

CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Centronuclear and myotubular myopathies

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Centronuclear myopathy, myotubular myopathy.¹

BINI, 601248

RYR1, 180901

MTMR14, 611089

1.2 OMIM# of the disease

Myotubular myopathy, XLCNM, MTM, XLMTM, CNMX, X-linked recessive centronuclear myopathy, 310400

Centronuclear myopathy 1, CNM1, autosomal dominant, 160150

Centronuclear myopathy 2, CNM2, autosomal recessive, 255200

1.5 Mutational spectrum

MTM1: Around 400⁶⁻¹² mutations have been reported in all exons of the gene and include point mutations (missense, nonsense and splicing mutations), insertions and small and large deletions. The majority of mutations are clustered in exons 4, 8, 9, 11 and 12. The most common mutation identified is c.1261-10A>G, which has been demonstrated to affect normal splicing, and occurs in ~7% of patients. Large deletions that affect one or more exons occur in ~7% of patients. Large deletions including part or the entire upstream *MAMLD1* gene cause a contiguous gene syndrome with hypospadias and myotubular myopathy in males.¹³ A duplication of exon 10 has been recently described in an affected male.¹⁴

DNM2: Thirteen heterozygous missense changes or in-frame deletions or insertions have been reported with hotspots at position 368, 369, 465, 522, 618 and 619.^{5,15-20} In the middle domain, the recurrent p.R465W mutation is most common, likely accounting for ~25% of families, whereas p.E368K and p.R369W are found in ~20% and ~10% of families, respectively. The PH domain mutation p.R522H is found in roughly 10% of families, whereas mutations of residues 618 and 619 account for about 15% of families. A distinct subset of mutations cause autosomal-dominant Charcot-Marie-Tooth neuropathy (CMTDIB and CMT2M).²¹⁻²³

BINI: Five homozygous mutations have been reported in patients with CNM2 including three missense changes (p.K35N, p.D151N and p.R154Q) and two nonsense mutations (p.Q573X and K575X).²⁴⁻²⁶

RYR1: To date, *RYR1*-related CNM has been mainly associated with compound heterozygosity for recessive *RYR1* mutations, typically a missense mutation and a mutation predicted to reduce the amount of the functional RyR1 protein.^{3,4} The mutational spectrum includes missense mutations, frame-shifting small insertions and deletions, and splice-altering mutations. Three recurrent *RYR1* mutations associated with CNM have been reported in the South African

1.3 Name of the analyzed genes or DNA/chromosome segments

Gene	Name	Locus	Disease
<i>MTM1</i>	Myotubular myopathy 1 gene	Xq28	Myotubular myopathy
<i>DNM2</i>	Dynamin 2 gene	19p13.2	Centronuclear myopathy 1
<i>BINI</i>	Bridging integrator 1 or Amphiphysin 2	2q14.3	Centronuclear myopathy 2
Other genes related to myotubular/centronuclear myopathy			
<i>RYR1</i>	Ryanodine receptor 1	19q13.1	Centronuclear myopathy 2
<i>MTMR14</i>	Myotubularin-related 14, HJUMPY	3p25.3	Centronuclear myopathy 1

Contrary to what is indicated in OMIM, the reported mutation in *MYF6* did not cause a recognized form of centronuclear myopathy.²

RYR1 mutations have been mainly implicated in CNM2 associated with autosomal-recessive inheritance.^{3,4} Implication of heterozygous *RYR1* mutations in dominant CNM awaits confirmation.

MTMR14/*HJUMPY* heterozygous inactivating variants have been reported in sporadic cases; whether they are disease-causing or acting as modifier of the phenotype remains to be determined.⁵

1.4 OMIM# of the gene(s)

MTM1, 300415

DNM2, 602378

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population due to multiple founder effects.³ Cases of *RYR1*-related CNM with a single heterozygous *RYR1* missense, either of *de novo* occurrence²⁷ or inherited from an asymptomatic parent,³ have been reported in a number of cases. These findings may reflect autosomal-dominant inheritance with variable penetrance or the presence of a mutation on the second allele not detected by routine sequencing.

MTMR14: Two inactivating heterozygous variants have been found in patients with sporadic CNM, including one with an additional *DNM2* heterozygous mutation.⁵

Neonatal severe cases should be first tested for all exons of *MTM1* and *DNM2* exons 8 and 16. In female neonates, *MTM1* mutation is associated with skewed X-inactivation or, less frequently, other X-chromosomal abnormalities. Childhood or adult onset is more likely associated with *DNM2* and *RYR1* mutations, respectively. In cases of clear recessive inheritance, *BIN1* and *RYR1* should be tested first.

1.6 Analytical methods

Bidirectional sequencing of coding regions of genomic DNA with flanking intronic sequences is currently the method of choice for screening of the *MTM1* (NM_000252), *DNM2* (isoform 1; NM_001005360) and *BIN1* (isoform 8; NM_004305) genes. In complement of sequence analysis, a multiplex ligation-dependent probe amplification (MLPA) kit for detection of dosage anomalies of one or more exons of the *MTM1* gene is available (SALSA MLPA kit P309-A1 *MTM1*, MRC, Holland). Some *MTM1* mutations are detected only through RNA and protein analysis²⁸ from cell lines (fibroblasts, lymphoblasts or myoblasts) or biopsies using RT-PCR and western blot, respectively. cDNA/protein analysis using RT-PCR or western blot is also a useful tool in *RYR1*-related CNM2 where the amount of functional RyR1 protein is often reduced.³ Because of its large size, *RYR1* may be better tested by cDNA sequencing from a muscle biopsy. Next-generation sequencing may also be a cost-effective alternative in the near future in cases where *RYR1* testing is contemplated.

1.7 Analytical validation

Mutation identification should be performed by *de novo* amplification and sequencing from the patient's DNA sample. Analytical validation is undertaken by comparison with database entries (mutations and polymorphisms) and published data. Special care is required for interpretation, as novel mutations and variants of unknown clinical significance are identified particularly in large genes such as *RYR1*. Testing of other affected/unaffected relatives in the family to see if the mutation segregates with the disease, and the study of ethnically matched controls to exclude polymorphisms, may be necessary. Confirmation of the pathogenicity of *MTM1* and *RYR1* mutations is possible using RT-PCR and/or western blot.^{3,28,29}

1.8 Estimated frequency of the disease

(incidence at birth ('birth prevalence') or population prevalence)

The paediatric point prevalence (age < 18 years) of centronuclear and myotubular myopathies has been estimated to be < 1 in 100 000,³⁰ distributed among *MTM1* (45%), *DNM2* (15%), *RYR1* (10-15%) and *BIN1* (< 5%). The remaining ~20% of cases likely have mutations in yet to be identified genes.

1.9 If applicable, prevalence in the ethnic group of investigated person

The various forms of CNM have been found at roughly equal frequencies in all the ethnic groups studied.

1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	<input checked="" type="checkbox"/>	<input type="checkbox"/>
B. Predictive testing	<input checked="" type="checkbox"/>	<input type="checkbox"/>
C. Risk assessment in relatives	<input checked="" type="checkbox"/>	<input type="checkbox"/>
D. Prenatal	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Comment: Mutation testing is used mainly to confirm a suspected clinical diagnosis. A list of laboratories that perform testing can be found on the Orphanet web site (<http://www.orpha.net>) and GeneTests (www.genetests.org/). Prenatal diagnosis is available for families with known mutations, depending on severity and country regulations. Prenatal diagnosis should only be considered in families where pathogenicity for mutations has been clearly established, and is especially challenging for *RYR1* as this gene harbours a large number of variations with uncertain significance.

Preimplantation genetic diagnosis may be offered to families with the same molecular prerequisite as for prenatal diagnosis, depending on the regulatory environment in their country.

Predictive diagnosis for CNM is available for adults from families with known mutations and a risk of late-onset disease. In the context of predictive testing, specific pre-testing genetic counselling should be proposed according to the internationally accepted guidelines. Testing for *RYR1* mutations does not only test for CNM and other *RYR1*-related myopathies but also may be predictive for the malignant hyperthermia susceptibility (MHS) trait, an allelic but not consistently associated complication of *RYR1* mutations. The index case and relatives found to harbour *RYR1* mutations can be advised directly about their MHS risk if the mutation identified has been previously documented to be MHS-associated or can be referred for appropriate testing.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives	C: False negative
	Present	Absent	B: False positives	D: True negative
Test				
Positive	A	B	Sensitivity:	A/(A + C)
			Specificity:	D/(D + B)
Negative	C	D	Positive predictive value:	A/(A + B)
			Negative predictive value:	D/(C + D)

2.1 Analytical sensitivity

(proportion of positive tests if the genotype is present)

The analytical sensitivity depends on the analytical method used. The analytical sensitivity should be indicated in the laboratory report.

The sensitivity for DNA sequencing of genomic PCR products is around 98–100% for small mutations within exons and splice sites, but rare false negatives can be induced by rare polymorphisms in primer sequences causing allele dropout.

Deletions of whole exons or whole genes are not usually detected by sequencing of autosomal genes and mutations in introns, and promoters and enhancers are missed by methods focusing on coding exons. For *MTM1* studies, the sensitivity is higher than that for the other genes because deletions of whole exons or the entire gene is easily detected by absence of amplification in males and by MLPA analysis in males and females. An intragenic duplication in the *MTM1*

gene has been described in a male and has been detected by MLPA analysis. RNA and protein studies may allow detection of mutations outside exons. MLPA testing is also available for *RYR1* for a smaller subset of exons.

Thus, a negative result using current methods does not entirely exclude the diagnosis, if clinical features are present. This may depend either on analytical sensitivity or heterogeneity of the phenotype (clinical sensitivity).

2.2 Analytical specificity

(proportion of negative tests if the genotype is not present)

Sequence analysis: ~100%

MLPA analysis: 98–100%. What appears to be single-exon deletions may be due to a SNP in a primer-binding site and need to be confirmed by sequencing or other quantification methods.

2.3 Clinical sensitivity

(proportion of positive tests if the disease is present)

The clinical sensitivity is around 80% if all known implicated genes are tested. Mutation frequency for the known genes has been provided in section 1.8. Genetic testing is rarely carried out for all known genes; this limitation might be overcome with the introduction of next-generation sequencing.

2.4 Clinical specificity

(proportion of negative tests if the disease is not present)

The proportion is nearly 100%, but no data are available for this measure.

2.5 Positive clinical predictive value

(life-time risk to develop the disease if the test is positive)

The possibility is close to 100% for *MTM1* mutations. However, clinical heterogeneity has been reported and incomplete penetrance cannot be excluded for mutations associated with late onset like specific *DNM2* mutations. Inter- and intrafamilial clinical variability has to be taken into account in *RYR1*-related CNM where additional sequence variations running independently in the family may modify the phenotype. Female carriers for a *MTM1* mutation do not usually develop overt symptoms³¹ in the absence of skewed X-inactivation (which can be different comparing muscle and other tissues such as blood) or other X-chromosomal abnormalities, but the true prevalence of subtle features is not well known. For *MTMR14*, incomplete penetrance or mutations acting as modifier alleles have been suggested.⁵

In addition, specific *DNM2* mutations are found in patients with Charcot–Marie–Tooth neuropathy who do not develop centronuclear myopathies (CMTDIB and CMT2M²³).

2.6 Negative clinical predictive value

(probability of not developing the disease if the test is negative)

Index case in that family had been tested:

The negative clinical predictive value is likely to be near 100%.

Index case in that family had not been tested:

Not applicable as other yet undiscovered genes could cause the disease.

3. CLINICAL UTILITY

Clinical utility refers to the ability of genetic test results, either positive or negative, to provide information that is of value in the clinical setting.³²

3.1 (Differential) diagnosis: The tested person is clinically affected (To be answered if in 1.10 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No	<input type="checkbox"/> (continue with 3.1.4)	
Yes	<input checked="" type="checkbox"/>	
	Clinically	<input type="checkbox"/>
	Imaging	<input type="checkbox"/>
	Endoscopy	<input type="checkbox"/>
	Biochemistry	<input type="checkbox"/> western blot for <i>MTM1</i> and <i>RYR1</i>
	Electrophysiology	<input type="checkbox"/>
	Other (please describe)	<input type="checkbox"/>

CNM is defined on the basis of clinical and, most importantly, histopathological assessments. To date, a comprehensive assessment comprising detailed evaluation of clinical, histopathological and, whenever possible, muscle MRI features should be performed prior to genetic testing and therefore represents a prerequisite to genetic testing rather than a diagnostic alternative.^{16,33,34} The diagnosis should then be confirmed at the genetic level by the identification of the mutation. In the future, next-generation sequencing might be proposed before the completion of the detailed clinical and histopathological studies. A genetic diagnosis is important for counselling and recurrence risk purposes.

Biochemistry:

At least 95% of patients with *MTM1* mutations show a decreased level of myotubularin by western blot analysis.^{28,29} For *MTM1*, this test can be performed from muscle and non-muscle cells as lymphoblasts or fibroblasts. *RYR1* mutations may or may not lead to a detectable decrease in the protein level in muscle sample.

Histology:

Centronuclear myopathies are characteristically defined by the presence of central nuclei placed in rows in the muscle fibres, but there often exist a number of fibres with one or more internalized nuclei. The central nuclei are only one of the morphological features, which characterize centronuclear myopathies, thus, there are a number of structural abnormalities of the muscle fibres that could provide guidance about the type of CNM.³⁴ For instance, a triad of morphological abnormalities is usually found in *DNM2*-related CNM: increased numbers of central and internal nuclei, radiating sarcoplasmic strands with oxidative enzyme reactions (so called 'spokes on a wheel') and type 1 muscle fibre predominance and hypotrophy.^{15,35,36} In *MTM1*-related CNM, an increased number of centralized nuclei and type 1 muscle fibre predominance and hypotrophy are reported and may be accompanied by the presence of necklace fibers, at least in adult cases.³⁷ To get the best of the morphological study of CNM, one should analyze the muscle biopsies with both histochemistry and electron microscopy. Indeed, at the ultrastructural level, there is a significant difference between the group of *DNM2*-, *BIN1*- and *MTM1*-CNM and *RYR1*-related myopathies, because despite of the ultrastructural particularities found in this first group of diseases, the sarcomeres appear preserved with a normal sequential structure, whereas in the *RYR1*-related myopathies, wide areas of sarcomeric disorganization with loss of the regular sarcomeric sequence are constantly observed.^{4,34}

3.1.2 Describe the burden of alternative diagnostic methods to the patient

MRI, EMG and DNA sampling are acceptable.

The first suggestion of any primary muscle disease, including centronuclear myopathy, necessitates histological analysis of a muscle biopsy that is an invasive sampling.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Unknown. The future application of next-generation sequencing may position the genetic approach before histological confirmation.

3.1.4 Will disease management be influenced by the result of a genetic test?

No

Yes

Therapy (please describe) There are no specific pharmacological agents currently that are consistently administered in different genetic forms of CNM. See 'management' part concerning the risk of MH for patients with RYR1 mutation and the precautions to be taken before anaesthesia.

Prognosis (please describe) The most important prognostic indicator is the degree of respiratory impairment, which varies considerably between the different genetic forms. *MTM1* mutations in males are usually associated with a more severe disease and an unfavourable prognosis. CNM associated with mutations in the *DNM2* and *RYR1* genes as a group often have later onset and less severe respiratory involvement and overall a better prognosis. Some cases carrying *RYR1* mutations may show substantial improvement over time, ³ although usually in proportion to severity at presentation, whereas *DNM2* mutation-positive cases follow a slow or moderately progressive course.³⁸

Management (please describe) The genetic result will help to focus multidisciplinary clinic follow-up and treatments, including regular assessments of neuromuscular function and monitoring for contractures, scoliosis and joint dislocations, which are frequently associated and may require orthotic or orthopaedic intervention. After an initial effort of active treatment, unfavourable prognosis in severely affected neonates harbouring *MTM1* mutations may lead to conservative management or withdrawal of ventilatory support. Some individuals with RYR1-related CNM and, possibly their heterozygous carrier parents, may be at an increased risk of suffering MH reactions in response to volatile anaesthetics and muscle relaxants (in particular halothane and suxamethonium). Genetic confirmation of the diagnosis should lead to the initiation of appropriate testing and preventive measures around operative procedures. Primary cardiomyopathies have not been reported in patients with genetically confirmed CNM, but cardiac arrhythmia has been noted in a patient with a *BIN1* homozygous mutation.²⁶ Thus a follow-up of cardiac functions is advised for *BIN1* mutation-positive cases and genetically unconfirmed cases.

3.2 Predictive setting: The tested person is clinically unaffected but carries an increased risk based on family history

(To be answered if in 1.10 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?

If the test result is positive (please describe)

Medical risk such as MH should be considered in patients with *RYR1* mutation.

Discussion about recurrence risk for future pregnancies should be offered according to the mode of transmission of the mutation.

If the test result is negative (please describe)

Tests of other disease-causing genes causing similar phenotypes should be pursued.

3.2.2 Which options in view of lifestyle and prevention does a person at risk have if no genetic test has been done (please describe)?

Specialist follow-up is indispensable.

3.3 Genetic risk assessment in family members of a diseased person

(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?

Yes, in all cases where proven pathogenic mutations validate the segregation of the disease.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

Family members can be screened for the mutations in the index patient, and mutation carriers can be spared the need for muscle biopsy and other diagnostic procedures.

Depending on the mode of inheritance, family members may also be found not to be at risk and thus spared any need for testing.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?

Yes.

3.4 Prenatal diagnosis

(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?

Yes; depending on severity and country regulations. See paragraph 1.10.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Yes, for the patient and the family. A molecular confirmation of the diagnosis will limit unnecessary further diagnostic investigations, which can be invasive (and expensive). Patients and family may find encouragement and support by becoming members of associations that welcome affected families. A molecular diagnosis enables carriers to make informed reproductive decisions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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