Recent advances in the molecular mechanisms of Mayer-Rokitansky-Küster-Hauser syndrome (Review)

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Abstract. Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is a disease caused by congenital absence of the uterus and two-thirds of the upper vagina. The pathogenic mechanism of MRKHS may involve gene abnormalities, and there are various case reports associating MRKHS with the Wnt family member 4 (*Wnt4*) mutation. Analysis of genes mapped to regions in which deletion and duplication are frequently detected in patients with MRKHS has shown involvement of LIM homeobox 1 (*LHX1*), HNF1 homeobox B (*HNF1B*) and T-box 6 (*TBX6*). In addition, there are case reports of MRKHS caused by chromosomal translocation and epigenetic function may be involved in MRKHS onset. Overexpression of *HOXA* and overexposure to estrogen may contribute to the onset and regulation of expression by methylation as a pathogenic mechanism. Determination of the molecular basis of MRKHS is in progress, but current treatment only includes vaginal enlargement and vaginoplasty for improved quality of life. Clinical application of uterine transplantation to allow childbearing by MRKHS patients is under investigation and clinical trials are underway around the world.

Contents

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1. Introduction

Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is a disease caused by congenital absence of the uterus and two-thirds of the upper vagina (1). Women with MRKHS develop normal secondary sexual characteristics and have a female chromosome pattern (46,XX) (1). MRKHS occurs in one in 4,500 women globally (1) and is the second leading cause of primary amenorrhea (2). Numerous women with MRKHS experience uterine pregnancy. The syndrome consists of sporadic type I and type II forms associated with renal and skeletal malformation, as well as auditory disorders (3,4). Types I and II MRKHS account for 44 and 56% of all cases, respectively (5). MRKHS was previously considered as a sporadic disease (1) and the cause was unknown for many years. To date, there are only 68 cases of familial MRKHS reported (6).

Prenatal diagnosis and genetic counseling are not considered useful due to the apparently sporadic nature of MRKHS (1). MRKHS is rare congenital disease, therefore, the molecular mechanism remains unclear. However, recent studies have identified causative genes for MRKHS. Furthermore, in monozygotic twins, one develops MRKHS and the other does not, which is due to differences in phenotype. This indicates that the pathogenesis of MRKHS is associated with epigenetic mechanisms linked to environmental and stochastic factors (7).

To understand the potential molecular mechanisms of MRKHS in detail, a comprehensive literature search was conducted up to December 2016 using the Pubmed database. The following search terms were used: 'Mayer-Rokitansky-Küster-Hauser syndrome', 'MRKHS', 'Mullerian agenesis/aplasia', 'Mullerian agenesis/aplasia', 'vaginal agenesis/aplasia', 'uterine agenesis/aplasia', 'transplantation'. To the best of our knowledge, the current review is the first to analyze MRKHS at the genetic level.

2. MRKHS and gene mutation

Certain studies have described MRKHS as a multifactorial disorder; however, onset of MRKHS is predominantly caused by a single gene mutation. Based on the observation that the Mullerian duct was not formed in Wnt family member 4 (Wnt4) knockout mice (8), Biason-Lauber *et al* (9) conducted a genetic

analysis in 18-year-old patients with MRKHS and showed that the *Wnt4* mutation also occurred in women with MRKHS (9). *Wnt4* mutation inhibits repression of ovarian steroid enzymes and causes abnormal expression of 17α hydroxylase (10), causing these patients to exhibit hyperandrogenism. However, only four patients with MRKHS were found to have *Wnt4* mutations (9-11) and a cohort study in patients with genital development anomalies failed to show the *Wnt4* mutation (12).

Analysis of the function of genes mapped to regions in which deletion and duplication are frequently detected in patients with MRKHS has led to identification of the involvement of LIM homeobox 1 (*LHX1*), HNF1 homeobox B (*HNF1B*) and T-box 6 (*TBX6*) in early development of the disease. *LHX1* is necessary for formation of the Mullerian duct-derived uterine and vaginal epithelia (13). Ledig *et al* (14) found chromosome 17q12 deletion, including loss of *LHX1*, in 6% of patients with MRKHS. *HNF1B*, which is also on chromosome 17q12 (14), is a Pit-Oct-Unc homeodomain transcription factor that is frequently expressed in the Mullerian duct during development (15). Haploinsufficiency of *HNF1B* causes *LHX1* downregulation and uterine hypoplasia, and chromosome 16p11.2 deletion induces MRKHS due to loss of the transcription factor. *TBX6* is involved in paraxial mesoderm formation and somitogenesis in human embryos (16). Splicing variants and missense mutations of the above-mentioned genes have also been observed in patients with MRKHS (17,18).

3. Chromosomal translocation in MRKHS

To the best of our knowledge, there are only 4 case reports of MRKHS that may have been caused by chromosomal translocation. These include two t(8;13)(q12;q14) cases reported in 1988 (19) and a t(8;13)(q22.1;q32.1) case described in 1999 (20), all of which were analyzed before use of chromosomal microarray analysis; therefore, the chromosomal breakpoint was not identified. In 2016, Williams *et al* (21) examined the genes of a 17-year-old Caucasian female with hypoplasia of the uterus and vagina, with MRKHS and genotype (46,XX). None of her family had MRKHS. A t(3;16)(p22.3;p13.3) translocation was identified. This genetic analysis indicated that the breakpoint was CKLF like MARVEL transmembrane domain containing 7 (*CMTM7*) in chromosome 3p22 and interleukin 3 (IL3) in chromosome 16p13.3. Based on these results, 10 genes [tripartite motif containing 71 (*TRIM71*), CCR4-NOT transcription complex subunit 10 (*CNOT10*), olfactory receptor family 1 subfamily F member 1 (*OR1F1*), zinc finger protein 213 (*ZNF213*), *ZNF200*, *ZNF205*, *CMTM7*, C-C motif chemokine receptor 4 (*CCR4*), *IL32* and *MEFV*, pyrin innate immunity regulator] were identified as possibly involved in MRKHS (21). However, the requirement for additional cohort studies was highlighted due to these results, which were obtained from an analysis of a single patient with MRKHS (Table I).

4. MRKHS and epigenetic abnormalities

It has been identified that one of monozygotic twins develops MRKHS and the other does not, which indicates that the disease is due to differences in phenotype. Therefore, the pathogenic mechanism of MRKHS may involve epigenetic changes due to environmental and stochastic factors (7). Rall *et al* (22) investigated differences in transcription products and methylation levels between patients with MRKHS and healthy volunteers using genome-wide analyses. Microarray analysis revealed 293 transcription products with different expression levels and 194 CpG islands with different methylation patterns, compared with those in healthy volunteers. By evaluating two gene clusters, nine potentially causative genes [homeobox A5 (*HOXA5*), *HOXA9*, WNT1 inducible signaling pathway protein 2 (*WISP2*), cadherin 5 (*CDH5*), paternally expressed 10 (*PEG10*), microfibrillar associated protein 5 (*MFAP5*), leucine rich repeat containing 32 (*LRRC32*), Ral GEF with PH domain and SH3 binding motif 2 (*RALGPS2*) and sphingomyelin phosphodiesterase 3 (*SMPD3*)] were identified. Six of these genes (*CDH5*, *MFAP5*, *WISP2*, *HOXA5*, *PEG10* and *HOXA9*) are involved in development of female genitalia. Subsequent network analyses identified *WISP2*, *HOXA5*, *HOXA9*, GATA binding protein 4 (*GATA4*) and Wilms tumor 1 (*WT1*) as key genes in MRKHS (Table II).

WT1 and *GATA4* regulate sex determination and differentiation via anti-Mullerian hormone (*AMH*) (23). *WT1* and *GATA4* are demethylated in patients with MRKHS when compared with healthy volunteers. *WT1* and *GATA4* promote AMH expression, leading to the degeneration of the Mullerian duct. Activating mutation of either the gene for the AMH receptor, resulting in the inappropriate excessive production of AMH, or the receptor itself, is the underlying cause of MRKHS (22). *HOXA9* is expressed in the region that becomes the oviduct (24); exposure to diethylstilbestrol produces ectopic expression of HOXA9, leading to developmental anomaly of the upper Mullerian duct (24,25). Furthermore, *HOXA5* is a transcription factor of p53 and progesterone receptor (26). Ectopic expression of *HOXA5*, similarly to *HOXA9*, inhibits Mullerian duct differentiation (27).

WISP2 is significant in smooth muscle cell proliferation and migration, and is induced by estrogen in the uterus (28). Estrogen regulates *AMH* expression levels (29) and overexposure to estrogen during development activates *AMH* promotors (22). Exposure of a fetus to endocrine-disrupting chemicals in the uterus and abnormally high levels of maternal hormones contributes to ectopic expression of *HOXA* genes. Rall *et al* (22) suggested that overexposure to estrogen and ectopic expression of *HOXA* may lead to female genital hypoplasia and cause MRKHS. However, it was noted that other factors may also activate the *AMH* promoter and further studies are required.

5. Clinical practice for MRKHS

Treatment of MRKHS includes vaginal enlargement and vaginoplasty to enable sexual behavior, surrogate delivery, and uterine transplantation for patients who wish to have a child. The major methods are the Frank method (30) of inserting a device into the vagina that gradually enlarges the vagina, and the Ingram method (31), which uses a device to enlarge the vagina using the patient's body weight. Vaginal enlargement is performed prior to vaginoplasty and many patients request vaginoplasty due to insufficient sexual satisfaction (30). Vaginal enlargement may be achieved using the Vecchietti method of traction using olive-shaped beads, the Davydov

Table I. Chromosomal translocations in MRKHS.

Author, year	Translocation site	Onset	Phenotype	Refs.
Kucheria *et al*, 1988	t(8;13) (q12;q14)	Unknown	MRKHS	(19)
	t(8;13) (q12;q14)	Unknown	MRKHS, renal hypoplasia	(19)
Amesse *et al*, 1999	t(8;13) (q22.1;q32.1)	Sporadic	MRKHS, amastia, amelia, urine reflux, urinary incontinence	(20)
Williams *et al*, 2016	t(3;16) (p22.3;p13.3)	Sporadic	MRKHS	(21)

MRKHS, Mayer-Rokitansky-Küster-Hauser syndrome.

Table II. Epigenetic abnormalities in MRKHS.

Author, year	Gene	Locus	Function	Refs.
Miyamoto, 2008	Wilms tumor gene 1 (*WT1*)	11p13	Sexual determination and control of sexual differentiation	(23)
	GATA-binding protein 4 (*GATA4*)	8p23.1	Sexual determination and control of sexual differentiation	(23)
Taylor, 2008	Homeobox A9 (*HOXA9*)	7p15.2	Fallopian tube development	(24)
Sauter *et al*, 2005	Homeobox A5 (*HOXA5*)	7p15.2	Transcriptional regulation of p53	(26)
Mason *et al*, 2004	WNT1 inducible signaling pathway protein 2 (*WISP2*)	20q13.12	Smooth muscle cell proliferation and migration	(28)

MRKHS, Mayer-Rokitansky-Küster-Hauser syndrome.

method of laparoscopically forming the vagina using the peritoneum, the McIndoe method of forming the vagina by skin grafting, and the Sigmoid method, which uses the sigmoid colon (30).

Surrogate delivery is an option for patients with MRKHS who want to have a biological child because they have normal ovarian function (1). Friedler *et al* (32) described 125 patients with MRKHS who underwent *in vitro* fertilization, with 71 infants born by surrogate delivery worldwide. To the best of our knowledge, there are no case reports regarding the birth of a girl with MRKH to a mother with MRKHS (32). Surrogate delivery is formally prohibited in Europe, whereas there is no legal regulation of surrogate delivery in Japan (33). However, the Japan Society of Obstetrics and Gynecology does not permit surrogate delivery, as the wellbeing of children should be placed above all else. Surrogate delivery has many problems, including the physical and mental load on the surrogate mother, complicated family relations due to surrogate delivery, and negative social opinions surrounding the contract for surrogate delivery (33).

6. Expected treatment with uterine transplantation

Uterine transplantation is another option for patients who desire to have a child. Brännström *et al* (34) reported the case of a patient (age, 35 years) with MRKHS who received a uterus from a 61-year-old woman who had delivered two children (34). *In vitro* fertilization was performed using the patient's ova and sperm from her partner. One year after uterine transplantation, she successfully underwent embryo implantation and had a male infant (body weight, 1,775 g) at 31 weeks and 5 days gestation. Thus, patients with MRKHS have successfully undergone uterine transplantation (34). In Japan, uterine transplantation has been examined in cynomolgus monkeys (35,36). The uterus was exchanged between two cynomolgus monkeys and one successfully achieved natural pregnancy following menstruation (36). In cynomolgus monkeys, uterine atrophy occurred subsequent to uterine transplantation. It remains unclear as to why uterine transplantation causes uterine atrophy, although insufficient uterine blood flow is assumed to be one of the reasons for these issues. Uterine blood flow is significant in uterine viability, therefore two technical proedures were examined in the cynomolgus monkeys. The first method was indocyanine green (ICG) fluorescence imaging for evaluation of uterine blood flow (37,38). ICG fluorescence imaging, an angiographic technique that is simple to use and minimally invasive, enabled intraoperative real-time evaluation of uterine hemodynamics. The second method involves use of the ovarian vein rather than the uterine vein as an anastomosis blood vessel (38). The ovarian vein is a thick vessel that runs along the upper part of the pelvis, and previous reports demonstrate that the ovarian vein may contribute to drainage of the uterus to a great extent (37-41). The vascular anastomosis with larger diameter leads to less complicated surgery, and the warm ischemic time is effectively reduced (39). Furthermore, use of the ovarian vein appears to

be less invasive and safer for donors (38). Another concern is pregnancy-induced hypertension following uterine transplantation. Certain reports demonstrate that the incidence of pregnancy-induced hypertension appears to be higher in liver and renal transplantation patients versus the general population (42,43). Pregnancies following organ transplantation carry a high risk of pregnancy-induced hypertension, which indicates that insufficient uterine blood flow, organ rejection or administration of immunosuppressive drugs may lead to hypertension.

Thus, clinical studies regarding uterine transplantation are advanced in many countries and application in humans is anticipated in the near future.

7. Conclusion

Recent studies have shown that the pathogenic mechanisms of MRKHS include single-gene mutations and epigenetic changes. Determination of the cause of MRKHS is in progress; however, prenatal diagnosis and genetic counseling are currently less useful. Vaginal enlargement and vaginoplasty are performed as treatment strategies for MRKHS, although such treatment does not lead to fertility. Clinical application of uterine transplantation may be the solution for patients with MRKHS who hope to deliver a biological child following gestation within the uterus.

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