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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: malignant hyperthermia

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Malignant hyperthermia (MH).[1,2]

1.2 OMIM# of the disease
145600.

1.3 Name of the analyzed genes or DNA/chromosome segments
RYR1 (chr.19q13.1), *CACNA1S* (chr. 1q3).[3,4]

1.4 OMIM# of the gene(s)
180901 (*RYR1*), 114208 (*CACNA1S*).

1.5 Mutational spectrum
30 functionally confirmed causative point mutations (*RYR1*), about 200 MH-associated mutations in RYR1, few mutations in *CACNA1S* (of minor importance).[5–8]

1.6 Analytical methods
Sequence analysis of the entire coding region (*RYR1*: 16 000 bp); sequence analysis of selected exons, mutation scanning of the entire coding region, mutation scanning of selected exons (direct sequencing, DHPLC, MLPA, restriction enzyme analysis).[9–13]

1.7 Analytical validation
>95% specificity, depending on the correctness of the phenotype.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)
Genetic incidence: 1:3000–1:10 000.[14]
Clinical prevalence: 1:60 000–1:100 000.[15,16]

1.9 If applicable, prevalence in the ethnic group of investigated person
Not applicable.

1.10 Diagnostic setting

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

Comment D:
Meaningful but not yet approved.

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)
100%.

2.2 Analytical specificity (proportion of negative tests if the genotype is not present)
100%.

2.3 Clinical sensitivity (proportion of positive tests if the genotype is present)[20,21]
>70%.

2.4 Clinical specificity (proportion of negative tests if the disease is not present)[20,21]
The clinical specificity can be dependent on variable factors, such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.
>95%.

2.5 Positive clinical predictive value (life time risk to develop the disease if the test is positive)[20,21]
Life-time risk to develop the disease when patient is exposed to 'trigger' anesthetics is >75%.

2.6 Negative clinical predictive value (probability not to develop the disease if the test is negative)[20,21]
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:
~90%.

Index case in that family had not been tested:
~15%.

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3. CLINICAL UTILITY

3.1 (Differential) diagnosis: The tested person is clinically affected

Besides MH, a number of RYR1 mutations have been described to be associated with rare congenital myopathies. These include myopathies with cores (central core disease (CCD): MIM #11700; specific forms of multiminicore disease (MmD): MIM#255320) or central nuclei (centronuclear myopathy: MIM#160150) that are associated with a wide range of phenotypes. CCD is closely linked with MH, as both disorders share the same gene locus. In the other congenital myopathies, *RYR1* mutations are rather an exception, but the MH risk must also be considered high until more information becomes available.[22–27]

In contrast to this, there are disorders or syndromes that are very similar to classical MH, for example, serotonin syndrome or neuroleptic malignant syndrome. Other myopathies, such as Duchenne or Becker's muscular dystrophy, may induce 'MH-like' symptoms under general anesthesia due to other pathophysiological pathways than for MH.[19]

3.1.1 Can a diagnosis be made other than through a genetic test?[17-19,28,29]

No	☐ (continue with 3.1.4)	
Yes	☒	
	Clinically	☒
	Imaging	☐
	Endoscopy	☐
	Biochemistry	☐
	Electrophysiology	☐
	Other (please describe)	☒ *In vitro* contracture test (also called caffeine halothane contracture test): contracture of muscle fascicles from a fresh muscle biopsy (weight ~200 mg) following exposure to halothane and caffeine.

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

Patients need surgery (open muscle biopsy). Contracture test must be performed within few hours of harvest. IVCT/CHCT can be performed only in special MH centers.[1,2]

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

Cost for muscle biopsy and IVCT: about €2000 in Europe. In the USA, the test is the CHCT version with a cost of about $6000.

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

No	☐	
Yes	☒	
	Therapy (please describe)	*Malignant hyperthermia can be successfully treated with a specific antidote (Dantrium).*
	Prognosis (please describe)	*Is excellent if triggering agents of malignant hyperthermia (volatile anaesthetics, depolarizing muscle relaxants) are avoided during general anaesthesia.*
	Management (please describe)	*Triggering agents of malignant hyperthermia (volatile anaesthetics, depolarizing muscle relaxant succinylcholine) must be avoided during general anaesthesia; special preparation of the anaesthesia machine is required before general anaesthesia, relatives of those diagnosed are advised to be tested and followed precautions as above.*

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

MH predisposed persons are clinically unaffected until exposed to MH trigger agents.

Only patients who are tested MH positive need a special anaesthetic management during surgery. MH negative tested persons can be handled like the 'normal' patients; regardless of the family history.

3.2.1 Will the result of a genetic test influence lifestyle and prevention?[1,2,5]

Yes.

If the test result is positive (please describe):
The patient gets an anesthesia-warning card to alert the anesthesiologist to problems during anesthesia. The card should always be carried by the holder. Extreme caution when exercising in hot environment and with extreme exercise.

If the test result is negative (please describe):
For clinical reasons of safety the patient needs to undergo a negative confirmation test (muscle biopsy, halothane/caffeine provocation test).

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)?

Person should be alternatively tested with the IVCT/CHCT (muscle biopsy) to determine the MH risk. Otherwise the patient should consider himself at risk for MH.

3.3 Genetic risk assessment in family members of a diseased person

50%.

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

Yes, if a mutation is found. If the index patient does not have a mutation, MH susceptibility is still a possibility because of heterogeneity.

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

Yes.

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

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

Prenatal diagnosis is not yet approved solely for MH diagnosis but would be a promising option and would make sense if the familial MH mutation is known. PND could increase patient safety, for example, for the newborn of MH positive parents (MH-positive mother or father, newborn is 50% at risk) under the situation of a Cesarean section. In this case MH triggering agents (given under general anesthesia) must be avoided even if the mother is negative.

On the other hand, prenatal diagnosis is an important option for other congenital *RYR1*-related disorders and if such an indication is given the search for MH-associated mutations could be taken under consideration.

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. If a mutation associated with CCD or MmD is found, the patient should be followed for evidence of muscle weakness. Prenatal counseling is advised in such cases.

Family members should be treated as MH susceptible until IVCT/CHCT test is done with a negative result.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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