CLINICAL UTILITY GENE CARD UPDATE

Clinical utility gene card for: Meckel syndrome – update 2016

Carsten Bergmann^{*,1,2}, Valeska Frank¹ and Riitta Salonen³

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

MKS, Meckel syndrome, Meckel–Gruber syndrome, Dysencephalia splanchnocystica.^{1–14}

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, type 6 MIM# 612284, type 7 MIM# 267010, type 8 MIM# 613885, type 9 MIM# 614209, type 10 MIM# 614175, type 11 MIM# 615397, type 12 MIM# 616258.

1.3 Name of the analyzed genes or DNA/chromosome segments

MKS1, TMEM216 (MKS2), TMEM67 (MKS3), CEP290 (MKS4), RPGRIP1L (MKS5), CC2D2A (MKS6), NPHP3 (MKS7), TCTN2 (MKS8), B9D1 (MKS9), B9D2 (MKS10), TMEM231 (MKS11), KIF14 (MKS12), TMEM107 (MKS13) and TMEM138, TMEM237.

1.4 OMIM# of the gene(s)

MKS1, MIM# 609883; TMEM216, MIM #613277, TMEM67, MIM# 609884; CEP290, MIM# 610142; RPGRIP1L, MIM# 610937; CC2D2A, MIM# 612013; NPHP3, MIM# 608002; TCTN2, MIM# 613885; B9D1, MIM# 614209; B9D2, MIM# 614175; TMEM231, MIM# 614949, KIF14, MIM# 611279; TMEM107, MIM# 616183; TMEM138, MIM# 614465; TMEM237, MIM# 614423.

1.5 Mutational spectrum

Data according to published literature and HGMD database (<https://portal.biobase-international.com>).

Exact figures are still hard to provide on the contribution of each of the above genes to the total mutational load in Meckel–Gruber syndrome. Although there is evidence for further genetic heterogeneity, major MKS genes are *MKS1*, *MKS3/TMEM67* and *MKS6/CC2D2A*, followed by *MKS4/CEP290*. Although all kind of pathogenic variants (missense and nonsense mutations, splice site mutations, deletions and insertions) are present, the majority is truncating, whereas in *MKS3* also missense mutations are frequent.

Although some genotype–phenotype correlations may allow for prioritization of genes in single cases, efficient testing has only been possible since establishment of next-generation sequencing (NGS) and

the possibility of simultaneous investigation of all genes to be discussed in a fetus.

1.6 Analytical methods

In consanguineous and multiplex pedigrees, initial linkage analysis (targeted and genome-wide) with subsequent sequencing in case of compatible haplotypes is possible, but often replaced by sequencing now.

In sporadic cases originating from non-consanguineous marriages, direct sequencing (by Sanger's method or NGS) is usually performed due to private variants in most cases.

1.7 Analytical validation

(Potential) pathogenic variants are bidirectionally sequenced, preferentially on a second DNA sample of the index patient. Segregation analysis in the parents of the index patient to ensure compound heterozygosity and/or to exclude a large deletion on the other allele for a homozygous variant should be performed. In case of a novel variant, family studies of affected and non-affected persons can be helpful, as well as testing of ethnically matched controls to exclude a pathogenic variant. Gene transcripts should be analyzed in case of potential splicing variants.

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, MKS is much more frequent.

(most probably > 1/5000–10 000).

1.10 Diagnostic setting

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

¹Center for Human Genetics, Bioscientia, Ingelheim, Germany; ²Department of Medicine, University Freiburg Medical Center, Freiburg, Germany; ³Norio-Centre, Rinnekoti Foundation, Helsinki, Finland

*Correspondence: Professor C Bergmann, Center for Human Genetics, Bioscientia, Konrad-Adenauer-Strasse 17, Ingelheim 55218, Germany. Tel: +49 6132 781 476; Fax: +49 6132 781 298; E-mail: carsten.bergmann@bioscientia.de or carsten.bergmann@uniklinik-freiburg.de

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2. TEST CHARACTERISTICS

Genotype or disease		A: True positives	C: False negatives
		B: False positives	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)

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 is not known so far. Currently, more than a dozen genes with a number of variants have been identified as the cause for Meckel syndrome. There is variation of the distribution of these variants in different populations, and additional genes can be expected to be identified in future years.

2.4 Clinical specificity

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

A hallmark of ciliopathies is their significant clinical and genetic heterogeneity with considerable overlap between different entities. In particular, Meckel syndrome is allelic to a group of other cilia-related disorders:

- Joubert syndrome (CC2D2A, CEP290, RPGRIP1L, TCTN2, TMEM67, TMEM138, TMEM216, TMEM231, TMEM237)
- Bardet-Biedl syndrome (CEP290, MKS1)
- Nephronophthisis (CEP290, NPHP3, RPGRIP1L, TMEM67)

Recently, single fetuses with features of MKS were described with variants in EVC2 and EXOC4. The first fetus was found to carry a novel homozygous variant (in-frame insertion of eight amino acids) in EVC2, a gene usually described to cause the ciliopathy Ellis-van Crefeld syndrome (EVC). Typical features for EVC such as skeletal and cardiac findings were lacking in this individual. The other fetus was described to harbor a novel homozygous missense variant in EXOC4 that encodes an exocyst protein recruited to the basal body. Both of these fetuses were detected by exome sequencing and had consanguineous parents and were of Arab origin.

2.5 Positive clinical predictive value

(life-time 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). In any case (index case tested or not), there is no risk to develop the disease for an unaffected individual (always present before birth).

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: 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 usually lethal.

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

Clinical work-up and imaging might be less cost-intensive, however, the obtained data is less clear with lower specificity and sensitivity.

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

No ☐

Yes ☒

Therapy (please describe)	Not relevant in lethal cases.
Prognosis (please describe)	Usually lethal perinatally or in early infancy.
Management (please describe)	Termination of pregnancy in prenatally diagnosed cases is an option for many couples.

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/or preimplantation genetic diagnosis (PGD) 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)?

Not applicable.

3.3 Genetic risk assessment in family members of a diseased person

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

Carrier testing of family members becomes possible.

Please note: due to the rarity of the disease, this is primarily important for couples that are related or of Finnish origin (eg, MKS1 founder mutation).

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 typically after chorionic villi sampling. Ultrasound scan usually detect clinical features characteristic of MKS such as cystic kidneys and malformations of the 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)

Early prenatal diagnostics and/or PGD become possible as well as carrier testing of family members.

Please note: due to the rarity of the disease, this is primarily important for couples that are related or of Finnish origin (eg, MKS1 founder mutation).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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