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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Central core disease

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Central core disease (CCD) and related phenotypes.

1.2 OMIM# of the disease

#117000.

1.3 Name of the analysed genes or DNA/chromosome segments

Skeletal muscle ryanodine receptor (*RYR1*) gene.

1.4 OMIM# of the gene(s)

*180901.

1.5 Mutational spectrum

Presently, more than 200 mutations in the *RYR1* gene have been reported, some exclusively associated with CCD or other *RYR1*-related myopathies, others with the malignant hyperthermia susceptibility (MHS) trait, or both.[1–3] *RYR1* mutations associated with CCD are mainly dominant and, less frequently, recessive, in contrast to *RYR1*-related multi-minicore disease (MmD), which is predominantly associated with recessive inheritance.[4] The *RYR1* mutational spectrum associated with CCD comprises mainly heterozygous dominant missense mutations and small deletions or duplications.[5–13]

1.6 Analytical methods

Selection criteria:

Considering that cores on muscle biopsy are a nonspecific finding and variations of uncertain significance are particularly common in the *RYR1* gene, genetic testing in CCD should only be initiated based on a comprehensive assessment of clinical, histopathological and, increasingly, muscle MRI features at a specialist neuromuscular centre. A certain combination of features, none of them specific in isolation, is suggestive of *RYR1* involvement and should prompt *RYR1* mutation screening. In general, it is of note that CCD is part of clinical and histopathological spectrum of *RYR1*-related myopathies and in particular shows some overlap with MmD (see also Clinical Utility Gene Card: Multi-minicore Disease).

- *Clinical features:* Most patients with *RYR1*-related CCD typically have mild-to-moderate axial and proximal weakness pronounced in the hip girdle.[1] Marked facial and extraocular involvement is not a typical feature. Bulbar and respiratory involvement is uncommon and, if at all present, mild. A primary cardiomyopathy is not a feature in *RYR1*-related CCD and suggests (a) different genetic condition(s).
- *Histopathological features:* Typical *RYR1*-related CCD is characterised by well-defined, single or multiple, central or eccentric cores running a significant extent along the longitudinal muscle fibre axis on muscle biopsy.[14] In cases with suggestive clinical features but less specific histopathological findings such as type 1 predominance, uniformity,[15] or cores and rods,[16,17] muscle MRI may be more indicative of *RYR1* involvement than muscle biopsy (see below).
- *Muscle MR imaging:* Muscle MR imaging in *RYR1*-related CCD shows a characteristic and consistent pattern of selective involvement, which may aid genetic testing and distinguish from core myopathies with different genetic backgrounds. The particular pattern of selective involvement in *RYR1*-related CCD is as follows: 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. Within the lower leg, there is prominent involvement of the peroneal group compared with the tibialis anterior, and of the soleus compared with the gastrocnemii. Although still discernible, the contrast between affected and unaffected muscles is often not as prominent in recessive compared with dominant *RYR1*-related CCD.[18–20]

RYR1 mutation screening:

Genomic sequencing of coding regions and flanking intronic sequence by conventional Sanger sequencing is currently the main strategy for *RYR1* mutation screening in CCD. In future, array CGH, next generation sequencing and/or multiplex ligation-dependent probe amplification are likely to enable the additional detection of larger deletions, duplications and genomic rearrangements,[21] although the latter are likely to have a more prominent role in recessively inherited *RYR1*-related myopathies such as MmD[22] than typical, dominantly inherited CCD.

1.7 Analytical validation

Direct sequencing of both DNA strands is performed. Some *RYR1* variants, often those associated with recessive inheritance (see also Clinical Utility Gene Card: Multi-minicore Disease), may not be detectable on genomic sequencing and cDNA analysis will be required. Any sequence variant identified on genomic DNA sequencing is confirmed on a second analysis of the index case' DNA sample. If a

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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. Functional studies 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 CCD or other *RYR1*-related myopathies is not accurately known. A regional study in the north of England[23] estimated a frequency for CCD of 1 in 250 000. The carrier frequency for heterozygous *RYR1* mutations in the Japanese population[9] is expected to be as high as 1 in 2000. The genetic incidence of the allelic MHS trait and the clinical prevalence of overt malignant hyperthermia (MH) reactions has been estimated at 1 in 3000–10 000 and 1 in 60 000–100 000, respectively,[24] but may be as high as 1 in 2000.[25]

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

Not applicable for CCD. However, specific MH-related *RYR1* mutations or other *RYR1*-related myopathies have been found to be more prevalent in certain populations.[26,27]

1.10 Diagnostic setting

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

Comment:

- *Predictive testing:* In many cases, testing for *RYR1* mutations does not only test for CCD but also for the MHS trait, an allelic but not consistently associated complication of mainly dominantly inherited *RYR1* mutations.[24] 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.
- *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 a *RYR1* mutation previously identified in an affected index case has been excluded.
- *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 CCD and other *RYR1*-related myopathies because of not only the large number of *RYR1* variations of uncertain significance but also variable clinical expressivity of pathogenic *RYR1* mutations even in the same family (see also section 2.5). We would therefore only consider prenatal diagnosis in families where pathogenicity for (a) *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.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: False positives	C: False negatives D: True negatives
	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 *RYR1* testing in CCD are currently available. However, analytical sensitivity is likely to be $<100\%$ if no diagnostic test for large-scale deletions, duplications, splice mutations or genomic rearrangements has been performed. Many of these variations are not detectable on genomic sequencing and will require cDNA sequencing. However, large-scale deletions, duplications, splice mutations or genomic rearrangements are more likely to have a role in recessively inherited, *RYR1*-related myopathies such as certain subgroups of MmD[22] (see also Clinical Utility Gene Card for: Multi-minicore Disease).

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 other CCD families.
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.
7. Functional proof of pathogenecity.

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

No precise data regarding the analytical specificity of *RYR1* testing in CCD are currently available. However, *RYR1* sequence variations of uncertain significance are common, with only a small proportion of those having been functionally characterised to date, with an associated risk of false-positive results.

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 for *RYR1* mutation screening also depends on the method used for mutation screening, as for example rarely larger copy number variations or genomic rearrangements may be missed on routine sequencing, and, more importantly, the stringent application of clinical and histopathological selection criteria as outlined in Paragraph 1.6.

Although a recent study in the Japanese population involving larger patient numbers indicates that *RYR1* is the causative gene in more than 90% of patients with CCD,[9] there is also evidence for genetic heterogeneity accounting for the imperfect clinical sensitivity of *RYR1* screening in CCD:

- In a large series of 86 families with typical features of CCD, *RYR1* involvement was excluded by cDNA analysis or linkage analysis in 7 families.[28]
- Central cores and multi-minicores as the main feature on muscle biopsy have been reported in a number of genetically distinct myopathies, often associated with clinical features unusual in the context of *RYR1*-related CCD such as a primary cardiomyopathy or prominent distal involvement. Dominant missense mutations in the β-myosin heavy-chain gene, *MYH7*,[29] may give rise to central cores on muscle biopsy with a distinct associated myopathy phenotype with or without cardiac impairment.[30] A cardiomyopathy associated with cores on muscle biopsy has also been documented in a mildly affected family harbouring dominant *ACTA1* mutations[31] and severely affected siblings with homozygous truncating recessive titin mutations.[32]
- Central cores and multi-minicores as a secondary feature on muscle biopsy have been reported associated with mutations in the *ACTA1*,[33] *DNM2*[34] and *NEB*[35] genes, however, in most of these cases other findings, namely nemaline rods or centralised internal nuclei, are the most prominent histopathological feature. Combination of central cores and nemaline rods in particular may also be seen with certain *RYR1* mutations.[16,17]

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)
No precise data regarding the clinical specificity of *RYR1* testing in CCD are currently available, however, clinical specificity is likely to be $<100\%$ 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
(lifetime risk to develop the disease if the test is positive)
Penetrance of CCD-associated *RYR1* mutations is likely to be near 100% with, however, marked inter- and intrafamilial clinical variability. Cases with a CCD presentation and a *RYR1* sequence variant inherited from an asymptomatic or paucisymptomatic parent have indeed been reported and are increasingly being recognised. Although other genetic modifiers cannot be excluded, this is often due to the presence of a second *RYR1* variant on the background of a dominantly inherited *RYR1* mutation, often associated with the MHS trait, running in the family. For example, it has been reported that offspring of asymptomatic parents harbouring a MH mutation may develop a myopathy, due to homozygosity for the MH-associated *RYR1* variant in the child.[36] Along the same lines, King-Denborough syndrome, another *RYR1*-related myopathy with dysmorphic features, has recently been attributed to compound heterozygositiy for a dominant MH mutation running in the family and a second *RYR1* variant in the child not always detected on traditional sequencing but reducing the amount of functional RyR1 protein.[37] These examples illustrate a complex inheritance pattern associated with *RYR1*-related disorders, with some *RYR1* mutations behaving as dominants with regards to the MHS trait but as recessives with regards to congenital myopathy phenotypes. Pathogenicity can only be reliably assigned and predicted if sequencing of the entire *RYR1* gene has been performed and all *RYR1* variants potentially contributing to a at risk genotype have been identified.

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 $<100\%$ in *RYR1*-related CCD, 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 mutations can be ruled out (ie, by sequencing both parents), then 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 *RYR1* mutations is important in the differential diagnosis of patients with clinical features of a congenital myopathy and histopathological findings suggestive of CCD.

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 CCD is a clinical and, most importantly, a histopathological diagnosis, a primary molecular genetic analysis is indicated only in familial cases with typical clinical features, which must include muscle weakness, and known associated *RYR1* mutations. In all other cases, a comprehensive assessment comprising detailed evaluation of clinical, histopathological and, where 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, is required in the index case to inform the choice of genetic testing and to establish the diagnosis. A muscle biopsy is

also important to obtain cDNA as some causative mutations, particularly those associated with recessive core myopathies (see also Clinical Utility Gene Card for: Multi-minicore Disease), may not be detectable on genomic sequencing. A muscle biopsy in particular is an invasive procedure and will require local or general anaesthesia but its rate of complications is usually very low. Muscle MR imaging may require sedation in young children <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 clinicopathological diagnosis of CCD will help to focus multidisciplinary management, therapeutic interventions and follow-up as outlined below.
	Therapy (please describe)	*There are no specific pharmacological agents currently consistently administered in RYR1-related CCD. However, preliminary data for example on the use of salbutamol in RYR1-related myopathies[38] suggest that genetic testing in CCD may also provide the basis for rationale pharmacological therapies in the future.*
	Prognosis (please describe)	*Confirmation of the genetic defect in a patient with a clinicopathological diagnosis of CCD contributes to the definite resolution of a congenital myopathy with not entirely specific clinical and histopathological features, and provides the basis for prognostic statements. Positive prognostic indicators in RYR1-related CCD are the relative lack of cardiorespiratory involvement, namely primary cardiomyopathies. Most individuals affected by CCD show a stable or only very slowly progressive course. Life expectancy is unaffected in most cases.*
	Management (please describe)	*The genetic result will help to focus 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. Exercise-induced myalgias are a common feature of some patients with RYR1-related CCD and may require medical intervention. Some individuals with RYR1-related CCD may be at an increased risk of suffering MH reactions in response to volatile anaesthetics and muscle relaxants, and genetic confirmation of the diagnosis will lead to initiation of appropriate testing and preventive measures around operative procedures.[20] Initiation of pharmacological treatments such as salbutamol may be of benefit in some individuals with RYR1-related CCD. The risk of a primary cardiomyopathy is probably higher in RYR1- negative patients with CCD and follow-up should be planned accordingly.*

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?
Yes.

If the test result is positive (please describe):
Genetic confirmation of the clinicopathological diagnosis of *RYR1*-related CCD will help to focus 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 *RYR1* have been excluded and no clinicopathological features of CCD are present. Follow-up should be arranged as outlined in Paragraph 3.1.4 if clinicopathological features of CCD are present but no *RYR1* mutation could be identified.

3.2.2 Which options in view of lifestyle and prevention do a person at-risk have if no genetic test has been done (please describe)?
If the person has a positive family history of CCD 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 CCD 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, if a heterozygous dominant *RYR1* mutation (or two recessive *RYR1* mutations in trans) of proven pathogenicity have been identified, provided 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.

We personally do recommend testing also for asymptomatic parents and other relatives, both to determine the precise inheritance pattern in the family but also to advice the parents about their potential MHS risk. As the associated MHS risk has been determined only for a proportion of known *RYR1* variants, we do recommend MHS precautions even if the associated MHS risk of the specific *RYR1* mutation is uncertain. We also generally recommend IVCT testing in patients or asymptomatic carriers older than 16 years of age, where the associated MHS risk of the *RYR1* variant identified has not been previously documented.

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 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*-related CCD will help to anticipate future course, plan interventions and prevent potential complications. It will also end an often 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 public/private partnership organisation, which offers clinical diagnostic testing of the *RYR1* gene.

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