly diagnosed patients. This is, however, probably not the main explanation for the discrepancy, as most of the studies were very thorough in the attempt to avoid misdiagnosis.[11–13] Alternatively, our very stringent inclusion criteria may have omitted a few CMs with atypical features like high creatine kinase. Of the 15 excluded cases because of atypical features, however, 10 had definitely not CM, as alternative etiologies were identified or they turned out to be asymptomatic family members.

Citizens in Denmark are easily traceable, as they are centrally registered, and therefore, the lower prevalence in our study is not likely caused by problems in identifying patients. A number of inherited muscle diseases, such as some limb-girdle muscular dystrophies[14] and myotonic dystrophy type 2, differ markedly in prevalence in Denmark vs other countries, and this could also be the case for CMs. In support of this, CM has the same low prevalence in Northern England (1.37:100,000, including Bethlem myopathy

Table 3 Characteristics of patients with or without genetic diagnosis

ID/sex/age at examination, y	Gene/mutation	Protein consequence	Histology	Course	Walk, mo old	Ophthalmoplegia/ptoses	Face/voice/palate/facial palsy/neck	Limbs	FVC % exp	Contractures/scoliosis/other	Occupation
Genetically diagnosed patients											
ACTA1	NM_001100.3										
16/M/23	c.16 G>A	p.Glu6Lys	CFTD	→	24	N/N	Oblong/NV/H/F/StW, NK6	UL 7P, 9D, LL 7P = D	47		MD
42/M/12	c.128A>G	p.Gln43Arg	TI	→	42	N/N	Dysarthria, short frenulum/H/F+++/NK4	UL 3P, 7D, LL 2P, 6D	90		Student
44/M/15	c.142G>A	p.Gly48Ser	CFTD	↑	30	N/N	H/F/NK6	UL 5P, 9D, LL 6P, 9D	55		Student
49/F/10	c.1106C>T	p.Pro369Leu	TI/NM	→	24	N/N	H/NK6/dysphagia, tired chewing	UL 4P, 6D, LL 5P, 9D	53		School
TPM2	NM_003289.3	p.Glu6Lys									
34/F/14	c.415_417delGAG	p.Glu139del	NA	→	23	N/Y	Oblong/H/F/NK7/tired chewing	UL 5P, 9D, LL 5P, 8D	58	S	Student
35/F/39	34 daughter	p.Glu139del	NM/CFTD	→	15	N/Y(Su)	Oblong/H/FNK6/tired chewing	UL 6P, 9D, LL 8P = D	74	Pes cavus	NI
TPM3	NM_152263.2										
5/M/27	c.503G>A	p.Arg168His	CFTD	→	17	N/N	Triangular/NV/H++/NK7	UL 8P, 10D, LL 10P, 9D	46	(C)/(S)	IT expert
91/M/19	c.502C>T	p.Arg168Cys	CFTD	↑	24	N/N	Oblong/NV, dysarthria/H/NK6, malocclusion	UL 7P, 9D, LL 8P, 7D	57BiPAP	RN	Student
NEB	NM_004543.4										
7/F/29	c.2836-2A>G[a]; c.5763+5G>A	p.?; p.?	NM	↓	22	N/N	H/F/NK7/dysphagia	UL 5P, 8D, LL 4P, 6D	77	/S/Rec patella lux (Su)	Part-time job
18/M/27	Brother to 53		NM	→	15	N/N	Oblong/F/NK10	UL 7P, 9D, LL 8P, 9D	72		Economist
53/M/24	c.2415+1G>A; c.2415+1G>A	p.?; p.?	ND	→	12	N/N	H/F/NK10	UL 6P, 8D, LL 9P = D	83	Hyperlax FE	Shop ass
47/F/26	c.10354T>C; c.17725G>T	p.Tyr3452His; p.Glu5909*	NA	↓	14	N/N	Retrognathia(Su)/NV/H/F//NK5/dysphagia	UL 7P, 10D, LL 7P, 3D	83	A(Su)//Rec K lux(Su)	Pensioner
48/F/7	c.11330dup[a]; c.10354T>C	p.?; p.Tyr3452His	NM	→	12	N/N	H/F/NK7	UL 6P, 6D, LL 7P, 4D	86		School
58/M/49	c.12130C>T; c.17503_17505del[a]	p.Arg4044*; p.Asp5835del	NA		Late	N/N	H/NK9	UL 8P, 7D, LL 10P, 5D	79	E, FF/	Full-time work
RYR1AD	NM_000540.2										
6/F/36	c.14818G>C	p.Ala4940Thr	CC/NM	→	18	N/N	Oblong/NV/H/NK5	UL 8P = D, LL 7P, 8D	62	A/S(Su)	Office
24/M/22	c.14582G>A	p.Arg4861His	CC?	→	Never	N/N	H/(F)/NK5	UL 5P, 7D, LL 2P, 6D	62	K, HF(Su)/S(Su)	Pensioner

Continued

Table 3 Continued

ID/sex/age at examination, y	Gene/mutation	Protein consequence	Histology	Course	Walk, mo old	Ophthalmoplegia/ptoses	Face/voice/palate/facial palsy/neck	Limbs	FVC % exp	Contractures/scoliosis/other	Occupation
25/F/38	c.14567C>G	p.Ala4856Gly	CC	→	14	N/N	(H)/NK9	UL 7P, 10D, LL 7P, 9D	90		Part-time draftsman
31/F/27	c.14422-14423delinsAA[a]	p.Phe4808Asn	CC	→	Never	N/N	NV/H/(F)/NK7	UL 5P, 8D, LL 3P, 8D	90	Hip lux	Pensioner
33/F/14	c.7523G>A	p.Arg2508His	T1	→	28	N/Y	Oblong//NV, dysarthria/H/F/NK8 tired chewing	UL/P, 10D, LL 7P, 10D		A/S/hyperlax	School
61/M/62	c.13913G>A	p.Gly4638Asp	CC	→	24	(Y)/Y	NV/H/F/NK9	UL 6P, 10D, LL 7P, 8D	94		Medical doctor
64/F/27	Daughter of 61		CC	→	24	N/N	NV/H/NK10	UL 7P, 10D, LL 8P, 9D	NA	A/hyperlordotic	Sales assistant
83/M/63	c.14567C>T[a]	p.Ala4856Val		→	15	N/N	(F)/NK10	UL 8P, 10D, LL 8P = D	97		Chauffeur
84/M/19	Son of 83		NA	↑	20	N/N	H/F)/NK10	Normal	100		Electrician trainee
62/M/18	c.14567C>T[a]	p.Ala4856Val		↑	18	N/N	NV/H/F/NK10	Normal	75		Student
89/M/31	c.14929G>A[a]	p.Glu4977Lys	M	→	12	N/N	Oblong/H/F/NK10	UL 9P = D, LL 10P = D	77	Cong hip lux	Gardener, sick leave
94/M/22	c.13891T>C[a]	p.Tyr4631His	CC/NM/CFTD	→	32	N/N	NV/H/NK9	UL 5P, 7D, LL 6P, 8D	82	A/S/hyperlax E+Fi	Full-time office job
105/F/28	c.479A>G	p.Gly159Glu	CC	→	24	N/N	Oblong/NV/H/(F)/StW/NK6	UL 8P, 9D, LL 6P, 9D	NA	A, Aa(Su)//RS, hyperlax Fi	Psychologist
RYR1AR	NM_000540.2										
2/M/50	c.2427_2446dup[a]; c.325C>T	p.Pro816Hisfs*75; p.Arg109Trp	CN/D	→	36	Y/N	NV/H+++/F/NK6	UL 4P, 8D, LL 4P, 10D	68		Full-time work
9/M/10	c.325C>T; c.2989C>T	p.Arg109Trp; p.Arg997*	CFTD	→	15	Y/Y	Triangular//H/(F)/NK3, tired chewing	UL 4P, 7D, LL 3P, 9D	45		School
70/M/22	c.718C>T; c.2897C>T[a]	p.Gln240*; p.Pro966Leu	CFTD	↑	16	Y/Y	H/F/tired chewing, dysphagia, NK9	UL 6P, 10D, LL 5P, 9D	74	A, HF//rec hip+ Sh lux	NI
81/F/28	Sister to 107		ND	→	15	N/N	F/NK3	UL 3P, 9D, LL 2P, 8D	72		Social worker
107/F/33	c.325C>T; c.7308_7309delTG[a]	p.Arg109Trp; p.?	CN	→	24	Y/N	NV/H/F/NK2/tired chewing, dysphagia	UL 2P, 6D, LL 2P, 8D	NA	Wheelchair	Part-time social worker
DNM2	NM_004945.3	p.?									
8/M/25	c.1393C>T	p.Arg465Trp	CN	→	18	(Y)/Y	Oblong/F/NK7	UL 8P, 10D, LL 10P, 9D	74		Part-time student
46/M/19	c.1840G>A	p.Ala614Thr	CN	↓	17	Y/Y	Skewed cranium/NV, dysarthria/H/F/NK3	UL 2P, 5D, LL 2P, 5D	19	RN	Pensioner
50/F/69	c.1393C>T	p.Arg465Trp	CN	→		(Y)/Y	F/NK6	UL 5P, 6D, LL 5P, 1D	81		Retired (died)

Continued

Table 3 Continued

ID/sex/age at examination, y	Gene/mutation	Protein consequence	Histology	Course	Walk, mo old	Ophthalmoplegia/ptoses	Face/voice/palate/facial palsy/neck	Limbs	FVC % exp	Contractures/scoliosis/other	Occupation
82/F/41	c.1393C>T	p.Arg465Trp	CN	→	9	N/N	H/F/NK8	UL 7P, 8D, LL 7P, 4D	68		Part-time teacher
67/F/20	c.1102G>A	p.Glu368Lys	CN	→	14	(Y)/(Y)	Oblong//H/(F)/N/NK6	UL 6P, 7D, LL 7P, 5D	56	A(Su), FF//RN	Part-time student
85/F/52	c.1553G>A	p.Arg518His	CN/CFTD	→	12	Y/N	Oblong/NV/H/NK5	UL 9P, 8D, LL 8P, 5D	88		Health care worker
MTM1	NM_000252.2										
37/M/14	c.1353+1G>A	p.?	CN	→	N	Y/Y	Oblong/NV/H/F/NK2	UL 2P, 5D, LL 2P, 3D	IV	/S(Su)	Special terms stud
80/M/18	c.674T>C	p.Ile225Thr	CN	→	36	Y/N	F/NK2	UL 2P, 6D, LL 1P, 3D	19	A(Su)//wheelchair	Special terms stud
102/M/24	c.1037 G>C	p.Trp346Ser	CN/CFTD	↑	18	Y/N	Oblong/NV/H/(F)/NK4	UL 4P, 9D, LL 4P, 8D	25	Pes cavus/clawfoot	Student
SEPN1	NM_020451.2	Er									
17/F/34	c.802C>T; c.1574T>G	p.Arg268Cys; p. Met525Arg	NM/D	→	12	N/N	NV/H/F/StW, NK0	UL 7P, 8D, LL P = D = 8	IV	(C)/S(Su)	Part-time job
101/F/20	c.893T>C; c.1396C>T[a]	p.Leu298Pro; p. Arg466Trp	NA	↓		N/(Y)	Triangular/NV/H/(F)/StW/NK2	UL 7P, 10D, LL 4P, 9D	22	/S(Su)	Pensioner
103/F/27	c.*1107T>C; c.943G>A	p.?; p.Gly315Ser	MCD	↓	12	N/N	NV/H/(F)/StW, NK4	UL 6P, 10P, LL 4P, 9D	30BiPAP	A, RN/S	Pensioner
TTN	NM_133378.4	p.?; p									
14/M/13	c.16745C>G; c.97719C>G[a]	p.Ser5582*; p. Tyr32573*	CN	↓	Never	N/N	Retrognathia/NV/H++/(F)/NK3	UL 3P, 6D, LL 2P, 4D	NIV	Hand K(Su)/S(Su)	Dead
SCN4A	NM_000334.4	P									
52/F/30	c.673C>T; c.3626G>T[a]	p.Arg225Trp; p. Cys1209Phe	M	→	18	Y/N	Oblong/NV/H/F/StW, NK5	UL 7P, 10D, LL 6P, 0D	82	Hyperlordosis	Laboratory tech part time
Characteristics of not genetically diagnosed patients											
1/M/66	NA	NA	CC, NM, Dy	↓	NA	N	NV/H+++/StW, NK3	UL 6P, 9D, LL 5P, 3D	70	Oromandibular, FE, A//pes cavus	Pensioner
54/M/69	NA	NA	CC	→	NA	N	(F)/NK10	UL 8P, 9D, LL 7P = D	64	Oromandibular, Sh, K, A, wrists	Pensioner
3/F/18[b]	NA	NA	M	→	20	N	NV/NK10	10	75		Student
4/M/13	NA	NA	T1	→	20	N	NV/NK9	UL 9P, 10D, LL 9P = D	75		School
10/M/35[b]	NA	NA	MCD	↓	NA	Y/N	Oblong/NV/F/NK2	UL 2P, 7D, LL 2P, 3D	IV	(All joints)/S(Su)/wheelchair	Pensioner
12/F/59[b]	NA	NA	M	↓	NA	N	/NK8	UL 6P, 7D, LL 4P = D	100	A(Su), plantarflex/	Secretary PT

Continued

Table 3 Continued

ID/sex/age at examination, y	Gene/mutation	Protein consequence	Histology	Course	Walk, mo old	Ophthalmoplegia/ptoses	Face/voice/palate/facial palsy/neck	Limbs	FVC % exp	Contractures/scoliosis/other	Occupation
95/F/32	NA	NA	Normal	→	10	N	/NK10	UL 9P, 10D, LL 9P = D	100		NI
56/M/32	NA	NA	M	→	NA	N	/NK9	UL = LL 9P, 10P	NA	A, Fi, K//hyperlax	Draftsman
15/F/18[c]	NA	NA	CFTD	→	16	N/Y	NV/H/NK10	Normal	100	/S	School
19/M/22[b]	NA	NA	MCD	→	Never	N/N	Oblong/H/NK3	UL 2P, 6D, LL 2P, 5D	35	K, E, Fi, hip(Su), A, Aa/S(Su)	Student
20/M/14[b]	NA	NA	T1	→	20	N/Y	Oval, retrognathia/NV/H/NK10	UL 9P, 10P, LL 10P = D	100		School
22/F/28[b,c]	NA	NA	T1	→	16	(Y)/Y	H/F/NK9	UL 6P, 10D, LL 6P, 9D	73		Dietician PT
28/F/55[b]	NA	NA	NA	→	NA	N	(H)/NK8	UL = LL 8P, 10	100	/(S)	Physiotherapist
39/M/40	NA	NA	CFTD	→	NA	N	StW, NK10	UL 8P, 10D, LL 9P, 10D	84		NI
51/F/35	NA	NA	CFTD	→	NA	N	NK6	Asym, UL P4, 9D, LL P7, D10	82	KF, HF(Su), RN/S/hyperlax	Psychologist PT
72/F/38	NA	NA	NA	→	14	N	(H)/StW, NK8	10	92	FF//rec patella lux	Teacher PT
71/F/11	NA	NA	M	→	13, AM	N	(H)/StW, NK5/tired chewing	UL 5P, 10D, LL 7P, 6D	52	KF, HF, EF, A(Su), thumb/S	Special school
29/F/41	NA	NA	M	↓	NA	N	Oblong/NV/H/StW, NK9	UL 9P, 10D, LL 9P, 5D	90	A	Graphic designer
32/F/21[b]	NA	NA	CCD	↑	NA	N	Oblong/NV/H/F/NK6	UL 5P, 8D, LL 4P, 8P	82		Student
41/M/21[b]	NA	NA	M	↓	NA	N/Y	H/NK10	UL 9P = D, LL 8P, 9D	94	A	Student
55/F/17[b]	NA	NA	CFTD	→	NA	N/Y	NV/H/F/NK8	UL 6P, 9D, LL 8P, 8D	53	FF, HF, KE, RN, A/S	Student
59/M/44[b]	NA	NA	CNM	→	24	N	(H/F)/NK4	UL 5P, 9D, LL 3P, 5D	72	A, hyperlax	Jeweler
63/F/14	NA	NA	Normal	→	NA	N/Y	NV/H/F	NA	60		Special school
65/M/26[b]	NA	NA	M	→	24	N	Oblong/NV/(H)/NK10	UL 9P, 10D, LL 9P, 10D	89	Sh	NI
66/F/11[c]	NA	NA	M	→	34	N	(H)/NK9	UL 7P, 5D, LL 8P, 6D	NA	//Rec lux; K, A, Sh	Special school
68/M/8[b]	NA	NA	M	↑	23	N	F/NK9, tired chewing	UL 8P = D, LL 9P = D	78		School
74/M/13[b]	NA	NA	CFTD	→	17	Y/Y	H/F/NK10	UL 8P, 9D, LL 0P, 8D	91	/S/hyperlax	School
75/F/25[b]	NA	NA	NA	↑	NA	N	NV/F/NK10	UL 8P, 10D, LL 10P = D	65		Childcare PT

Continued

Table 3 Continued

ID/sex/age at examination, y	Gene/mutation	Protein consequence	Histology	Course	Walk, mo old	Ophthalmoplegia/ptoses	Face/voice/palate/facial palsy/neck	Limbs	FVC % exp	Contractures/scoliosis/other	Occupation
86/M/11[b]	NA	NA	NA	→	16	N	Oblong/H/(F) (NK10	UL 8P, 9D, LL 9P = D	NA	Clubfoot, hyperlordotic	Special school
87/M/8	NA	NA	T1	→	19	N	Oblong/NV/H/F/NK9	9	79	Flat feet, hyperlordotic	Student
88/F/43	NA	NA	M	NA	NA	N	(NV)/H	Normal	NA		Self-employed
90/M/32[b]	NA	NA	M	→	Late	N	NV/H/F/NK9	UL 9P, 10D, LL 9P, 10P	100		Special school
92/M/7[b,c]	NA	NA	T1	→	21	N	F	Normal	100	Hyperlax	School
96/F/5[c]	NA	NA	M	→	24	N/Y	H/NK10	UL 6P, 10D, LL 10	71		Kindergarten
97/F/37[b]	NA	NA	CNM + C	↓	NA	N	Retrognathia/NV/H/F/NK6	UL 9P, 10D, LL 8P, 9D	46	A, hands dorsiflex/S (Su)/slim hands	Graphic designer PT
106/F/33[b]	NA	NA	M	→	48	N	Oblong/H/F/NK5	UL 3P, 4D, LL 6P, 4D	NA	RS, A/slim fingers	NI

Abbreviations: A = Achilles; Aa = ankle adduction; C = contractures; CC = central core; CCD = central core disease; CFTD = congenital fiber-type disproportion; CN = central nuclei; CNM = centronuclear myopathy; D = distal; *DNM2* = dynamin 2; Dy = dystrophic; E = elbow; F = facial palsy; FE = finger extensors; FF = finger flexors; Fi = fingers; FVC = forced vital capacity; H = high palate; HF = hip flexors; IV = invasive ventilation; K = knee; KE = knee extension; LL = lower limb; M = myopathic; MC = multicore; MCD = multimini core disease; MD = medical doctor; *MTM1* = myotubularin 1; N = no; NA = results not available; ND = not done; NI = no information; NK = average of neck extension and neck flexion; NM = nemaline myopathy; NV = nasal voice; P = proximal; PT = part time; RN = rigid neck; RS = rigid spine; *RYR1* = ryanodine receptor 1; S = scoliosis; *SEPN1* = selenoprotein 1; Sh = shoulder; StW = sternocleid wasting; Su = surgery; TI = type I dominance; UL = upper limb; W = wrist flexors; Y = yes; () = slight; * = with splinters.
Cases with mutation in *ACTA1*, *TPM2/3*, *DNM2*, *MTM1*, and *SCN4A* were published previously.[20–24]

[a] Novel mutations.

[b] Exome sequencing of congenital myopathy genes[25] except *SPEG* (Broad Institute).

[c] Exome sequencing of congenital myopathy genes[25] except *SPEG*, *KLHL40/41*, and *PTPLA* (*HACD1*) (Nijmegen University).

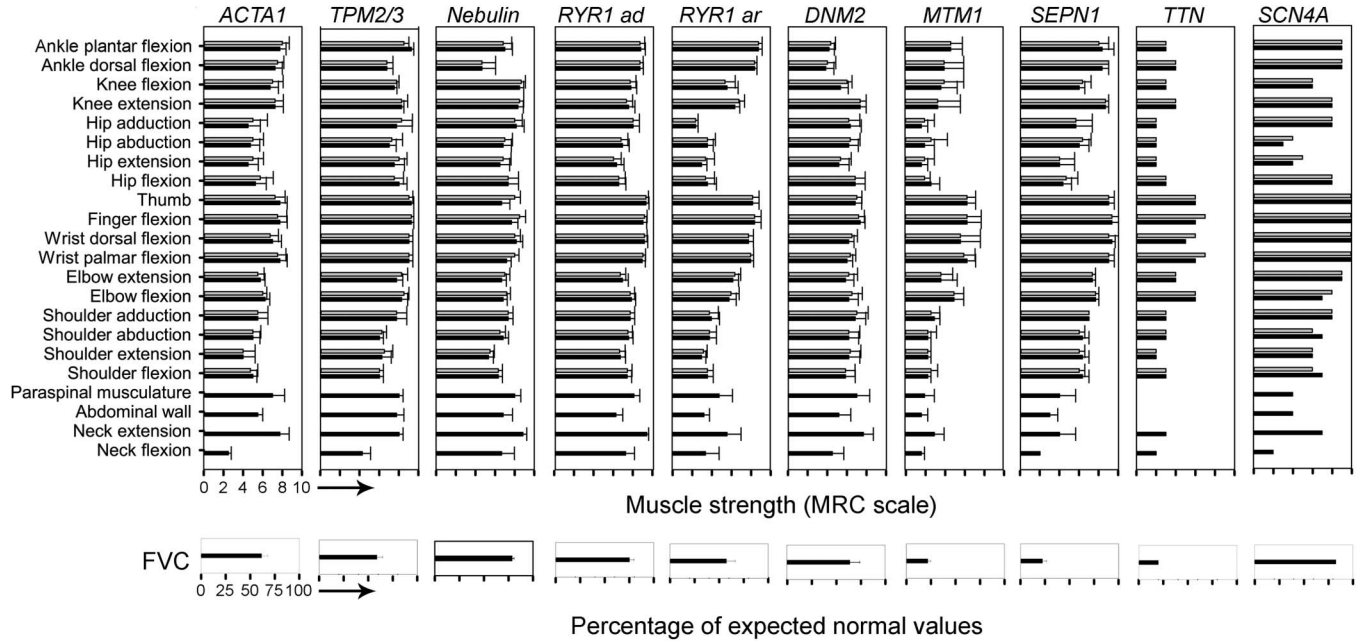
with a prevalence of 0.77) as in Denmark, where the genetic influence from historic Viking invasions is great.[15]

A London-based study[1] observed a different pattern of histology, as the majority of their patients had CCD, whereas histologic findings of cores, CNM, NM, and CFTD/T1 were more evenly distributed among our patients. This difference in histology also points to a different genetic background and supports that not only the prevalence but also the genetic make-up of CM varies among geographic regions. Concurring with this hypothesis, the genetic etiology in the London-based study was very different from ours. They found *RYR1* mutations in 59% and *DNM2* in 0% of their CMs, whereas *RYR1* mutations were observed in 22% of our cases and *DNM2* mutation in 7.3%. The difference in *RYR1* mutations in our population is probably not explained by different age distribution, as *RYR1* patients usually survive past early childhood.[2] The *DNM2* patients, however, are relatively mildly affected and may go unrecognized for years, which would make them underrepresented in a very young population. We also found a higher percentage of patients with *NEB* mutations in our cohort. This discrepancy, however, could relate to differences in testing strategies, where we sequenced all nonrepetitive coding sequences of *NEB*, whereas only a single frequent deletion was assessed in the previous study.[1] Also, the genetic background may influence the distribution of genetic etiology.

We identified the genetic etiology in 56% of patients. Two recent studies (same group) describing retrospective data in mostly pediatric patients reported the genetic cause in 67%–79%.[1,2] Our lower diagnostic rate can partly be explained by methods of selecting patients, as we included many patients with unspecific myopathic biopsies and that subgroup only had a genetic etiology identified in 21% of cases. Leaving the patients with unspecific myopathic histology out, we found a genetic etiology in 63% if CFTD/T1 was included, and 83% without CFTD/T1. Differences in the success rate of identifying genetic etiology are therefore most likely caused by differences in histology among the included cohorts. An alternative explanation might be that our patients were older than those in previous studies and that those who die before age 5 years often have mutations in *ACTA1* or *MTM1*,[2] which are relatively easy to identify. Finally, the genetic background may vary as discussed above.

The chance of identifying genetic etiology was highly dependent on histology. A much higher percentage with a "specific" histology like cores, NM,

Figure 2 **Detailed muscle strength and vital capacity in various genetic subtypes of congenital myopathy**



For Medical Research Council (MRC); gray bars left side, black bars right side. Bottom: forced vital capacity (FVC) in percentage of expected normal values.

or CNM had a genetic etiology identified. In the subgroup with confirmed CM and NM, genetic etiology was identified in 100%. However, the specificity of CM is not 100%, as 1 patient with desmin mutation also had NM. NM in patients with desmin mutations has only been reported in a few cases,[16] but was attributed to the known protein accumulation in desminopathy. "Specific histology" for CM, however, was only found in 3/10 patients with a phenotype compatible with CM, but with alternative genetic diagnoses (CMS, desminopathy, ColVI, or XII). A patient with selenoprotein deficiency had nemaline bodies in 2 muscle fibers. Although this might be an incidental finding, this patient was grouped together with the NMs.

The detailed physical examination performed in this study suggests some new clinical clues to the genetic etiology. In the genetically resolved nemaline/CFTD/T1 group, *ACTA1* patients were generally weaker than *NEB* patients.[17] However, in contrast to the *NEB* patients, patients affected by *TPM2* and *3* aberrations had a disproportionately higher respiratory affection, and half of the *NEB* patients had almost paralytic ankle dorsiflexion coexisting with MRC 7–8 in proximal muscles and a relatively preserved hand function. The preferential weakness of ankle dorsiflexors in some *NEB* patients is well established.[18,19] The only patient with combined CFTD and pronounced ophthalmoplegia had recessive *RYR1* disease. The recessive *RYR1* patients also exhibited a marked proximal-distal gradient in weakness, which was shared by the *MTM1* patients, but the *MTM1* patients had a much more noticeable respiratory affection. Severe ophthalmoplegia was, in agreement with a recent consensus statement,[19] exclusively observed with recessive *RYR1*, *DNM2*, and *MTM1* mutations. CCD was almost synonymous with dominant *RYR1* mutations, and these patients had much the same extremity affection as *SEPN1* patients, and both groups had a tendency to scoliosis. The *SEPN1* patients, however, had much more respiratory and axial involvement as known for this condition. Mutations in *DNM2* lead to CNM with ptosis and a lower extremity distal affection in all cases, but otherwise a relatively mild phenotype. Although these clinical clues are not 100% consistent, we believe that they contribute importantly when planning a genetic test strategy or interpreting test results.

Ten patients were initially judged to have a phenotype compatible with CM, but turned out to have mutation in a gene not strictly belonging to the genes recognized as genes inducing CM; 3 had mutations in the collagen VI gene, 3 in the collagen XII gene, 2 in the desmin gene, and 2 had CMS. The delineation of CM is not generally agreed upon, but we have, in line with others, chosen not to include collagen myopathies, as they typically have a progressive course and more contractures than other CMs. On follow-up, the widespread contractures in the 3 collagen VI patients led to the identification of mutations in the

collagen VI genes, and in the patients with desmin mutations, the course showed to be much more progressive than was the impression at the initial visit. Hence, in retrospect, the collagen VI myopathies and the desmin patients should not have been included. By contrast, there were no red flags in the phenotype of the collagen XII patients and the patients with CMSs. The prevalence would not have been significantly different if these patients were included, as the total patient number compared to the complete population is still very small.

In contrast to most previous studies, we included many adult patients with very early-onset weakness. We confirmed that for the majority, the disease course is nonprogressive and many patients are still engaged in an active work life.

Taken together, this study adds new knowledge about the geographic variation in prevalence, distribution of subtypes, and clinical characteristics in an older population with CM that may influence strategies for diagnostic testing and counseling of patients.

AUTHOR CONTRIBUTIONS

Nanna Witting: study concept and design, acquisition of data, analysis and interpretation of data, and drafting of manuscript. Ulla Werlauff: study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of manuscript for intellectual content. Morten Duno: acquisition of data, analysis and interpretation of data, and critical revision of manuscript for intellectual content. John Vissing: study concept and design, analysis and interpretation of data, and critical revision of manuscript for intellectual content.

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Phenotypes, genotypes, and prevalence of congenital myopathies older than 5 years in Denmark

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