



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

Karine Morcel, Bruno Dallapiccola, Laurent Pasquier, Tanguy Watrin, Laura Bernardini, Daniel Guerrier

► To cite this version:

Karine Morcel, Bruno Dallapiccola, Laurent Pasquier, Tanguy Watrin, Laura Bernardini, et al.. Clinical utility gene card for: Mayer-Rokitansky-Küster-Hauser syndrome.. European Journal of Human Genetics, 2012, 20 (2), 10.1038/ejhg.2011.158 . inserm-00622156

HAL Id: inserm-00622156

<https://inserm.hal.science/inserm-00622156>

Submitted on 7 Mar 2012

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

CUGC for Mayer-Rokitansky-Küster-Hauser syndrome

Article pg. 2-7

Abstract pg. 8

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

Karine Morcel^{1,2}, Bruno Dallapiccola³, Laurent Pasquier⁴, Tanguy Watrin^{1,5}, Laura Bernardini⁶ and Daniel Guerrier^{1,5}

¹ CNRS, UMR 6061-IGDR, F-35043 Rennes, France

² CHU Rennes, Pôle d'Obstétrique Gynécologie et Médecine de la Reproduction, F-35033 Rennes, France

³ Bambino Gesù Pediatric Hospital, IRCCS, Piazza S. Onofrio 4, 00165, Rome, Italy

⁴ CHU Rennes, Pôle de Pédiatrie et Génétique, F-35033 Rennes, France

⁵ Rennes 1, UEB, IFR 140, Faculté de Médecine, F-35043 Rennes, France

⁶ Mendel Laboratory, Casa Sollievo della Sofferenza Hospital, IRCCS, Viale dei Cappuccini s.n.c., 71013 San Giovanni Rotondo (FG), Italy

Correspondence: Dr D Guerrier, CNRS, IGDR-UMR 6061, Equipe « Génétique des Pathologies Liées au Développement », 2 avenue du Professeur Léon Bernard, CS 34317, 35043 Rennes Cedex, France.
Tel: +33-(0)223 234679; Fax: +33-(0)223 234478; E-mail: daniel.guerrier@univ-rennes1.fr

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	<input type="checkbox"/>	<input type="checkbox"/>
B. Predictive Testing	<input type="checkbox"/>	<input type="checkbox"/>
C. Risk assessment in Relatives	<input type="checkbox"/>	<input type="checkbox"/>
D. Prenatal	<input type="checkbox"/>	<input type="checkbox"/>

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		A: true positives	C: false negatives
		absent		B: false positives	D: true negatives
test	pos.	A	B	<u>sensitivity:</u> A/(A+C)	
	neg.	C	D	<u>specificity:</u> 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

Acknowledgement

This work was supported by EuroGentest, an EU-FP6 supported NoE, contract number 512148 (EuroGentest Unit 3: "Clinical genetics, community genetics and public health", Workpackage 3.2)

References

1. Lindner TH, Njolstad PR, Horikawa Y, Bostad L, Bell GI, Sovik O: **A novel syndrome of diabetes mellitus, renal dysfunction and genital malformation associated with a partial deletion of the pseudo-POU domain of hepatocyte nuclear factor-1beta.** *Hum Mol Genet* 1999, **8**(11):2001-2008.
2. Nik-Zainal S, Strick R, Storer M, Huang N, Rad R, Willatt L, Fitzgerald T, Martin V, Sandford R, Carter NP *et al:* **High incidence of recurrent copy number variants in patients with isolated and syndromic Mullerian aplasia.** *J Med Genet* 2011, **48**(3):197-204.
3. Cheroki C, Krepischi-Santos AC, Szuhai K, Brenner V, Kim CA, Otto PA, Rosenberg C: **Genomic imbalances associated with mullerian aplasia.** *J Med Genet* 2008, **45**(4):228-232.
4. Bernardini L, Gimelli S, Gervasini C, Carella M, Baban A, Frontino G, Barbano G, Divizia MT, Fedele L, Novelli A *et al:* **Recurrent microdeletion at 17q12 as a cause of Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome: two case reports.** *Orphanet J Rare Dis* 2009, **4**:25.

5. Ledig S, Schippert C, Strick R, Beckmann MW, Oppelt PG, Wieacker P: **Recurrent aberrations identified by array-CGH in patients with Mayer-Rokitansky-Kuster-Hauser syndrome.** *Fertil Steril* 2010.
6. Gervasini C, Grati FR, Lalatta F, Tabano S, Gentilin B, Colapietro P, De Toffol S, Frontino G, Motta F, Maitz S et al: **SHOX duplications found in some cases with type I Mayer-Rokitansky-Kuster-Hauser syndrome.** *Genet Med* 2010, **12**(10):634-640.
7. Morcel K, Watrin T, Pasquier L, Rochard L, Le Caignec C, Dubourg C, Loget P, Paniel BJ, Odent S, David V et al: **Utero-vaginal aplasia (Mayer-Rokitansky-Kuster-Hauser syndrome) associated with deletions in known DiGeorge or DiGeorge-like loci.** *Orphanet J Rare Dis* 2011, **6**(1):9.
8. Bendavid C, Pasquier L, Watrin T, Morcel K, Lucas J, Gicquel I, Dubourg C, Henry C, David V, Odent S et al: **Phenotypic variability of a 4q34-->qter inherited deletion: MRKH syndrome in the daughter, cardiac defect and Fallopian tube cancer in the mother.** *Eur J Med Genet* 2007, **50**(1):66-72.
9. Cheroki C, Krepischi-Santos AC, Rosenberg C, Jehee FS, Mingroni-Netto RC, Pavanello Filho I, Zanforlin Filho S, Kim CA, Bagnoli VR, Mendonca BB et al: **Report of a del22q11 in a patient with Mayer-Rokitansky-Kuster-Hauser (MRKH) anomaly and exclusion of WNT-4, RAR-gamma, and RXR-alpha as major genes determining MRKH anomaly in a study of 25 affected women.** *Am J Med Genet A* 2006, **140**(12):1339-1342.
10. Uliana V, Giordano N, Caselli R, Papa FT, Ariani F, Marcocci C, Gianetti E, Martini G, Papakostas P, Rollo F et al: **Expanding the phenotype of 22q11 deletion syndrome: the MURCS association.** *Clin Dysmorphol* 2008, **17**(1):13-17.
11. Folch M, Pigem I, Konje JC: **Mullerian agenesis: etiology, diagnosis, and management.** *Obstet Gynecol Surv* 2000, **55**(10):644-649.
12. Biason-Lauber A, Konrad D: **WNT4 and sex development.** *Sex Dev* 2008, **2**(4-5):210-218.
13. Morcel K, Camborieu L, Guerrier D: **Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome.** *Orphanet J Rare Dis* 2007, **2**:13.

Clinical utility gene card for:

Karine Morcel^{1,2}, Bruno Dallapiccola³, Laurent Pasquier⁴, Tanguy Watrin^{1,5}, Laura Bernardini⁶ and Daniel Guerrier^{1,5}

¹ CNRS, UMR 6061-IGDR, Equipe « Génétique des Pathologies Liées au Développement », F-35043 Rennes, France

² CHU Rennes, Pôle d'Obstétrique Gynécologie et Médecine de la Reproduction, F-35033 Rennes, France

³ Bambino Gesù Pediatric Hospital, IRCCS, Piazza S. Onofrio 4, 00165, Rome, Italy

⁴ CHU Rennes, Pôle de Pédiatrie et Génétique, F-35033 Rennes, France

⁵ Univ Rennes 1, UEB, IFR 140, Faculté de Médecine, F-35043 Rennes, France

⁶ Mendel Laboratory, Casa Sollievo della Sofferenza Hospital, IRCCS, Viale dei Cappuccini s.n.c., 71013 San Giovanni Rotondo (FG), Italy

Correspondence: Dr D Guerrier, CNRS, UMR 6061, Equipe « Génétique des Pathologies Liées au Développement », 2 avenue du Professeur Léon Bernard, CS 34317, 35043 Rennes Cedex, France.
Tel: +33-(0)223 234679; Fax: +33-(0)223 234478; E-mail: daniel.guerrier@univ-rennes1.fr

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).

OMIM# of the Disease:

277000 (MRKH, CAUV), 601076 (MURCS)

Analysed Genes or DNA/Chromosome Segments:

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

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].

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.