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Higher incidence of linked malformations in siblings of Mayer–Rokitansky–Küster–Hauser-syndrome patients

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BACKGROUND: Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome is a malformation of the female genital tract (vaginal aplasia, rudimentary uterus, normal fallopian tubes and high ovaries). The incidence is one in 4000 female newborns. The aim of the present study was to record genital and associated malformations among siblings and relatives of MRKH patients in order to draw possible conclusions regarding the etiology of the syndrome: heredity (dominant versus recessive) or spontaneous malformation. METHODS: Using a standardized questionnaire, affected MRKH patients were asked about other cases of MRKH and/or associated malformations among siblings and relatives. RESULTS: No other cases of MRKH syndrome had occurred among the siblings or relatives of 73 MRKH patients; however, 13 associated malformations were recorded among a total of 103 siblings. Musculoskeletal malformations were markedly increased (3.27 times higher) in comparison with the prevalence of congenital malformations among newborns in the normal population. CONCLUSIONS. This study shows that dominant inheritance cannot play a role in the etiology of MRKH syndrome, as no further cases of MRKH syndrome occurred among any of the siblings. The study provides support for the view that the syndrome has a multifactorial pathogenesis. Siblings/relatives of MRKH patients should be examined for associated musculoskeletal/urogenital malformations.

Keywords: MRKH syndrome; VCUAM classification; genital malformation; hereditary transmission

Introduction

Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome is a form of aplasia of the Müllerian ducts in which the fusion and further differentiation of the distal parts of the ductal system fail to take place during embryogenesis between the 28th and 45th day after conception. The frequency of the syndrome is reported to be one in 4000 female newborns (Chervenak *et al*., 1982; Communal *et al*., 2003; Oppelt *et al*., 2006). At the current birth rate of ~700 000 newborns per year in Germany (2004 data, German Federal Office of Statistics Press Office, 2006), this represents an incidence of ~80 new cases per year.

Clinically, MRKH syndrome is marked by vaginal aplasia with a rudimentary uterus (*uterus bipartitus solidus rudimentarius cum vagina solida*) and normal or hypoplastic fallopian tubes, as well as normally developed, hormonally functioning ovaries (Oppelt *et al*., 2006). The karyotype (46XX) and secondary sexual characteristics are typically female. The diagnosis of MRKH syndrome is mainly established during adolescence. An absence of menstruation, with or without periodic lower abdominal pain and/or coital problems, leads the patients to consult a gynecologist. The associated malformations of the kidneys, musculoskeletal system, heart, vessels and neurological disturbances that are often observed in MRKH syndrome should also be noted (Oppelt *et al*., 2006).

The forms and aims of treatment have changed over the course of time. Whereas during the 20th and early 19th centuries, the focus was mainly on relieving the premenstrual syndrome through ovariectomy (Kleinwächter, 1881), attention nowadays focuses on the formation of a neovagina capable of allowing coitus.

The etiology of MRKH syndrome is unclear and continues to be a matter of controversy. Teratogenic substances such as thalidomide (Hauser and Schreiner, 1961; Heidenreich *et al*., 1977), raised galactose levels or reduced galactose-1-phosphate uridyltransferase (GALT) activity (Pittock *et al*., 2005), spontaneous mutations (Fleischman *et al*., 2002; Kula *et al*., 2004; Griesinger *et al*., 2005) and recessive inheritance (Petrozza *et al*., 1997) have been considered as causes of MRKH syndrome. In addition, the possibility of dominant hereditary transmission has been discussed, due to the increased familial frequency of the syndrome (Jones and Mermut, 1972; Duncan *et al*., 1979). This hypothesis is contradicted by the fact that two cases of monozygotic discordant twins

have been reported in the literature, among whom one twin each had vaginal aplasia. MRKH syndrome was even confirmed in one case (Heidenreich *et al*., 1977). This is further supported by the existence of direct descendants of MRKH patients born from surrogate mothers; no genital malformations were diagnosed in any of the children (either female or male) (Petrozza *et al*., 1997).

The aim of the present study was to investigate whether an increased rate of other genital anomalies and/or associated malformations can be observed among siblings and first-degree relatives of affected MRKH patients.

Materials and Methods

Between April 2001 and July 2005, MRKH syndrome was diagnosed in 83 patients in the departments of gynecology at the Universities of Erlangen and Tübingen, and staging procedures were carried out. During the work-up, all of the patients underwent diagnostic laparoscopy and renal ultrasonography and/or magnetic resonance imaging (MRI) of the pelvis, including the renal system. Symptomatic associated malformations were then further evaluated using ultrasound, MRI and/or radiography.

Using a specially designed questionnaire, the patients were asked about the following potential malformations among each of their siblings and first-degree relatives:

(i) genital malformations;
(ii) renal malformations;
(iii) skeletal anomalies;
(iv) muscular diseases;
(v) heart defects;
(vi) impaired hearing or abnormalities in the ear.

In addition, the following data were recorded:

(i) other MRKH cases among the relatives of the mother or father;
(ii) number of spontaneous abortions suffered by the mother.

Of the 83 patients, 73 (88%) completed this special questionnaire. The oldest patient at the time of data collection was aged 53, and the youngest was 17. The average age was 28.45 (SD 8.56).

All 73 patients were classified in accordance with the vagina cervix uterus adnexa-associated malformation (VCUAM) classification (Oppelt *et al*., 2005) (Table I) and assigned to the following subgroups in accordance with the classification by Duncan *et al*. (1979).

(i) Forty-five patients (61.5%) with typical MRKH syndrome.
(ii) Twelve patients (16.5%) with an atypical form.
(iii) Sixteen patients (22%) with Müllerian duct aplasia, renal aplasia and cervicothoracic somite dysplasia association.

All of the patients were informed that the data were to be analyzed in the context of a research study, and provided written consent. Approval for the study was obtained from the ethics committee at the University of Erlangen.

Results

In the questionnaires analyzed, 59 of the 73 patients (81%) stated that they had a total of 103 siblings (average 1.41 siblings per MRKH patient). Of this group, 11 of the 59 patients (18.64%) reported known malformations in a total of 13 siblings and two distant relatives. These were distributed among seven sisters (46.7%), six brothers (40%) and two cousins (13.3%) (Table II). Overall, the incidence of malformation among the siblings was 12.62% ($n = 13$ of 103 siblings). Among the distant relatives (two cousins with microcephaly), only affected relatives were recorded (Table II). Two of the MRKH patients stated that they had several siblings with associated malformations (Patients no. 3294 and 3258, Table II).

The group studied included one MRKH patient with a heterozygotic twin sister (Patient no. 3116, Table II) in whom a mitral valve defect was diagnosed. One monozygotic twin sister of an affected patient (Patient no. 3103) had no malformations.

With regard to malformations among distant relatives, one patient stated that two cousins had skeletal malformations (Patient no. 3394, Table II). Skeletal abnormalities also occurred among more distant relatives (a second cousin and her daughter; Patient no. 3417, Table II). None of the 73 patients reported any other cases of MRKH syndrome among her relatives.

The data showed a total of 125 pregnancies among the 73 mothers of the MRKH patients. A total of 22 spontaneous abortions were reported in 14 of the 73 mothers (19.17%; Table II).

The 15 malformations among siblings and distant relatives were distributed as follows (Table II):

(i) six malformations of the skeletal system (40%);
(ii) three cardiac malformations (20%);
(iii) three malformations/functional disturbances of the musculature (20%);
(iv) one gonadal malformation (6.6%);
(v) one severe dental malalignment (6.6%);
(vi) one renal malformation (6.6%).

Discussion

The etiology of MRKH syndrome is still largely unexplained and appears to be variable. Points that are not controversial are the time at which it develops (the 6th to 12th week of pregnancy) and the appearance of associated malformations due to the topographic vicinity of the mesonephric (Wolffian) duct and paramesonephric (Müllerian) ducts (Oppelt *et al*., 2007). Hypotheses proposed to explain the cause of the disease include teratogenic noxae, particularly thalidomide embryopathy (Heidenreich, 1988; Oppelt *et al*., 2007), and spontaneous mutations (Chervenak *et al*., 1982). However, the majority of publications assume that the syndrome is hereditary, pointing to the increased familial frequency of the cases (Jones and Mermut, 1972; Griffin *et al*., 1976; Heidenreich, 1988; Tummers *et al*., 2003). Despite this, no increased vertical frequency has been demonstrated in any of the publications to date. This may be due to the fact that MRKH patients are unable to have their own genetic children without assisted reproduction or, there is a lack of comprehensive family tree analyses and corresponding screening of the siblings of MRKH patients (Petrozza *et al*., 1997; Beski *et al*., 2000; Steinkampf *et al*., 2003). An increased familial incidence of MRKH syndrome was not confirmed in the present group of 73 patients.

In 1977, Heidenreich *et al*. reported a case of MRKH in a monozygotic twin with an apparently normal sister in whom later examinations identified a duplex uterus (Heidenreich,

Table I. Classification of the MRKH patients in accordance with the VCUAM classification (Oppelt *et al*., 2005)/Duncan classification (Duncan *et al*., 1979) and malformations among their siblings and relatives.

Series no.	Patient no.	VCUAM classification						Siblings				Mis	Comments
		V	C	U	A	M		1	2	3	4		
1	101	V5b	C2b	U4b	A#	M0	Typ. MRKH	•	○			1	ND
2	155	V5b	C2b	U4b	A#	M0	Typ. MRKH	•	○			2	ND
3	205	V5b	C2b	U4b	A#	M0	Typ. MRKH					1	
4	288	V5b	C2b	U4b	A0	M0	Typ. MRKH	○	○				ND
5	376	V5b	C2b	U4b	A0	M0	Typ. MRKH	•	•			1	ND
6	384	V5b	C2b	U4b	A0	M0	Typ. MRKH	○					ND
7	390	V5b	C2b	U4b	A0	M0	Typ. MRKH	○	○	•	•		ND
8	1104	V5b	C2b	U4b	A#	M#	Typ. MRKH	•	•				ND
9	1138	V5b	C2b	U4b	A0	M0	Typ. MRKH	•	•			2	ND
10	1193	V5b	C2b	U4b	A0	M0	Typ. MRKH						
11	1231	V5b	C2b	U4b	A0	M0	Typ. MRKH	•	○				ND
12	1239	V5b	C2b	U4b	A3a	M0	Typ. MRKH	○					ND
13	2454	V5b	C2b	U4b	A0	M0	Typ. MRKH	○					ND
14	2585	V5b	C2b	U4b	A0	M#	Typ. MRKH						
15	2899	V5b	C2b	U4b	A0	M0	Typ. MRKH	•					ND
16	3047	V5b	C2b	U4b	A#	M#	Typ. MRKH	○x	○x				1st ○: fencer position2nd ○: scoliosis; chest deformity
17	3116	V5b	C2b	U4b	A0	M0	Typ. MRKH	•x				1	Mitral valve defectHeterozygotic twin
18	3147	V5b	C2b	U4b	A0	M0	Typ. MRKH	○				4	ND
19	3294^	V5b	C2b	U4b	A0	M0	Typ. MRKH	•	•	•x	•x	3	3rd •: dysmelia in right hand4th •: cardiac arrhythmia2 cousins: microcephaly
20	3350	V5b	C2b	U4b	A0	M0	Typ. MRKH	•					ND
21	3434	V5b	C2b	U4b	A0	M0	Typ. MRKH	•					ND
22	3477	V5b	C2b	U4b	A0	M0	Typ. MRKH						
23	3478	V5b	C2b	U4b	A0	M0	Typ. MRKH	•					ND
24	3481	V5b	C2b	U4b	A0	M0	Typ. MRKH	○x					Unilateral testis
25	3532	V5b	C2b	U4b	A#	M#	Typ. MRKH	•	•				ND
26	3575	V5b	C2b	U4b	A#	M#	Typ. MRKH	○	○				ND
27	3656	V5b	C2b	U4b	A0	M0	Typ. MRKH	○	○				ND
28	3729	V5b	C2b	U4b	A#	M#	Typ. MRKH	•	•				ND
29	3802	V5b	C2b	U4b	A#	M#	Typ. MRKH	○					ND
30	3810	V5b	C2b	U4b	A#	M#	Typ. MRKH	○					ND
31	3843	V5b	C2b	U4b	A#	M#	Typ. MRKH	•	○	○			ND
32	3861	V5b	C2b	U4b	A#	M#	Typ. MRKH	○					ND
33	3883	V5b	C2b	U4b	A#	M#	Typ. MRKH	○					ND
34	3885	V5b	C2b	U4b	A#	M#	Typ. MRKH	○					ND
35	3892	V5b	C2b	U4b	A#	M#	Typ. MRKH	○					ND
36	3960	V5b	C2b	U4b	A#	M#	Typ. MRKH	•					PCO
37	4270	V5b	C2b	U4b	A#	M#	Typ. MRKH	•x	•				Absent scapular muscles
38	4284	V5b	C2b	U4b	A#	M#	Typ. MRKH	○					ND
39	4346	V5b	C2b	U4b	A#	M#	Typ. MRKH						
40	4398	V5b	C2b	U4b	A#	M#	Typ. MRKH	•	•				ND
41	4399	V5b	C2b	U4b	A#	M#	Typ. MRKH						
42	4649	V5b	C2b	U4b	A#	M#	Typ. MRKH	○	○x				Scheuermann's disease
43	4653	V5b	C2b	U4b	A#	M#	Typ. MRKH						
44	4877	V5b	C2b	U4b	A#	M#	Typ. MRKH	•	○				ND
45	4934	V5b	C2b	U4b	A#	M#	Typ. MRKH	•	○				ND
46	100	V5b	C2b	U4b	A#	MR	Atyp. MRKH	○	○				ND
47	331	V5b	C2b	U4b	A1a	MR	Atyp. MRKH	○				1	ND
48	368	V5b	C2b	U4b	A0	MR	Atyp. MRKH	•	•				ND
49	752	V5b	C2b	U4b	A0	MR	Atyp. MRKH						ND
50	1617	V5b	C2b	U4b	A0	MR	Atyp. MRKH	•	•	○	○x	1	Potter syndrome
51	1891	V5b	C#	U4b	A0	MR	Atyp. MRKH	•	○				ND
52	2179	V5b	C2b	U4b	A0	MR	Atyp. MRKH	•	•	•x			Prader–Willi–Labhart syndrome
53	2885	V5b	C2b	U4b	A#	MR	Atyp. MRKH	○	○				ND
54	2910	V5b	C2b	U4b	A2a	MR	Atyp. MRKH						
55	3231	V5b	C2b	U4b	A0	M+	Atyp. MRKH						
56	3258	V5b	C2b	U4b	A0	MR	Atyp. MRKH	•x	○x	○x			1st •: muscular dystrophy2nd ○: funnel breast3rd ○: mitral valve defect
57	3394	V5b	C2b	U4b	A1b	MR+	Atyp. MRKH	•x				1	Hip dysplasia
58	448	V5b	C2b	U4b	A0	MRCS+	MURCS						
59	751	V5b	C2b	U4b	A3a	MRS	MURCS	○					ND
60	1094	V5b	C2b	U4b	A#	MRS	MURCS						
61	1232	V5b	C2b	U4b	A#	MSN	MURCS	•x					Dental malalignment
62	1402	V5b	C2b	U4b	A1b	MRS+	MURCS						
63	1504	V5b	C2b	U4b	A#	MS	MURCS						
64	1664	V5b	C2b	U4b	A0	MRS+	MURCS	○	○				ND

Continued

Table I. *Continued*

Series no.	Patient no.	VCUAM classification						Siblings				Mis	Comments
		V	C	U	A	M		1	2	3	4		
65	1832	V5b	C2b	U4b	A2b	MRS	MURCS	•	○				ND
66	2097	V5b	C2b	U4b	A#	MRC	MURCS	•x				2	Cardiac septal defect
67	2285	V5b	C2b	U4b	A1b	MRSN	MURCS	•				1	ND
68	2599	V5b	C2b	U4b	A0	MS	MURCS	○					ND
69	2969	V4	C2b	U4b	A0	MRN+	MURCS	○				1	ND
70	3021	V5b	C2b	U4b	A0	MS+	MURCS	•	○	○	○		ND
71	3103	V5b	C2b	U4b	A0	MC+	MURCS	•					ND, monozygotic twins
72	3417	V5b	C2b	U4b	A1b	MRS+	MURCS	○					Second cousin and her daughter: arm+hand malformation
73	3521	V5b	C2b	U4b	A0	MRS	MURCS	•x	•	○		EP	Osteosarcoma

•, Female; ○, male; x, abnormalities detected; EP, ectopic pregnancy; Mis, mother had spontaneous abortion(s); ND, no abnormalities detected; PCO, polycystic ovaries; Typ., typical; Atyp., atypical; VCUAM, vagina cervix uterus adnexa-associated malformation.
^The patient had a total of five siblings.
V5b, complete atresia; V4, hypoplasia; C2b, bilateral atresia/aplasia; U4b, bilaterally rudimentary or aplastic; A1b, unilateral tubal malformation, ovaries normal; A2b, bilateral hypoplasia/gonadal streak; A3a, unilateral aplasia; A0, normal; A#, unknown; M0, no associated malformation; M#, unknown; MR, renal system; MS, skeleton, MC, cardiac; MN, neurologic; M+, other.

1988). Additional cases of increased familial frequency have been reported: two sisters with MRKH syndrome without associated anomalies (Jones and Mermut, 1972); two sisters with MRKH syndrome who both developed pulmonary stenosis simultaneously (Kula *et al*., 2004); two sisters in whom one had a typical MRKH syndrome and the other had a completely absent uterus (Griffin *et al*., 1976) and two sisters in whom one sister had only one associated malformation, scoliosis (Griffin *et al*., 1976).

In contrast to these case reports, which strongly suggest dominant inheritance, there is an analysis of IVF programs involving MRKH patients in the USA. There were 34 genetic children (17 boys and 17 girls) of MRKH patients born through surrogate motherhood, and the only abnormality observed was a middle ear defect in one boy (Petrozza *et al*., 1997). Similar results were obtained in a study in England, reporting five surrogate pregnancies that resulted in three spontaneous abortions, one singleton pregnancy, one twin pregnancy and one triplet pregnancy, with a total of six live births, for some of which the sex was not stated (Beski *et al*., 2000). No malformations among the children were reported. These studies exclude autosomal-dominant inheritance. This view is supported by case reports of discordant monozygotic twins among whom one twin had MRKH and the other had a 'bilateral tibial longitudinal deficiency' (Steinkampf *et al*., 2003) or no abnormal findings (Heidenreich *et al*., 1977).

The group of patients described in the present study included both discordant monozygotic twins (Patient no. 3103, Table I) and also heterozygotic discordant twins (Patient no. 3116, Table I). In contrast to the normal second monozygotic twin, the second heterozygotic twin had an associated malformation (mitral valve defect, Table I).

Various genital and extragenital malformations associated with MRKH have been described and summarized (Griffin *et al*., 1976; Duncan *et al*., 1979; Heidenreich, 1988; Plevraki *et al*., 2004; Slavotinek *et al*., 2004; Griesinger *et al*., 2005; Oppelt *et al*., 2006). Changes in the lower urinary tract are the most important of these. Their frequency is reported as ranging from 20% to 44%; renal agenesis or aplasia, pelvic kidney, horseshoe kidney, renal sclerosis and double ureter/duplex kidney have been described (Hauser and Schreiner, 1961; Chervenak *et al*., 1982). Malformations of the skeletal system accompanying MRKH syndrome have been reported in 12% (Griffin *et al*., 1976; Chervenak *et al*., 1982; Oppelt *et al*., 2006), 15% (Heidenreich, 1988) and 44% (Pittock *et al*., 2005) of cases. They include fused vertebrae (Klippel–Feil syndrome) in the cervical and thoracic spine, scoliosis in the cervical, thoracic and lumbar spine, L5 sacralization, S1 lumbarization (Hauser and Schreiner, 1961; Oppelt *et al*., 2006), Scheuermann's disease (Oppelt *et al*., 2006), spina bifida (Chervenak *et al*., 1982), upper extremity anomalies involving thrombocytopenia-absent radius syndrome (Griesinger *et al*., 2005), syndactyly of the fingers (Oppelt *et al*., 2006) and lower extremity deformities (bilateral tibial longitudinal deficiency; Steinkampf *et al*., 2003) as well as chest deformity (rib–scapula dysplasia) and hip dysplasia (Oppelt *et al*., 2006).

Cardiac anomalies, neurological disturbances and anomalies of the ear, teeth and hearing occur occasionally. There have been cases of MRKH syndrome combined with pulmonary stenosis (Kula *et al*., 2004), Fallot's tetralogy (Griffin *et al*., 1976; Slavotinek *et al*., 2004), cardiac septal defects (Oppelt *et al*., 2006) and congenital aortic aneurysm (Hauser and Schreiner, 1961). The frequent occurrence of inguinal hernias is notable, although this may have been caused by 'testicular feminization' in older publications due to as yet inadequate differentiation of the syndromes.

The present study for the first time takes into account malformations among siblings and first-degree relatives of MRKH patients, independently of sex. The results show that associated malformations were present in 18 of the siblings or first-degree relatives of the 73 MRKH patients. An increased familial frequency of malformations among the relatives (both male and female) was observed in two families. In one case (Patient no. 3294, Tables I and II), one sister had dysmelia in the right hand, another sister had arrhythmia and two cousins both had microcephalus without reduced intelligence. In addition, the mother was reported to have had three

Table II. Categorization of malformations among siblings and relatives.

Classification	Patient no.	Associated malformations	Malformations among siblings						Malformations among relatives	No. of maternal spontaneous abortions
			1st sister	2nd sister	3rd sister	4th sister	1st brother	2nd brother		
Typical MRKH	3047						Fencer position	Scoliosis Chest deformities		
	3116		Mitral valve defect							1
	3294#				Dysmelia in right hand				2 cousins each with microcephaly	3
	3481						Unilateral testis			
	4270		Absent scapular muscles							
Atypical MRKH	1617	MR						Potter syndrome†		1
	2179	MR			Prader–Willi–Labhart syndrome					
	3258	MR					Funnel breast	Mitral valve defect		
	3394	MR+	Hip dysplasia							1
MURCS	1232	MSN	Severe dental malalignment							
	2097	MRC	Cardiac septal defect							2
	3417	MRS+							Second cousin and her daughter: arm+hand malformation	
MRKH patients with/without healthy sibling						**13/122** spontaneous abortions in total				

#The patient had a total of five siblings. †Died.
MRKH, Mayer–Rokitansky–Küster–Hauser syndrome. Typical MRKH: tubes, ovaries and renal system generated and developed. Atypical MRKH: malformation of the ovary or renal system.
MR, malformation of renal system; MRC, malformation of renal and cardiac systems; MRS, malformation of renal system and skeleton; MSN, malformation of skeleton and in nervous system; MURCS, Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia (association); PCO, polycystic ovaries; +, other malformation.

spontaneous abortions. In the other family (Patient no. 3258, Tables I and II), one sister had muscular dystrophy, one brother had a mitral valve defect and another had a funnel breast.

Despite the frequency of pathological conditions in the kidneys and lower urinary tract among MRKH patients (20–44%; see above), only one renal malformation was noted among the siblings and distant relatives in the present group of patients (one of 73 patients; 1.36%). This corresponds to the prevalence of ~1.54% in the normal population (Queisser-Lift and Spranger, 2006). As it is difficult to interpret whether this finding corresponds to reality or whether further diagnostic clarification has not yet been carried out due to a lack of symptoms, diagnostic investigations in the urogenital system are recommended for siblings and first-degree relatives of affected patients. Skeletal malformations were observed in both female siblings (two cases) and male siblings (two cases) and/or among other relatives (two cases). Cardiac defects were also noted in both sexes (Table II). The rate of associated malformations in this group was ~2.3 times higher than that in the normal population (5.38%) (Queisser-Lift and Spranger, 2006). This is also reflected in the percentage distribution among the individual organ systems, as shown in Table III. However, in the present group, only musculoskeletal malformations showed a significant difference in the malformation rate between MRKH siblings and the general population (3.27 times higher, $P < 0.003$ in Pearson's chi-squared test, Table III); in the urogenital and cardiovascular systems, the differences were not significant ($P = 1.0$ or 0.1; Table III). The authors are aware of the possibility of an underestimation of the true incidence of anomalies in the siblings due to the nature of the questionnaire. It was not possible to have a complete clinical examination of all siblings. Therefore, the present pilot study will be the basis of a European MRKH network

Table III. Comparison of the frequency of malformations in the present selected Mayer–Rokitansky–Küster–Hauser Group and in the normal population (Mainz population based birth Registry).

Organ system	Siblings of MRKH patients ($n = 103$, Erlangen+Tübingen)		Mainz Registry ($n = 40\,083$) per 10 000		Pearson's chi-squared test
	n	%	*n*	%	
Musculoskeletal system	8[a]	7.76	237	2.37	$P < 0.003$
Cardiovascular system	3[b]	2.91	147	1.47	$P = 0.10$
Internal and external urogenital system	2[c]	1.94	154	1.54	$P = 1.0$

[a]Patient No.: 1232, 2179, 3047, 3047, 3258, 3294, 3394, 4270.
[b]Patient No.: 2097, 3116, 3258.
[c]Patient No.: 1617, 3881.

investigation in order to reach greater sample sizes with the possibility of clinical examinations of the siblings.

The rate of spontaneous abortions among the mothers of MRKH patients (without age data), at 17.6% (22 spontaneous abortions in 125 pregnancies, Table II), was not significantly different from the spontaneous abortion rate in the first trimester in the normal population, which is reported in the literature as being up to 20% (Tummers *et al*., 2003). The age of parents of the MRKH patients was not registered in our data base.

Additional and complex investigations will ultimately be needed in order to conclusively explain the cause of the syndrome. Thanks to surrogate motherhood, modern reproductive medicine can enable MRKH patients to have their own genetic children. Larger numbers of cases of such children, twin pregnancies and more comprehensive family tree analyses, with the help of molecular-genetic studies, may make it possible to obtain further information about the etiology of the MRKH syndrome.

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References

Beski S, Gorgy A, Venkat G, Craft IL, Edmonds K. Gestational surrogacy: a feasible option for patients with Rokitansky syndrome. *Hum Reprod* 2000;**15**:2326–2328.

Chervenak FA, Stangel JJ, Nemec M, Amin HK. Mayer–Rokitansky–Küster–Hauser syndrome: congenital absence of vagina. *N Y State J Med* 1982;**82**:23–26.

Communal PH, Chevret-Measson M, Golfier F, Raudrant D. Sexuality after sigmoid colpopoiesis in patients with Mayer–Rokitansky–Küster–Hauser syndrome. *Fertil Steril* 2003;**80**:600–606.

Duncan PA, Shapiro LR, Stangel JJ, Klein RM, Addonizio JC. The MURCS association: Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia. *J Pediatr* 1979;**95**:399–402.

Fleischman RA, Letestu R, Mi X, Stevens D, Winters J, Debili N, Vainchenker W. Absence of mutations in the HoxA10, HoxA11 and HoxD11 nucleotide coding sequences in thrombocytopenia with absent radius syndrome. *Br J Haematol* 2002;**116**:367–375.

German Federal Office of Statistics Press Office. *Statistisches Bundesamt*. Press release, 17 March 2006.

Griesinger G, Dafopoulos K, Schultze-Mosgau A, Schroder A, Felberbaum R, Diedrich K. Mayer–Rokitansky–Küster–Hauser syndrome associated with thrombocytopenia-absent radius syndrome. *Fertil Steril* 2005;**83**:452–454.

Griffin JE, Edwards C, Madden JD, Harrod MJ, Wilson JD. Congenital absence of the vagina. The Mayer–Rokitansky–Kuster–Hauser syndrome. *Ann Intern Med* 1976;**85**:224–236.

Hauser GA, Schreiner WE. Mayer–Rokitansky–Kuester syndrome. Rudimentary solid bipartite uterus with solid vagina; in German. *Schweiz Med Wochenschr* 1961;**91**:381–384.

Heidenreich W. Genital and extragenital abnormalities in Mayer–Rokitansky–Küster syndrome; in German. *Dtsch Med Wochenschr* 1988;**113**:1092–1096.

Heidenreich W, Pfeiffer A, Kumbnani HK, Scholz W, Zeuner W. Discordant monozygotic twins with Mayer–Rokitansky–Küster syndrome; in German. *Geburtshilfe Frauenheilkd* 1977;**37**:221–223.

Jones HW, Mermut S. Familial occurrence of congenital absence of the vagina. *Am J Obstet Gynaecol* 1972;**114**:1100–1101.

Kleinwächter L. Zur Castration wegen functionierender Ovarien bei rudimentärer Entwicklung der Müllerschen Gänge. *Arch Gynäkol* 1881;**17**:475–489.

Kula S, Saygili A, Tunaoglu FS, Olguntürk R. Mayer–Rokitansky–Küster–Hauser syndrome with pulmonary stenosis. *Acta Paediatr* 2004;**93**:570–572.

Oppelt P, Renner SP, Kellermann A, Brucker S, Hauser GA, Ludwig KS, Strissel PL, Strick R, Wallwiener D, Beckmann MW. Clinical aspects of Mayer–Rokitansky–Kuester–Hauser syndrome: recommendations for clinical diagnosis and staging. *Hum Reprod* 2006;**21**:792–797.

Oppelt P, Renner SP, Brucker S, Strissel PL, Strick R, Oppelt PG, Doerr HG, Schott GE, Hucke J, Wallwiener D, Beckmann MW. The VCUAM (vagina cervix uterus adnexa-associated malformation) classification: a new classification for genital malformations. *Fertil Steril* 2005;**84**:1493–1497.

Oppelt P, von Have M, Paulsen M, Strissel PL, Strick R, Brucker S, Wallwiener D, Beckmann MW. Female genital malformations and their associated abnormalities: recommendations for clinical diagnosis and staging. *Fertil Steril* 2007;**87**:335–342.

Petrozza JC, Gray MR, Davis AJ, Reindollar RH. Congenital absence of the uterus and vagina is not commonly transmitted as a dominant genetic trait: outcomes of surrogate pregnancies. *Fertil Steril* 1997;**67**:387–389.

Pittock ST, Babovic-Vuksanovic D, Lteif A. Mayer–Rokitansky–Küster–Hauser anomaly and its associated malformations. *Am J Med Genet A* 2005;**135**:314–316.

Plevraki E, Kita M, Goulis DG, Hatzisevastou-Loukidou H, Lambropoulos AF, Avramides A. Bilateral ovarian agenesis and the presence of the testis-specific protein 1-Y-linked gene: two new features of Mayer–Rokitansky–Küster–Hauser syndrome. *Fertil Steril* 2004;**81**:689–692.

Queisser-Lift A, Spranger J. Fehlbildungen bei Neugeborenen. *Dtsch Ärztebl* 2006;**38**:A-2464, B-2136, C-2006.

Slavotinek AM, Dutra A, Kpodzo D, Pak E, Nakane T, Turner J, Whiteford M, Biesecker LG, Stratton P. A female with complete lack of Müllerian fusion, postaxial polydactyly, and tetralogy of Fallot: genetic heterogeneity of McKusick–Kaufman syndrome or a unique syndrome? *Am J Med Genet A* 2004;**129**:69–72.

Steinkampf MP, Dharia SP, Dickerson RD. Monozygotic twins discordant for vaginal agenesis and bilateral tibial longitudinal deficiency. *Fertil Steril* 2003;**80**:643–645.

Tummers P, De Sutter P, Dhont M. Risk of spontaneous abortion in singleton and twin pregnancies after IVF/ICSI. *Hum Reprod* 2003;**18**:1720–1723.

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