CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Meckel syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Meckel syndrome types 1–6, Meckel–Gruber syndrome, and dysencephalia splanchnocystica.^{1,2}

1.2 OMIM# of the disease

Type 1 MIM #249000, type 2 MIM #603194, type 3 MIM #607361, type 4 MIM #611134, type 5 MIM #611561, and type 6 MIM #612284.

1.3 Name of the analysed genes or DNA/chromosome segments

MKS1,^{3–5} *TMEM216* (*MKS2*),⁶ *TMEM67* (*MKS3*),^{4,5,7} *CEP290* (*MKS4*),^{8,9} *RPGRIP1L* (*MKS5*),¹⁰ and *CC2D2A* (*MKS6*).¹¹

1.4 OMIM# of the gene(s)

MKS1, MIM# 609883; *TMEM216*, MIM# 613277; *TMEM67*, MIM# 609884; *CEP290*, MIM# 610142; *RPGRIP1L*, MIM# 610937; and *CC2D2A* MIM# 612013.

1.5 Mutational spectrum

Data according to published literature and the HGMD database (release date 24 September 2010; <https://portal.biobase-international.com>)

MKS1: Major mutation c.1408-7_35del p.Gly470fs. In addition, 17 other mutations listed so far for patients with the Meckel–Gruber phenotype (three nonsense, one missense, seven canonical splice-site mutations, four small deletions/duplications, one silent mutation, and one intronic 143-bp deletion, both leading to aberrant splicing).^{3,12,13}

TMEM216/MKS2: Three different mutations described so far in patients with Meckel–Gruber syndrome (one nonsense, one splicing, and one missense mutation).⁶

TMEM67/MKS3: Wide mutational spectrum without significant hotspot mutation in non-isolated cohorts. So far, 37 different mutations described in patients with the Meckel–Gruber phenotype (5 nonsense, 17 missense, 7 canonical splice-site mutations, 7 small deletions/insertions/duplications, and 1 gross deletion described at genomic DNA level encompassing exons 17–21).^{3,13,14}

CEP290/MKS4: Recurrent mutation c.1219_1220del p.Met407fs in several families. A total of 13 different mutations described so far in patients with the Meckel–Gruber phenotype (five nonsense, two canonical splice-site mutations, and six small deletions/insertions/duplications).^{8,9}

RPGRIP1L/MKS5: Only four different mutations in MKS cases described so far (three nonsense and one missense mutation).

CC2D2A/MKS6: Major mutation c.1762C>T p.Val587fs. In addition, 17 mainly family-specific mutations identified in patients with MKS (four nonsense, one missense, six splice-site mutations,

five small deletions/insertions, and one gross deletion described at genomic DNA level encompassing exons 28–31).^{11,15}

Currently, it is still hard to give exact figures on the contribution of each of the above genes to the total mutational load in Meckel–Gruber syndrome. There will be further genetic heterogeneity. However, *MKS1*, *MKS3/TMEM67*, and *MKS6/CC2D2A* might be major MKS genes, followed by *MKS4/CEP290*.^{3,11,15,16} Currently, the role of *MKS2/TMEM216* in Meckel–Gruber syndrome can only be speculated upon, whereas *MKS5/RPGRIP1L* seems to be quite rarely mutated in typical cases of Meckel syndrome.

Mutations in all MKS genes are mainly truncating, whereas in *MKS3* missense mutations are also frequent.

1.6 Analytical methods

Consanguineous and multiplex pedigrees were assessed using initial linkage analysis of known loci with subsequent sequencing in case of compatible haplotypes.

Mainly sequencing was carried out in sporadic cases originating from non-consanguineous marriages because of family-specific mutations in most cases.

1.7 Analytical validation

Most of the mutations have been identified on research basis by sequencing using a protocol that is validated in most laboratories.

1.8 Estimated frequency of the disease

(incidence at birth ('birth prevalence') or population prevalence)
 1/20 000.

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

In Finland and other isolated and/or consanguineous cohorts, the prevalence was much more frequent (most probably > 1/5 000–10 000).

1.10 Diagnostic setting:

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

Comment: If the causative gene and mutation of MKS can be identified, carrier screening of the relatives becomes possible as well as molecular prenatal diagnosis and preimplantation diagnosis.

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2. TEST CHARACTERISTICS

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

Nearly 100%.

2.2 Analytical specificity

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

Nearly 100%.

2.3 Clinical sensitivity

(proportion of positive tests if the disease is present)

Clinical sensitivity 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.

Clinical sensitivity is not known so far. Currently, six genes with a number of mutations have been identified as the causes of Meckel syndrome. There is a big variation in the distribution of these mutations in different populations, and some additional genes are still to be identified.^{6,16,17}

2.4 Clinical specificity

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

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.

Nearly 100%.

2.5 Positive clinical predictive value

(lifetime risk to develop the disease if the test is positive)

100%.

2.6 Negative clinical predictive value

(probability not to develop the disease if the test is negative)

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:

Much <1%.

Index case in that family had not been tested:

Unknown.

3. CLINICAL UTILITY

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

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

Yes.

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)

Autopsy and histological verification of the typical findings is reasonable.

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

The condition is lethal.

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

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

No

☐

Yes

☒

Therapy (please describe)

None in typical lethal cases

Prognosis (please describe)

Lethal in early infancy

Management (please describe)

None, termination of pregnancy in prenatally diagnosed 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?

Early prenatal diagnostics and preimplantation diagnosis become possible.

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)?

Prenatal diagnosis by ultrasound scan and termination of pregnancy in case of an affected fetus.

3.3 Genetic risk assessment in family members of a diseased person
(To be answered if in 1.10 'C' was marked)

Yes, in genetic counselling carrier testing of family members becomes possible.

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

Yes.

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?

No.

3.4 Prenatal diagnosis

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

Early genetic testing from chorionic villi is possible. Ultrasound scan detects the multicystic kidneys and malformations of the head, brain, and extremities.

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

Yes.

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)

Preimplantation diagnosis becomes possible.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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