CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Multi-minicore disease

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Multi-minicore disease (MmD); multi-minicore myopathy; minicore myopathy; multicore myopathy with external ophthalmoplegia; moderate minicore myopathy with hand involvement; antenatal onset minicore myopathy with arthrogryposis.

The large number of synonyms reflects the variability of clinical and histopathological features, as well as genetic heterogeneity. MmD, introduced following the dedicated ENMC workshops on the condition,^{1,2} is the most common synonym, and is used consistently throughout this paper.

1.2 OMIM# of the disease

#255320, #117000 and #607552.

1.3 Name of the analysed genes or DNA/chromosome segments

Skeletal muscle ryanodine receptor (*RYR1*) gene/19q13.1; selenoprotein N (*SEPN1*) gene/1p35.

1.4 OMIM# of the gene(s)

*180901 (*RYR1*) and *606210 (*SEPN1*).

1.5 Mutational spectrum

RYR1 gene: More than 200 *RYR1* mutations have been reported to date, some exclusively associated with MmD and other congenital myopathy phenotypes, others with the malignant hyperthermia susceptibility (MHS) trait, or both.^{2–12} *RYR1* mutations associated with MmD are mainly recessive and, less frequently, dominant.⁷ The *RYR1* mutational spectrum associated with MmD is wide and comprises missense mutations, nonsense mutations, intronic splice mutations, deletions and duplications. Compound heterozygosity for missense and truncating *RYR1* mutations is a commonly observed genotype in MmD and other recessive, *RYR1*-related myopathies.^{7–9} Monoallelic expression of heterozygous *RYR1* missense mutations on the background of an imprinted maternal allele has been suggested in few families,¹³ but more recent data suggest that this is not a major contributory factor.

SEPN1 gene: *SEPN1* mutations associated with MmD are generally recessive and predominantly truncating,^{14,15} with only few missense mutations typically affecting functionally important domains of the protein such as the SECIS,¹⁶ or the selenocysteine redefinition element (SRE).¹⁷ Homozygous mutations are unexpectedly common even in families from non-consanguineous backgrounds, due to the presence of few founder mutations in different European populations. Forms of MmD due to recessive mutations in the *SEPN1* gene are considerably

rarer than those due to mutations in the *RYR1* gene (Muntoni and Jungbluth, unpublished observation).

1.6 Analytical methods

Selection criteria:

Considering that cores on muscle biopsy are a non-specific finding, and variations of uncertain significance are particularly common in the *RYR1* gene, genetic testing in MmD should only be initiated on the basis of a comprehensive assessment of clinical, histopathological and, increasingly, muscle MRI features at a specialist neuromuscular centre. Certain combinations of features are more indicative of either *SEPN1* or *RYR1* involvement, and should prompt mutation screening of the respective gene.

- Clinical features: Patients with *SEPN1*-related MmD have a consistent clinical phenotype characterized by marked axial weakness with spinal rigidity, early scoliosis and severe respiratory impairment often requiring non-invasive ventilation, even in still ambulant individuals.¹⁴ Extraocular muscle involvement (ophthalmoparesis) is extremely rare, but occasionally seen in the most severe cases (Ferreiro, unpublished observation). Cardiac involvement may occur secondary to marked respiratory impairment. Clinical features of *RYR1*-related MmD are more variable: Extraocular muscle involvement (ophthalmoparesis) is common, often associated with axial and proximal weakness, and mild-to-moderate bulbar and respiratory involvement.⁶ Other patients share clinical features with dominantly inherited CCD, featuring mild-to-moderate weakness pronounced in the hip girdle, but no extraocular or significant bulbar or respiratory involvement.⁵ Distal involvement with marked hyperlaxity pronounced in the upper limb is a frequently associated finding. A primary cardiomyopathy is not a feature in *SEPN1*- or *RYR1*-related forms of MmD.
- Histopathological features: *SEPN1*-related MmD typically show numerous, often poorly defined small core lesions spanning only few sarcomeres, and irregularly distributed throughout the fibre on longitudinal sections.¹⁴ *RYR1*-related MmD shows some overlap with CCD due to dominant mutation in the same gene, although by definition, cores are more often multiple and eccentric and do not run a significant extent along the fibre axis on longitudinal sections.⁶ In cases with suggestive clinical features but equivocal histopathological findings, muscle MRI may be more indicative of specific backgrounds than muscle biopsy.
- Muscle MR imaging: Muscle MR imaging in MmD shows different patterns of selective involvement depending on the genetic

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background and may aid genetic testing. In particular, in *SEPN1*-related MmD, within the thigh, the sartorius is usually the first and most prominently affected muscle. In *RYR1*-related MmD, within the thigh, there is selective sparing of the rectus femoris compared with the vasti, of the adductor longus compared with the adductor magnus, and of the gracilis compared with the sartorius. Although still discernible, the contrast between affected and unaffected muscles is often not as prominent in recessive *RYR1*-related MmD as in CCD due to dominant mutations in the *RYR1* gene. In addition to distinguishing these forms from each other, muscle MRI may also help to distinguish *SEPN1*- and *RYR1*-related MmD from genetically distinct congenital myopathies with or without spinal rigidity.^{18–20}

Mutation screening:

Genomic sequencing of coding regions including functionally important domains, such as the SECIS¹⁶ or the SRE,¹⁷ is currently the strategy of choice for screening of the *SEPN1* gene. Multiple ligation probe analysis will enable detection of large deletions in future.

Genomic sequencing of coding regions and flanking intronic sequence is currently the main strategy for *RYR1* mutation screening. In future, array CGH, next-generation sequencing and/or multiplex ligation-dependent probe amplification are likely to enable the detection of larger deletions, duplications and genomic rearrangements, relatively common in MmD and other recessive *RYR1*-related myopathies.

1.7 Analytical validation

Direct sequencing of both DNA strands is performed. Any sequence variants identified on genomic DNA sequencing is confirmed on a second DNA dilution from the index case. If a gross deletion or duplication is identified using, for example, next-generation sequencing, confirmation with a second technique is advisable. The pathogenicity of variants can be assessed using commercially available mutation interpretation software or alternative approaches to interrogate online data resources.

The majority of mutations in the *SEPN1* gene are truncating with few missense mutations reported affecting functionally important domains of the protein. Functional studies (ie, studies of the mutant RyR1 channel in patient myoblasts or homologous and heterologous expression systems) for the assessment of *RYR1* variations of uncertain significance are currently only available in selected cases on a research basis.

1.8 Estimated frequency of the disease

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

The birth prevalence or population prevalence of MmD is currently unknown. However, forms of MmD due to recessive mutations in the *SEPN1* gene are significantly rarer than those due to *RYR1* mutations (Muntoni and Jungbluth, unpublished observation). The carrier frequency for heterozygous *RYR1* mutations in the Japanese population has been estimated at 1 in 2000.²¹

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

Homozygous *SEPN1* mutations are unexpectedly common even in families from non-consanguineous backgrounds, due to the presence of few founder mutations in different European populations.¹⁴

The prevalence of *RYR1*-related MmD in specific ethnic groups is not known. However, specific malignant hyperthermia-related *RYR1* mutations or other *RYR1*-related myopathies have been found to be more prevalent in certain ethnic populations.^{9,22}

1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☒	☐
C. Risk assessment in relatives	☒	☐
D. Prenatal	☒	☐

Comment:

- Predictive testing: Testing for *RYR1* mutations does not only test for MmD and CCD, but also for the MHS trait, an allelic but not consistently associated complication of *RYR1* mutations. Although the association of some CCD-related dominant *RYR1* mutations and MHS has been well documented, the association is less clear with regards to more recently identified, recessive *RYR1* mutations. In families where the mutation identified has been previously documented to be MHS-associated, the index case and relatives found to harbour the same change can be advised directly about their MHS risk. In families where the mutation identified has not been previously documented to be MHS-associated, the index case and relatives found to harbour the same change can be referred for appropriate testing. Identification of homozygous or compound heterozygous *SEPN1* mutations in minimally symptomatic relatives of an index case predicts a high risk of developing respiratory failure, and indicates early polysomnographic studies.
- Risk assessment in relatives: Families with more than one pathogenic *RYR1* mutation running independently in the family have been recognised. It is therefore advisable to screen the entire *RYR1* gene in affected relatives with suggestive clinical and histopathological features, even if the *RYR1* mutation(s) previously identified in an affected index case has been excluded. Heterozygous carriers of *SEPN1* mutations remain asymptomatic.
- Prenatal diagnosis: It is expected that the greater availability of *RYR1* mutation screening will also increase requests for prenatal diagnosis. Prenatal diagnosis may be difficult in MmD and other *RYR1*-related myopathies due to the large number of *RYR1* variations of uncertain significance. We would therefore only consider prenatal diagnosis in families where pathogenicity for the *RYR1* mutation(s) identified has been clearly established, and no other sequence variations of uncertain significance have been identified on complete sequencing of both parents. Prenatal *SEPN1* mutation screening may be offered where two *SEPN1* mutations of proven pathogenicity have been previously identified *in trans* in the index case in the family.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: False positives	C: False negative D: True negative
	Present	Absent		
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)

No precise data regarding the analytical sensitivity of *SEPN1* and *RYR1* testing in MmD are currently available; however, analytical sensitivity is likely to be higher for *SEPN1* than for *RYR1* mutations. Analytical sensitivity for *SEPN1* testing is likely to be close to 100%. Analytical sensitivity for *RYR1* testing is likely to be substantially less than 100% if no diagnostic test for large scale deletions, duplications or genomic rearrangements has been performed

Criteria for determining the pathogenicity of an *SEPN1* mutation are as follows:

- (1) Nonsense mutation.
- (2) Splice-site mutations affecting canonical splice sequence or shown to alter splicing at mRNA/cDNA level.
- (3) Out-of-frame and in-frame deletion or insertion.
- (4) *De novo* compound heterozygous missense mutation (with proven paternity and absence of disease in parents).
- (5) Missense mutation affecting functionally important domains such as the SECIS¹⁶ or the SRE.¹⁷
- (6) Missense mutations previously shown to segregate in MmD families.

Criteria for determining the pathogenicity of an *RYR1* mutation are as follows:

- (1) Nonsense mutation.
- (2) Splice-site mutations affecting canonical splice sequence or shown to alter splicing at mRNA/cDNA level.
- (3) Out-of-frame and in-frame deletion or insertion.
- (4) *De novo* missense mutation (with proven paternity and absence of disease in parents).
- (5) Missense mutation previously shown to segregate in an MmD family.
- (6) Missense mutation involving a highly conserved amino acid. For other missense mutations, the search for segregation in the family should be performed if possible.

2.2 Analytical specificity

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

No precise data regarding the analytical specificity of *SEPN1* and *RYR1* testing in MmD are currently available. However, *RYR1* sequence variations of uncertain significance are common; only a small proportion of those have been functionally characterized to date, with an associated risk of false positives.

2.3 Clinical sensitivity

(proportion of positive tests if the disease is present)

In general terms, clinical sensitivity is dependent on variable factors such as age at testing, and a positive or negative family history. More specifically, clinical sensitivity, particularly for *RYR1* mutation screening also depends on the method used for mutation screening, as for example, larger copy number variations or genomic rearrangements are relatively common in *RYR1*-related MmD and other recessive *RYR1*-related myopathies, and may be missed on routine sequencing. Most importantly, the stringent application of clinical and histopathological selection criteria as outlined in paragraph 1.6 is a major determinant of clinical sensitivity for *SEPN1* and *RYR1* testing in MmD.

Although recent larger series indicate recessive *SEPN1* and *RYR1* mutations as a common cause of MmD, there is also evidence for

genetic heterogeneity accounting for the imperfect clinical sensitivity of *SEPN1* and *RYR1* screening in MmD:

- in the original series of 62 families with suggestive features of the 'classical' phenotype of MmD, only 12 families were found to carry causative *SEPN1* mutations.¹⁴ Although some of the remaining 50 families were subsequently found to be *RYR1*-related, *RYR1* mutations could be excluded in others.
- multi-minicores and central cores as the main feature on muscle biopsy have been reported in a number of genetically distinct myopathies, often associated with dominant inheritance or clinical features unusual in the context of *SEPN1*- or *RYR1*-related MmD, such as a primary cardiomyopathy. A primary cardiomyopathy associated with multi-minicores on muscle biopsy has also been documented in a mildly affected family harbouring dominant *ACTA1* mutations,²³ and severely affected siblings with homozygous truncating titin mutations.²⁴ Missense mutations in the β -myosin heavy-chain gene, *MYH7*,²⁵ may give rise to cores on muscle biopsy with a distinct associated-myopathy phenotype with or without cardiac impairment.²⁶
- central cores and multi-minicores as a secondary feature on muscle biopsy have been reported to be associated with mutations in the *ACTA1*,²⁷ *DNM2*²⁸ and *NEB*²⁹ genes; however, in most of these cases, other findings, namely nemaline rods or centralized internal nuclei, were the more prominent histopathological feature.

2.4 Clinical specificity

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

No precise data regarding the clinical specificity of *RYR1* or *SEPN1* testing in MmD are currently available; however, clinical specificity is likely to be less than 100% for *RYR1* testing, considering the large number of sequence variations of uncertain significance identified in the *RYR1* gene. In most cases, a detailed clinical assessment and muscle biopsy will have been performed before genetic testing; therefore, presence of the condition is a prerequisite for the initiation of genetic testing, but also of importance for the interpretation of *RYR1* variations of uncertain significance.

2.5 Positive clinical predictive value

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

Penetrance of MmD-related *SEPN1* mutations is likely to be near 100%. Inter- and intra-familial clinical variability has to be taken into account in *RYR1*-related MmD, where additional sequence variations running independently in the family may modify the phenotype.

2.6 Negative clinical predictive value

(probability not to develop 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% for *SEPN1* testing, but less than 100% in *RYR1*-related MmD, as pedigrees with more than one disease-causing *RYR1* mutation running independently in different branches of the family, as well as locus heterogeneity, have been recognised. In a prenatal diagnosis situation, where the possibility of additional pathogenic *RYR1* mutations can be ruled out (eg, by completely sequencing DNA from both parents), the negative clinical predictive value is expected to be close to 100%.

Index case in that family had not been tested:

When the index case in that family had not been tested, predictive testing in another family member should only be proposed when the

family member fulfils the clinical and pathological criteria as outlined in paragraph 1.6.

3. CLINICAL UTILITY

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

Genetic testing for *SEPN1* and *RYR1* mutations is important in the differential diagnosis of patients with clinical features of a congenital myopathy and histopathological findings suggestive of MmD.

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

No	☐ (continue with 3.1.4)	
Yes	☒	☒
	Clinically	☒
	Imaging	☒
	Endoscopy	☐
	Biochemistry	☐
	Electrophysiology	☐
	Other (please describe)	☒ Muscle Biopsy

Because MmD is a clinical and, most importantly, a histopathological diagnosis, a primary molecular genetic analysis is indicated only in familial cases with typical clinical features and known-associated *SEPN1* or *RYR1* mutations. In most other cases, a comprehensive assessment comprising detailed evaluation of clinical, histopathological and, possible, muscle MRI imaging features should be performed before genetic testing, and therefore represents a prerequisite to genetic testing rather than a diagnostic alternative.

3.1.2 Describe the burden of alternative diagnostic methods to the patient?

Detailed clinical neuromuscular assessment, a muscle biopsy with or without muscle MRI imaging, is required in the index case to inform the choice of genetic testing and to establish the diagnosis. A muscle biopsy, in particular, is an invasive procedure and will require local or general anaesthesia, but its complication rate is usually low. Muscle MR imaging may require sedation in young children less than 5 years of age. Molecular genetic analysis may replace above procedures in similarly affected relatives of index cases, where the genetic diagnosis has been unequivocally established.

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

Unknown.

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

No ☐
Yes ☒

The genetic resolution of the clinico-pathological diagnosis of MmD will help to focus multidisciplinary management, therapeutic interventions and follow-up as outlined below. Identification of SEPN1 mutations should lead to close monitoring of the respiratory function even in asymptomatic patients, allowing early detection and management of respiratory failure.

(Continued)

Therapy (please describe)	<i>There are no specific pharmacological agents currently consistently administered in SEPN1- or RYR1-related MmD. However, preliminary data, for example, on the use of Salbutamol in RYR1-related myopathies³⁰ and the role of the SEPN1 gene product in antioxidant defence systems³¹ suggests that genetic testing in MmD may also provide the basis for rationale pharmacological therapies in future. Assisted ventilation is the elective symptomatic treatment for SEPN1-related MmD and significantly improves life expectancy.</i>
Prognosis (please describe)	<i>Confirmation of the genetic defect in a patient with a clinico-pathological diagnosis of MmD contributes to the definite resolution of a congenital myopathy without entirely specific clinical and histopathological features, and provides the basis for prognostic statements. Positive and negative prognostic indicators dependent on the genetic background, respectively, are the relative lack of cardiorespiratory involvement in RYR1-related MmD and the prominent respiratory impairment in the SEPN1-related form.</i>
Management (please describe)	<i>The genetic result will help to focus on the multidisciplinary clinical 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. SEPN1-related MmD carries a high risk of scoliosis and respiratory impairment, and both complications ought to be actively monitored for, with a view to timely intervention planning. Exercise-induced myalgias are a common feature of some patients with RYR1-related MmD and may require medical intervention. Some individuals with RYR1-related MmD and, possibly their heterozygous carrier parents, may be at an increased risk of suffering malignant hyperthermia reactions in response to volatile anaesthetics and muscle relaxants,³² and genetic confirmation of the diagnosis will lead to initiation of appropriate testing and preventive measures around operative procedures. Initiation of pharmacological treatments such as Salbutamol may be of benefit in some individuals with RYR1-related MmD, whereas administration of antioxidants such as acetylcysteine may become a potential pharmacological approach in the SEPN1-related form in future.³¹ The risk of primary cardiomyopathies is probably higher in SEPN1- and RYR1-negative patients with MmD, and follow-up should be planned accordingly.</i>

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):

Genetic confirmation of the clinic-pathological diagnosis of RYR1- or SEPN1-related MmD will help to focus on the multidisciplinary follow-up and management as outlined in Paragraph 3.1.4.

If the test result is negative (please describe):

Follow-up is dispensable if familial mutations in *SEPN1* or *RYR1* have been excluded, and no clinico-pathological features of MmD are present. Follow-up should be arranged as outlined in Paragraph 3.1.4 if clinico-pathological features of MmD are present, but no *SEPN1* or *RYR1* mutations could be identified.

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)?

If the person has a positive family history of MmD and is clinically affected, follow-up should be arranged as outlined in Paragraph 3.1.4. If the person has a positive family history of MmD and is clinically not affected, specialist follow-up is dispensable, unless suggestive symptoms developed.

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 *SEPN1*-related MmD, if two recessive mutations are identified *in trans*. Yes, in *RYR1*-related MmD, if two recessive mutations *in trans* or a heterozygous dominant mutation of proven pathogenicity are identified, provided that sequencing of the entire *RYR1* gene has been performed and no additional *RYR1* mutations are running independently in the family.

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

No.

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 2.10 'D' was marked)

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

Yes (but note cautions as outlined in Paragraph 1.10).

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe) Yes. In many cases, the genetic diagnosis contributes substantially to a diagnostic conclusion, particularly if histopathological findings are not entirely typical. Recognising a particular congenital myopathy as *RYR1*- or *SEPN1*-related MmD will help to anticipate future course, plan interventions and prevent potential complications. It will also end a lengthy diagnostic process for affected individuals and their families.

CONFLICT OF INTEREST

Suzanne Lillis and Stephen Abbs are employed by GSTS Pathology, a joint venture private partnership organisation, which offers clinical diagnostic testing of the *RYR1* gene.

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- Jungbluth H, Muntoni F, Ferreiro A, Core Myopathy Consortium: 150th ENMC International Workshop: Core Myopathies, 9–11th March 2007, Naarden, The Netherlands. *Neuromuscul Disord* 2008; **18**: 989–996.
- Monnier N, Ferreiro A, Marty I, Labarre-Vila A, Mezin P, Lunardi J: A homozygous splicing mutation causing a depletion of skeletal muscle *RYR1* is associated with multi-minicore disease congenital myopathy with ophthalmoplegia. *Hum Mol Genet* 2003; **12**: 1171–1178.
- Ferreiro A, Monnier N, Romero NB *et al*: A recessive form of central core disease, transiently presenting as multi-minicore disease, is associated with a homozygous mutation in the ryanodine receptor type 1 gene. *Ann Neurol* 2002; **51**: 750–759.
- Jungbluth H, Müller CR, Halliger-Keller B *et al*: Autosomal-recessive inheritance of *RYR1* mutations in a congenital myopathy with cores. *Neurology* 2002; **59**: 284–287.
- Jungbluth H, Zhou H, Hartley L *et al*: Minicore myopathy with ophthalmoplegia caused by mutations in the ryanodine receptor type 1 gene. *Neurology* 2005; **65**: 1930–1935.
- Zhou H, Jungbluth H, Sewry CA *et al*: Molecular mechanisms and phenotypic variation in *RYR1*-related congenital myopathies. *Brain* 2007; **130** (Part 8): 2024–2036.
- Monnier N, Marty I, Faure J *et al*: Null mutations causing depletion of the type 1 ryanodine receptor (*RYR1*) are commonly associated with recessive structural congenital myopathies with cores. *Hum Mutat* 2008; **29**: 670–678.
- Wilmshurst JM, Lillis S, Zhou H *et al*: *RYR1* mutations are a common cause of congenital myopathies with central nuclei. *Ann Neurol* 2010; **68**: 717–726.
- Bevilacqua JA, Monnier N, Bitoun M *et al*: Recessive *RYR1* mutations cause unusual congenital myopathy with prominent nuclear internalisation and large areas of myofibrillar disorganisation. *Neuropathol Appl Neurobiol* 2011; **37**: 271–284.
- Jungbluth H: Multi-minicore disease. *Orphanet J Rare Dis* 2007; **2**: 31.
- Treves S, Jungbluth H, Muntoni F, Zorzato F: Congenital muscle disorders with cores: the ryanodine receptor calcium channel paradigm. *Curr Opin Pharmacol* 2008; **8**: 319–326.
- Zhou H, Brockington M, Jungbluth H *et al*: Epigenetic allele silencing unveils recessive *RYR1* mutations in core myopathies. *Am J Hum Genet* 2006; **79**: 859–868.
- Ferreiro A, Quijano-Roy S, Pichereau C *et al*: Mutations of the selenoprotein N gene, which is implicated in rigid spine muscular dystrophy, cause the classical phenotype of multimicore disease: reassessing the nosology of early-onset myopathies. *Am J Hum Genet* 2002; **71**: 739–749.
- Arbogast S, Ferreiro A: Selenoproteins and protection against oxidative stress: selenoprotein N as a novel player at the crossroads of redox signaling and calcium homeostasis. *Antioxid Redox Signal* 2010; **12**: 893–904.
- Allamand V, Richard P, Lescure A *et al*: A single homozygous point mutation in a 3'untranslated region motif of selenoprotein N mRNA causes *SEPN1*-related myopathy. *EMBO Rep* 2006; **7**: 450–454.
- Maiti B, Arbogast S, Allamand V *et al*: A mutation in the *SEPN1* selenocysteine redefinition element (SRE) reduces selenocysteine incorporation and leads to *SEPN1*-related myopathy. *Hum Mutat* 2009; **30**: 411–416.
- Jungbluth H, Davis MR, Muller C *et al*: Magnetic resonance imaging of muscle in congenital myopathies associated with *RYR1* mutations. *Neuromuscul Disord* 2004; **14**: 785–790.
- Fischer D, Herasse M, Ferreiro A *et al*: Muscle imaging in dominant core myopathies linked or unlinked to the ryanodine receptor 1 gene. *Neurology* 2006; **67**: 2217–2220.
- Mercuri E, Clements E, Offiah A *et al*: Muscle magnetic resonance imaging involvement in muscular dystrophies with rigidity of the spine. *Ann Neurol* 2010; **67**: 201–208.
- Wu S, Ibarra MC, Malicdan MC *et al*: Central core disease is due to *RYR1* mutations in more than 90% of patients. *Brain* 2006; **129** (Part 6): 1470–1480.
- Girard T, Urwyler A, Censier K, Mueller CR, Zorzato F, Treves S: Genotype-phenotype comparison of the Swiss malignant hyperthermia population. *Hum Mutat* 2001; **18**: 357–358.
- Kaindl AM, Ruschendorf F, Krause S *et al*: Missense mutations of *ACTA1* cause dominant congenital myopathy with cores. *J Med Genet* 2004; **41**: 842–848.
- Carmignac V, Salih MA, Quijano-Roy S *et al*: C-terminal titin deletions cause a novel early-onset myopathy with fatal cardiomyopathy. *Ann Neurol* 2007; **61**: 340–351.
- Fananapazir L, Dalakas MC, Cyran F *et al*: Missense mutations in the beta-myosin heavy-chain gene cause central core disease in hypertrophic cardiomyopathy. *Proc Natl Acad Sci USA* 1993; **90**: 3993–3997.
- Muelas N, Hackman P, Luque H *et al*: *MYH7* gene tail mutation causing myopathic profiles beyond Laing distal myopathy. *Neurology* 2010; **75**: 732–741.
- Jungbluth H, Sewry CA, Brown SC *et al*: Mild phenotype of nemaline myopathy with sleep hypoventilation due to a mutation in the skeletal muscle α -actin (*ACTA1*) gene. *Neuromuscul Disord* 2001; **11**: 35–40.
- Schessl J, Medne L, Hu Y *et al*: MRI in *DNM2*-related centronuclear myopathy: evidence for highly selective muscle involvement. *Neuromuscul Disord* 2007; **17**: 28–32.
- Romero NB, Lehtokari VL, Quijano-Roy S *et al*: Core-rod myopathy caused by mutations in the nebulin gene. *Neurology* 2009; **73**: 1159–1161.
- Messina S, Hartley L, Main M *et al*: Pilot trial of salbutamol in central core and multi-minicore diseases. *Neuropediatrics* 2004; **35**: 262–266.
- Arbogast S, Beuvin M, Frayssé B, Zhou H, Muntoni F, Ferreiro A: Oxidative stress in *SEPN1*-related myopathy: from pathophysiology to treatment. *Ann Neurol* 2009; **65**: 677–686.
- Rosenberg H, Rueffert H: Clinical utility gene card for: malignant hyperthermia. *Eur J Hum Genet* 2011; e-pub ahead of print 19 January 2011; doi:10.1038/ejhg.2010.248.

1 Jungbluth H, Beggs A, Bonnemant C *et al*: 111th ENMC International Workshop on Multi-minicore Disease. 2nd International MmD Workshop, 9–11 November 2002, Naarden, The Netherlands. *Neuromuscul Disord* 2004; **14**: 754–766.