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

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 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 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,
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).a 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.
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

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**ACTA1** – skeletal muscle α-actin 1; **AD** – autosomal dominant; **AR** – autosomal recessive; **CK** – creatine kinase; **CMS** – congenital myasthenic syndrome; **DES** – desmin; **DNM2** – dynamin 2; **DK7** – 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.*
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 (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 confirm a compound heterozygous state.

The remaining 5 novel variants were all missense variants in RYR1 located in the well-known hot-spot region for the dominantly inherited RYR1 disorder.10

Table 1 Histologic findings vs genotype

| Genes   | ACTA1 | TPM2 | TPM3 | NEB | ADYR1 | ARYR1 | DN2M | MTM1 | SCN4A | TTN | SEPN1 |
|---------|-------|------|------|-----|-------|-------|------|------|-------|-----|-------|
| N%      | 82%   | 100% | 46%  | 48% | 24%   | 24%   | 71%  | 155% | 6.0%  | 7.1%| 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; NEM = 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.

Neurology: Genetics

PHENOTYPES. From the detailed muscle examination, some patterns of weakness could be recognized for particular genotypes (table 3, figure 2). The AC-

Ophthalmoplegia was confined to DNM2 and recessive RYR1 and almost exclusively 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 very often are missense and predicted to be potentially pathogenic by SIFT, PolyPhen2, AlignGVGD, and MutationTaster in silico prediction softwares and were absent from the ExAC database (exac.broadinstitute.org), and from a Danish control cohort of 2000 WES. 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 confirm a compound heterozygous state.

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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 patient 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. 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. 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. 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 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 2 | Chance of identifying genetic etiology according to histology |
|---------|----------------------------------------------------------------|
|          | Proportion of histology | Proportion of gene identification |
|          | N (%)                  | CM gene N (%) | Non-CM gene N (%) |
| Unspecific histology (CFTD/T1/myopathy/fibrosis) | 49 | 12 | 7 |
| Specific histology (ex CFTD) | 44 | 34 | 7 |
| NM | 13 | 12 | 8 |
| Cores | 15 | 9 | 1 |
| CNM | 16 | 13 | 1 |
| CFTD/T1 | 32 | 9 | 2 |
| Myopathy/fibrosis/NO | 16 | 3 | 2 |
| 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.
| 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                       | 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                        | TPM2 NM_003289.3 |                     |           |        |            |                       |                                 |       |           |                                 |            |
| 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/       | 15     | N/Y(Su)    | Oblong/H/F/NK6/tired chewing | UL 6P, 9D, LL 8P = D            | 74    | Pes cavus |                                 | NI         |
| TPM3                        | 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)(I)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            | 57B/PAP | RN        |                                 | Student    |
| NEB                         | NEB NM_004543.4 |                     |           |        |            |                       |                                 |       |           |                                 |            |
| 7/F/29                      | c.2836-2A>G; 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    | Hyper lax 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*; 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 | p.Arg4044*; p.Asp5835del | NA        | Late   | N/N        | H/NK9                | UL 8P, 7D, LL 10P, 5D            | 79    | E, FF/   |                                 | Full-time work |
| RYR1AD                      | 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(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, H(F)/S(Su) |                               | Pensioner |

Continued
| ID/sex/age at examination, y | Gene/mutation | Protein consequence | Histology | Course | Walk, mo old | Ophthalmoplegia/palpation | Face/voice/palate/facial palsy/neck | Limbs | FVC % exp | Contractures/scoliosis/other | Occupation |
|-----------------------------|---------------|--------------------|-----------|--------|-------------|-------------------------|---------------------------------|-------|-----------|-------------------------------|------------|
| 25/F/38                     | c.14567G>C    | p.Ala4856Gly       | CC        | →      | 14          | N/N                     | (H)/NK9                         | UL 7P, LL 7P, 9D               | 90     | Hip lux               | Part-time draftsman         |
| 31/F/27                     | c.14422-14423delinsAA | p.Phe4808Asn    | CC        | →      | Never       | N/N                     | NV/H(F)/NK7                      | UL 5P, 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    | 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    | 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    | p.Ala4856Val       | ↑       | 18       | N/N         | NV/H/F/NK10            | Normal                          | 75     | Cong hip lux          | Student                     |
| 89/M/31                     | c.14929G>A    | p.Glu4977Lys       | M        | →      | 12          | N/N                     | Oblong/H/F/NK10                  | UL 9P = D, LL 10P = D           | Gardener, sick leave       |
| 94/M/22                     | c.13891T>C    | p.Tyr4631His       | CC/NM/ CFTD | →  | 32          | N/N                     | NV/H/NK9                         | UL 5P, 7D, LL 6P, 8D           | 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  |
| 2/M/50                      | c.2427_2446dup; 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           | School                           |
| 70/M/22                     | c.718C>T; c.2897C>T   | p.Gln240*; p. Pro966Leu | CFTD | ↑      | 16          | Y/Y                     | H/F/tired chewing, dysphagia, NK9 | UL 6P, 10D, LL 5P, 9D           | A, HF/rec hip + Sh lux       | Nl                             |
| 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* | p.Arg109Trp; p. Arg109Trp | CN     | →      | 24          | Y/N                     | NV/H/F/NK2/tired chewing, dysphagia | UL 2P, 6D, LL 2P, 8D           | Wheelchair                     |
| 50/F/69                     | c.1393C>T     | p.Arg465Trp        | CN        | →      | (Y)/Y      | F/NK6                  | UL 5P, 6D, LL 5P, 81            | Retired (died)                 |

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     |                       | 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            |
| 37/M/14                     | c.1353+1G>A    | p.?               | CN        | →      | N           | YYY                 | Oblong/NV/H/F/NK2           | UL 2P, 5D, LL 2P, 3D | IV     |                       | Special terms stud            |
| 80/M/18                     | c.674T>C       | p.Ile225Thr       | CN        | →      | 36          | Y/N                 | F/NK2                       | UL 2P, 6D, LL 1P, 3D | 19     |                       | Special terms stud            |
| 102/M/24                    | c.1037G>C      | p.Trp346Ser       | CN/CFTD   | †      | 18          | Y/N                 | Oblong/NV/H/F/NK4           | UL 4P, 9D, LL 4P, 8D | 25     |                       | Pensioner                    |
| 17/F/34                     | c.802C>T;      | p.Arg268Cys; p.   | NM/D      | →      | 12          | N/N                 | NV/H/F/StW, NK0             | UL 7P, 8D, LL 6P, D = 8 | IV     |                       | Part-time job                |
| 101/F/20                    | c.893T>C; c.1398C>T* | p.Leu298Pro; p. | NA        | ↓      | N/Y         | Triangular/NV/H/F/StW/ NK2 | UL 7P, 10D, LL 4P, 9D | 22     |                       | 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 | 30BPAP | A, RN/S                  | Pensioner                    |
| 14/M/13                     | c.16745C>G; c.97719C>GT* | p.Ser5582*; p. | CN        | ↓      | Never       | N/N                 | Retrognathia/NV/H+/+/F/ NK3 | UL 3P, 6D, LL 2P, 4D | NIV    |                       | Dead                         |
| 52/F/30                     | c.673C>T; c.36296C>T* | p.Arg225Trp; p. Cys1209Phe | M           | →      | 18          | Y/N                 | Oblong/NV/H/F/StW, NK5      | UL 7P, 10D, LL 6P, 0D | 82     |                       | Laboratory tech part time     |

Characteristics of not genetically diagnosed patients

| 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       |
|-----------------------------|----------------|-------------------|-----------|--------|-------------|---------------------|-----------------------------|-------|-----------|----------------------------|----------------|
| 1/M/66                      | NA             | NA                | NA        | ↓      | NA          | N                   | NV/H+/+/StW, NK3             | UL 6P, 9D, LL 6P, 4D | 70     |                       | Pensioner                  |
| 54/M/69                     | NA             | NA                | CC        | →      | NA          | N                   | (F)/NK10                    | UL 8P, 9D, LL 7P = D | 64     |                       | Pensioner                  |
| 3/F/18                      | 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                     | NA             | NA                | MCD       | ↓      | NA          | Y/N                 | Oblong/NV/F/NK2             | UL 2P, 7D, LL 2P, 3D | IV     |                       | Pensioner                  |
| 12/F/59                     | NA             | NA                | M         | ↓      | NA          | N                   | /NK8                        | UL 6P, 7D, LL 4P = D | 100    |                       | Secretary PT                |

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<sup>bc</sup>      | NA            | NA                  | CFTD      | →      | 16          | N/Y                   | NV/H/NK10                        | Normal                        | 100     | /S        | School                       |            |
| 19/M/22<sup>bc</sup>      | NA            | NA                  | MCD       | →      | Never       | N/N                   | Oblong/H/NK3                     | UL 2P, 6D, LL 2P, 5D             | 35       | K, E, Fi, hips, AA/SSu     | Student     |
| 20/M/14<sup>bc</sup>      | NA            | NA                  | T1        | →      | 20          | N/Y                   | Oval, retrognathia/NV/H/NK10     | UL 9P, 10P, LL 10P = D           | 100     | /S        | School                       |            |
| 22/F/28<sup>bc</sup>      | NA            | NA                  | T1        | →      | 16          | Y/Y                   | H/F/NK9                          | UL 6P, 10D, LL 6P, 9D            | 73       | A         | Dietician PT                 |            |
| 29/F/41                   | NA            | NA                  | M         | ↓      | NA          | N                      | Oblong/NV/H/SW, NK9              | UL 9P, 10D, LL 9P, 5D            | 90       | A         | Special school               |            |
| 15/F/32                   | 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       | FF/hyperlax                   | Psychologist PT |
| 72/F/38                   | NA            | NA                  | NA        | →      | 14          | N                      | (H)/StW, NK8                     | 10                               | 92       | FF/frec 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       | FF, KF, EF, A(Su), thumb/S  | Special school |
| 20/F/41                   | NA            | NA                  | M         | ↓      | NA          | N                      | Oblong/NV/H/SW, NK9              | UL 9P, 10D, LL 9P, 5D            | 90       | A         | Special school               |            |
| 32/F/21<sup>bc</sup>      | NA            | NA                  | CCD       | ↑      | NA          | N                      | Oblong/NV/H/F/NK6                | UL 5P, 8D, LL 4P, 8P             | 82       | A         | Student                      |            |
| 41/M/21<sup>bc</sup>      | NA            | NA                  | M         | ↓      | NA          | N/Y                   | H/NK10                           | UL 9P = D, LL 8P, 9D             | 94       | A         | Student                      |            |
| 55/F/17<sup>bc</sup>      | NA            | NA                  | CFTD      | →      | NA          | N/Y                   | NV/H/F/NK8                       | UL 6P, 9D, LL 8P, 8D             | 53       | FF, KF, RE, A/S             | Student     |
| 59/M/44<sup>bc</sup>      | 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       | A         | Special school               |            |
| 65/M/26<sup>bc</sup>      | NA            | NA                  | M         | →      | 24          | N                      | Oblong/NV/H/NK10                 | UL 9P, 10D, LL 9P, 10D           | 89       | Sh        | NI                            |            |
| 66/F/11<sup>bc</sup>      | NA            | NA                  | M         | →      | 34          | N                      | (H)/NK9                          | UL 7P, 5D, LL 8P, 6D             | NA      | //Rec lux; K, A, Sh        | Special school |
| 68/M/8<sup>bc</sup>       | NA            | NA                  | M         | ↑      | 23          | N                      | (H)/NK9, tired chewing           | UL 8P = D, LL 9P = D             | 78       | A         | School                       |            |
| 74/M/13<sup>bc</sup>      | NA            | NA                  | CFTD      | →      | 17          | Y/Y                   | H/F/NK10                         | UL 8P, 9D, LL 8P, 8D             | 91       | /S/hyperlax                  | School     |
| 75/F/25<sup>bc</sup>      | NA            | NA                  | NA        | ↑      | NA          | N                      | NV/F/NK10                        | UL 8P, 10D, LL 10P = D           | 65       | Childcare PT                |            |
with a prevalence of 0.77) as in Denmark, where the genetic influence from historic Viking invasions is great.15

A London-based study1 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 the London-based study1 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.

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The chance of identifying genetic etiology was highly dependent on histology. A much higher percentage with a “specific” histology like cores, NM,
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, 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. 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. The only patient with combined CFTD and pronounced ophthalmoplegia had recessive RYRI disease. The recessive RYRI 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, exclusively observed with recessive RYRI, DNM2, and MTM1 mutations. CCD was almost synonymous with dominant RYRI 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

![](image.png)

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