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CUGC for Mayer-Rokitansky-Küster-Hauser syndrome

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Clinical utility gene card for: Rokitansky-Küster-Hauser syndrome

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1. Disease characteristics

1.1 Name of the Disease (Synonyms):

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, MRKH type I or isolated MRKH or Rokitansky sequence, MRKH type II or MURCS association (Müllerian duct aplasia, Renal dysplasia and Cervical Somite anomalies), Congenital Absence of the Uterus and Vagina (CAUV), Genital Renal Ear Syndrome (GRES), Müllerian Aplasia (MA).

1.2 OMIM# of the Disease:

277000 (MRKH, CAUV), 601076 (MURCS)

1.3 Name of the Analysed Genes or DNA/Chromosome Segments:

1q21.1, 4q34-qter, 8p23.1, 10p14-15, 16p11.2, 17q12, 22q11.21, Xpter-p22.32

1.4 OMIM# of the Gene(s):

Putative candidate genes : 189907 (*TCF2*) [1, 2], 601999 (*LHX1*) [2-5], 312865 (*SHOX*) [6], 602427 (*TBX6*) [2], 609783 (*ITIH5*) [7].
Putative candidate locus : 274000 (TAR) [3, 5].

1.5 Mutational Spectrum:

Maximal deletion in 1q21.1: 398.5 kb [3, 5]; in 4q34-qter: 8 Mb [8]; in 8p23.1: 1.2 Mb [7]; in 10p14-15: 0.2 Mb [7]; in 16p11.2: 600kb [2]; in 17q12: 1.5 Mb [2, 3, 5] and in 22q11.21: 3 Mb [2, 3, 5, 7, 9, 10].
Maximal duplication in 1q21.1: 200 kb [3].
Partial duplication of the Xpter pseudoautosomal region 1 [6].

1.6 Analytical Methods:

Search for microrearrangements by means of Multiplex Ligation-dependent Probe Amplification (MLPA) using the SALSA P023 DiGeorge MLPA kit, Comparative Genomic Hybridization array (CGH array), Duplex PCR/Liquid Chromatography (DP/LC), and/or FISH

1.7 Analytical Validation

Validation of MLPA results or CGH array results by DP/LC or FISH

1.8 Estimated Frequency of the Disease

(Incidence at birth or "birth prevalence" or population prevalence):

1 in 4500 female births [11]

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: WNT4 syndrome is close but different from MRKH. It differs from this latter by an hyperandrogenism and gonadal affection [12]. It thus needs to be considered in regards to differential diagnosis [13].

2. Test characteristics

		genotype or disease	
		present	absent
test	pos.	A	B
	neg.	C	D

A: true positives C: false negatives
B: false positives D: true negatives

sensitivity:	A/(A+C)
specificity:	D/(D+B)
pos. predict. value:	A/(A+B)
neg. predict. value:	D/(C+D)

2.1 Analytical Sensitivity
(proportion of positive tests if the genotype is present)

Nearly 100% using analytical methods described above.

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

Nearly 100% using analytical methods described above.

2.3 Clinical Sensitivity
(proportion of positive tests if the disease is present)
The 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.

The synthesis of the literature [2-5, 9, 10] on the genome-wide analysis on MRKH patients, was used to estimate that only ~1% show a 1q21.1 rearrangement, ~1% in 16p11.2, ~6% in 17q12 and ~4% in 22q11.21, from a total of 153 cases.

2.4 Clinical Specificity
(proportion of negative tests if the disease is not present)
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.

100% of control subjects tested by MLPA (DiGeorge kit) showed negative results.

2.5 Positive clinical predictive value
(life time risk to develop the disease if the test is positive).

not applicable

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:

not applicable

Index case in that family had not been tested:

not applicable

3. Clinical Utility

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

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): Testosterone dosage

3.1.2 Describe the burden of alternative diagnostic methods to the patient

Initial clinical examination and transabdominal ultrasonography must be the first investigations in evaluating patients with suspected Müllerian aplasia. If necessary, magnetic resonance imaging (MRI) affords to clearly precise the malformation. A full check-up (transabdominal ultrasonography, spine radiography, and/or heart echography, audiogram) should be undertaken to search for associated malformations in order to determine the MRKH type (I or II). Testosterone dosage should help orientating the diagnosis towards MRKH or WNT4 syndrome.

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

Alternative diagnosis methods described above are, at present, the only way to accurately diagnose MRKH syndrome since the phenotype-genotype correlations still cannot be established. Clinical examination, imaging, and biological measurements, will in any case remain necessary to evaluate the level of care for patients.

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

No. ☐

Yes. ☒
Therapy (please describe)
Prognosis (please describe)
Management (please describe) The results of genetic tests will influence genetic counselling in case of surrogate pregnancy demand.

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)

If the test result is **negative** (please describe)

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)?

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?

Can improve genetic counselling

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?

In rare familial forms

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 diagnosis?

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)

Conflict of interest

The authors declare no conflict of interest

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Review of the analytical and clinical validity as well as of the clinical utility of DNA-based testing for mutations in the TCF2, LHX1, SHOX and ITIH5 genes in diagnostic settings and for risk assessment in relatives.