

Systematic Review

Identification of Genetic Causes in Mayer-Rokitansky-Küster-Hauser (MRKH) Syndrome: A Systematic Review of the Literature

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Abstract: Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a congenital condition characterizing females with absence of the uterus and part of the vagina. Several genetic defects have been correlated with the presence of MRKH; however, the exact etiology is still unknown due to the complexity of the genetic pathways implicated during the embryogenetic development of the Müllerian ducts. A systematic review (SR) of the literature was conducted to investigate the genetic causes associated with MRKH syndrome and Congenital Uterine Anomalies (CUAs). This study aimed to identify the most affected chromosomal areas and genes along with their associated clinical features in order to aid clinicians in distinguishing and identifying the possible genetic cause in each patient offering better genetic counseling. We identified 76 studies describing multiple genetic defects potentially contributing to the pathogenetic mechanism of MRKH syndrome. The most reported chromosomal regions and the possible genes implicated were: 1q21.1 (*RBM8A* gene), 1p31-1p35 (*WNT4* gene), 7p15.3 (*HOXA* gene), 16p11 (*TBX6* gene), 17q12 (*LHX1* and *HNF1B* genes), 22q11.21, and Xp22. Although the etiology of MRKH syndrome is complex, associated clinical features can aid in the identification of a specific genetic defect.

Keywords: Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome; Rokitansky; uterine aplasia; uterine anomalies; genetics



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1. Introduction

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, or Müllerian aplasia, is a syndrome that affects females and is characterized by the absence of the uterus and the upper part of the vagina. These individuals have a normal karyotype (46, XX) and usually normal ovarian function [1]. It is divided into two types: Type I is characterized by uterovaginal aplasia, while Type II is additionally related to extragenital anomalies, most commonly renal (30–40%), skeletal, ear, and cardiac anomalies [2,3]. The reported incidence rate of MRKH syndrome is around 1:5000 live female births and, due to this rarity, it is poorly investigated [2,4]. In most cases, MRKH syndrome is diagnosed due to the presence of primary amenorrhea. The impact of the MRKH diagnosis and the associated psychological burden on young girls is significant [5]. The treatment of the syndrome includes vaginal dilation or, in case of failure or non-compliance with treatment, operative creation of a neovagina. Concerning the fertility of MRKH individuals, surrogacy is an option; however, uterine transplantation has been recently introduced [6].

Embryologically, the female reproductive system in humans derives from the Müllerian or Paramesonephric Ducts (MDs), which give rise to the uterus, cervix, and the upper two-thirds of the vagina at around the fifth to sixth week of gestation [1,7,8]. Several gene defects can affect the embryogenetic pathways of the development of the female reproductive system and cause MRKH syndrome.

Evidence of the inheritance pattern of MRKH syndrome remains scarce, due to the fertility restrictions of MRKH patients in the past; hence, no family trees were available to study [9,10]. The majority of the cases are sporadic, though there have been reports of familial cases, with a recent increase in the latter due to the introduction of surrogacy and uterine transplantation [10,11]. First-degree relatives of MRKH patients seem to have a 1–5% risk of congenital uterine anomalies as in most multifactorial disorders [12]. The majority of the studies of familial cases suggest an autosomal dominant inheritance pattern limited to the female sex, implying that the genetic defect is typically inherited by the father [13]. Wolffian duct hypoplasia, or agenesis, and other defects such as renal anomalies, hearing impairment, and skeletal deformities have been reported in the males of these families, similar to MRKH patients [10,11,14]. Another finding of note is that some articles refer to the presence of discordant monozygotic twins with MRKH syndrome, implying that environmental factors, i.e., epigenetic changes, may play a role in gene expression affecting Müllerian duct development [15–23].

The aim of this study was to systematically review the available literature and to summarize all genetic defects that have been described in MRKH patients. In addition, this study aimed to present commonly studied genes in correlation with their associated clinical features in order to provide guidance to clinicians and geneticists in their efforts to identify a specific genetic defect in each patient. This information can aid in genetic counseling and lead to more favorable outcomes through the early detection of specific genetic defects in pregnancy and the possibility of gene therapy in the future. Ultimately, these insights could be of use in guiding further genetic studies on MRKH syndrome.

2. Materials and Methods

For the conduction of this systematic review, a protocol based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, was used, following the PRISMA assessment checklist [24]. The search terms for our research included: Mayer–Rokitansky–Küster–Hauser syndrome; Rokitansky; uterine aplasia; uterine abnormalities; and genetics. We searched four different databases: Pubmed, ScienceDirect, Scopus, and Web of Science. The search was performed in December 2021 and was updated on 25 May 2022. All studies that reported on the genome of human female patients with MRKH and/or CUAs from 1994 to 25 May 2022 were included; studies not published in English, studies on animals, non-research studies, non-genetic studies on MRKH or CUAs, and studies not concerning MRKH or CUAs were excluded. The study selection was conducted by two independent reviewers (V.T. and A.K.), while a third reviewer (L.M.) assisted in decision-making when there was a conflict of opinion. The retrieved articles were compiled and de-duplicated. Additional eligible studies were retrieved by hand searching the citations from all articles. All studies meeting the inclusion criteria were included in the review. For every eligible article, information regarding the date of publication, the main findings, and the number of patients and controls were recorded. The study did not involve contact with humans, so the need for ethical approval was waived. This review was not registered. The selection and screening process are presented in the PRISMA flowchart shown in Figure 1.

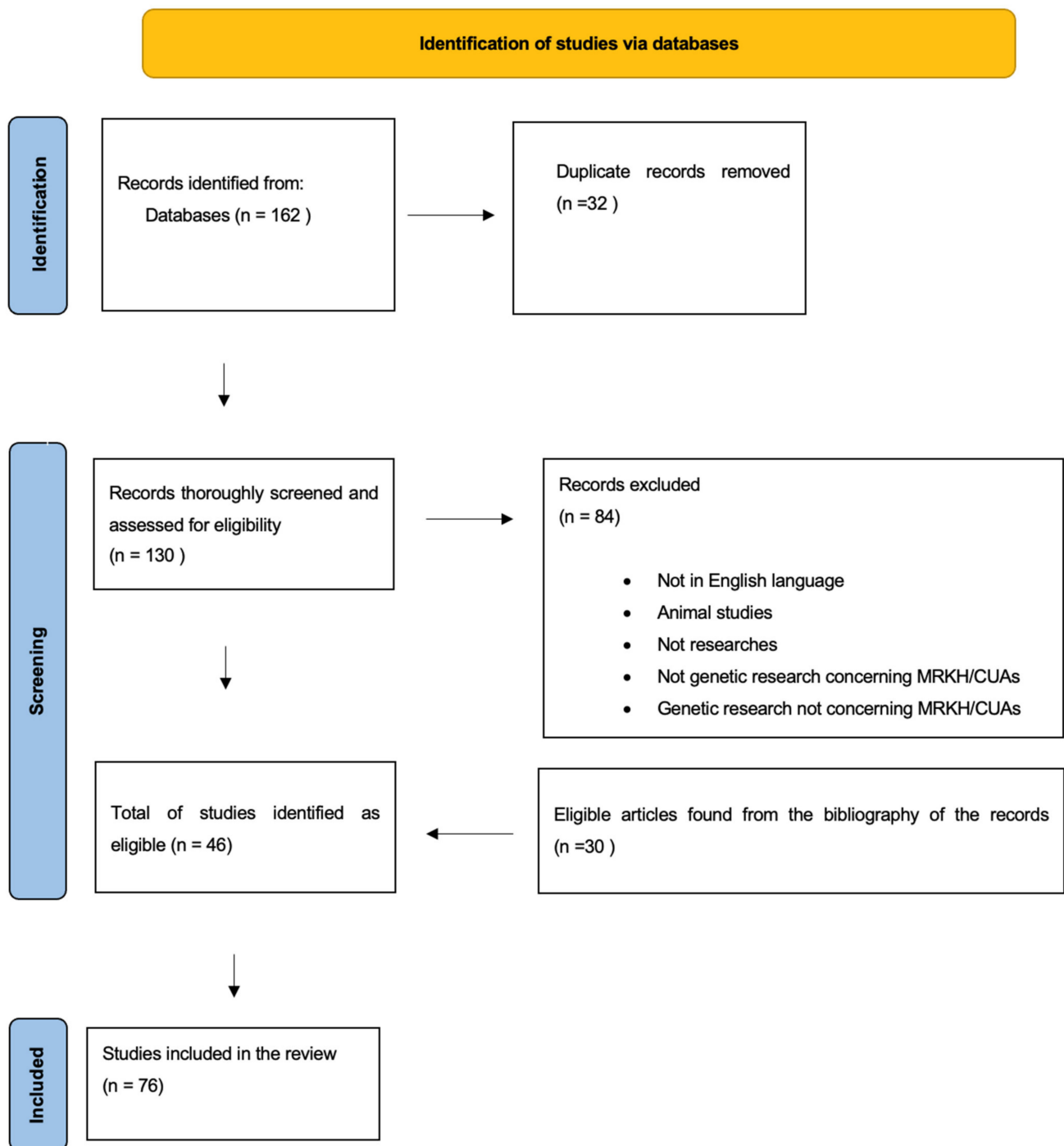


Figure 1. Identification process of the studies included in the Systematic Review.

3. Results

A total of 162 articles were identified from all databases using the search strategy, of which 32 were duplicates. In total, 30 eligible studies were identified from the hand search of the citations of the articles. According to both our inclusion and exclusion criteria, in total, 76 studies were considered eligible and included in this SR. Table A1 presents all 76 studies, sorted by year of publication, along with the main results and the number of individuals with MRKH syndrome or CUAs and controls who were studied.

The most reported chromosomal regions and the possible genes implicated are: 1q21.1 (*RBM8A* gene), 1p31-1p35 (*WNT4* gene), 7p15.3 (*HOXA* gene), 16p11 (*TBX6* gene), 17q12 (*LHX1* and *HNF1B* genes), 22q11.21, and Xp22.

Table 1 presents the chromosomal regions most commonly implicated in MRKH syndrome and CUAs and the suspicious genes involved, as indicated by animal and human studies. This table also presents the clinical features associated with defects in the respective genetic locations, the main results of non-human studies regarding these chromosomal regions, and whether they are linked with Type I or Type II MRKH.

Table 1. The most common chromosomal regions and genes associated with MRKH, their associated clinical presentation, animal studies of these genes, and phenotype of MRKH related to defects in these genes.

Chromosome Location	Suspected Genes Involved	Associated Syndromes	Non-Humans Study	Phenotype	References
1q21	<i>RBM8A</i>	TAR syndrome (thrombocytopenia, absence of the radius) [25–28]	<i>Drosophila melanogaster</i> : <i>RBM8A</i> encodes Y14 protein, which affects oocyte differentiation and determination of primordial germ cells [29]	Type I + II	[25–27,30]
16p11.2	<i>TBX6</i>	Autism spectrum disorders, neurological disorders, unaffected persons [28]	Mouse models: Deletion of <i>TBX6</i> presents skeletal (mainly vertebral) and urinary tract malformations [31,32]	Type I + II	[27,30,33–38]
17q12	<i>LHX1</i>	Anomalies in the embryogenesis, in body axis formation [28,39]	Mouse model: <i>LHX1</i> null mutant mice are characterized by absent uterus and oviducts [40] Mouse model: <i>LHX1</i> mutant mice had lack of kidneys and anencephaly [28,41] Mouse embryos with decreased <i>LHX1</i> activity had lower capacity of primordial germ cells (PGCs; [42])	Type I + II	[25,26,33,34,43–52]
	<i>HNF1B</i>	Renal cysts and diabetes [28]	Mouse models: Expression of <i>HNF1B</i> in MDs and in epithelial tissue of liver, pancreas, lungs and kidneys [53]		
22q11	Uncertain (<i>TBX1</i>)	DiGeorge or Velocardiofacial syndrome (heart defects, hypocalcemia, immunodeficiency, typical facial malformations, cognitive and behavioral disorders)		Type I + II	[25–27,33,54–57]

4. Discussion

In this review, we have thoroughly analyzed the studies examining the genetic causes of MRKH syndrome. We endeavored to present our findings comprehensively and aimed to help clinicians associate clinical presentations with specific genetic defects. The need for genetic advice has become increasingly important in recent years due to the introduction

of surrogacy and, most recently, uterine transplantation. The information included in this review regarding the genetic cause and pathogenesis of MRKH syndrome could significantly improve the counseling offered to individuals with MRKH and their families.

Our search confirmed that the genetic background of MRKH is poorly studied [25,28]. Mice models with targeted mutagenesis identified multiple genes that affect the development and differentiation of the female reproductive system during embryogenesis (Table 1). According to these studies, a number of candidate genes have been proposed as the causative factor for MRKH syndrome in humans and have been analyzed using array-comparative genomic hybridization (CGH) and whole-genome sequencing (WGS). Many MRKH patients have been reported to carry chromosomal anomalies that affect multiple chromosomal regions.

Despite the myriad of sporadic gene variants found through our search, we have identified a recurring pattern of affected chromosomal locations. Most reported chromosomal regions with their most implicated genes are: 1q21.1 (*RBM8A* gene), 1p31-1p35 (*WNT4* gene), 7p15.3 (*HOXA* gene), 16p11 (*TBX6* gene), 17q12 (*LHX1* and *HNF1B* genes), 22q11.21, and Xp22 [10,25,26,28,33,43–46,48,54,55,58–61].

1q21.1

Affected regions in 1q21.1, a well-known location in TAR syndrome cases (thrombocytopenia/absent radius), have been identified in patients with Müllerian malformations [25–28,30]. More accurately, variants of the *RBM8A* gene—which is located in this chromosomal region—have been proposed as the possible cause of MRKH syndrome and gonadal dysgenesis, as this gene mainly affects oocyte differentiation and determination of the primordial germ cells [28,29].

1p31-1p35

WNT4 is important in MD development during embryogenesis. It plays a double role in the female gonad: it controls female development and prevents testes formation [28,62–66]. For this reason, when MRKH syndrome is combined with signs of hyperandrogenism, heterozygous variants of the *WNT4* gene may be considered. Moreover, folliculogenesis in affected women can also be disrupted because of the gene's role in the development of the gonad [28,65].

7p15.3

The *HOX* clusters belong to a large family of homeobox-containing genes. The *HOXA* genes affect the development of the female reproductive system, as has been indicated by human and animal studies, and are, therefore, considered to be strong candidates for MRKH syndrome [10,67]. Despite their central role in the formation of MD, variants of these genes have been identified in only a few MRKH patients and are of unknown significance [10,68].

16p11.2

Deletions in 16p11.2 have been associated with autism and other neurological disorders (i.e., epilepsy, seizures, and learning disabilities), as well as congenital uterine anomalies [28,33]. The *TBX6* gene, which is located in this region, encodes a transcription factor that affects the embryogenetic development and, more specifically, the differentiation of the mesoderm. Therefore, it is suggested to be a putative candidate for MRKH syndrome [9,12,27,28,30,34,36–38].

17q12

It is known that 17q12 is the most affected chromosomal location in MRKH syndrome [25–27,33,43,45]. Associated anomalies of genetic defects in this location include renal cysts, mild facial malformations, severe cognitive disabilities, and seizures [26,46].

Specifically, *LHX1* (*LIM* homeobox protein 1) and *HNF1B* (hepatocyte nuclear factor 1B; also known as *TCF2*) genes seem to be important candidates based on the prevalence of their variants in MRKH patients and their established roles in the development of the reproductive and urinary system [28].

LHX1 has been associated with MRKH type II and unilateral renal agenesis [25,34,44]. The gene influences CNS formation [69,70] and has also been described in MRKH patients with mild mental and learning disabilities [26,28,44,48].

Variants and deletions of the *HNF1B* gene are characteristic in renal cysts and diabetes, which may be explained by the expression of the *HNF1B* gene in the kidney and pancreas; *HNF1B* is also expressed in the Wolffian and Müllerian ducts and plays a central role in their formation [53]. Some researchers have reported variants of the *HNF1B* gene in familial cases of CUAs, often associated with kidney malformations and Maturity Onset Diabetes of the Young (MODY) [49,50].

22q11.21

Deletions in 22q11.21 are responsible for DiGeorge or Velocardiofacial Syndrome (DG/VCFS). This syndrome can be manifested with variable phenotypes, occasionally including CUAs; therefore, MRKH syndrome may be a part of DG/VCFS. Changes in the *TBX1* gene, which is located in 22q11.21, are considered to be responsible for DGS/VCFS. However, this gene has not been associated with MRKH. This finding suggests that other genes in this region may be responsible for the appearance of CUAs [25–28,33,56].

Another issue of interest is the lack of large cohort studies associating a single gene variant solely with MRKH type I or MRKH type II. This may be due to the fact that genes that affect MD development during embryogenesis can also affect the development of the urinary system, owing to their common origin. Moreover, the sample of individuals in most genetic studies consists of both individuals with MRKH type I and individuals with MRKH type II; consequently, *LHX1* and *GREB1L* genes can affect the development of both the reproductive and urinary systems and, therefore, have been correlated mainly with MRKH II individuals [1,25,34,44,71–74]. As larger and more specialized studies using Whole-Exome Sequencing techniques emerge, other chromosomal locations and a clearer association between either MRKH type I or MRKH type II and a specific gene variant may be identified.

5. Conclusions

The genetic causes of MRKH syndrome remain elusive. Although some cases are familial, most cases are sporadic. In this study, we summarized and analyzed the most frequently reported genetic defects associated with MRKH syndrome in the available literature. The most reported chromosomal regions and the possible genes implicated are 1q21.1 (*RBM8A* gene), 1p31-1p35 (*WNT4* gene), 7p15.3 (*HOXA* gene), 16p11 (*TBX6* gene), 17q12 (*LHX1* and *HNF1B* genes), 22q11.21, and Xp22.

As there is a wider adoption of WGS techniques in MRKH studies, it is likely that, in the future, more genes and genetic regions will be identified. This information is particularly important because it can help clinicians associate clinical features in MRKH individuals with specific chromosomal regions and guide genetic counseling offered to patients and their families. Based on this knowledge, the prevention of the syndrome could also be possible through the development of appropriate gene therapy. However, larger cohort studies are necessary to elucidate the genetic basis of the syndrome.

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Data Availability Statement: Available upon request.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Studies included in this SR.

No.	1st Author Date of Publication Reference	Main Results	Group of Patients
1	Haiping Li, 2022 [75]	Variations of <i>EMX2</i>	40 MRKH individuals and 140 individual controls
2	Chunfang Chu, 2022 [76]	Variants of nine genes: <i>TBC1D1</i> , <i>KMT2D</i> , <i>HOXD3</i> , <i>DLG5</i> , <i>GLI3</i> , <i>HIRA</i> , <i>GATA3</i> , <i>LIFR</i> , and <i>CLIP1</i> ($n = 9$)	10 MRKH individuals
3	Domenico Dell'Edera, 2021 [77]	Microduplications in 22q11.21 ($n = 1$)	Case Report: a MRKH individual
4	Mikhael S, 2021 [78]	Variants of: <i>WNT4</i> , <i>LAMC1</i> , <i>RARA</i> , <i>HOXA10</i> , <i>PAX2</i> , and <i>WNT9B</i> , <i>TBX6</i> , <i>SHOX</i> , <i>MMP14</i> , and <i>LRP10</i>	111 MRKH individuals
5	Chen N, 2021 [79]	Variants of 7 genes: <i>PAX8</i> ($n = 4$), <i>BMP4</i> ($n = 2$), <i>BMP7</i> ($n = 2$), <i>TBX6</i> ($n = 1$), <i>HOXA10</i> ($n = 1$), <i>EMX2</i> ($n = 1$), and <i>WNT9B</i> ($n = 1$)	592 MRKH individuals (442 Chinese and 150 of mixed ethnicity) 941 individual controls
6	Pontecorvi P, 2021 [80]	Altered gene expression pattern in <i>PRKX</i> , <i>MUC1</i> , <i>HOXC8</i> , <i>GREB1L</i>	36 MRKH individuals
7	Jacquinet A, 2020 [81]	Variants of <i>GREB1L</i> ($n = 4$ families and 5 individuals)	9 families with CUAs and/or kidney malformations 68 individuals with CUAs
8	Monika Anant, 2020 [82]	18p deletion ($n = 1$)	Case Report: MRKH II individual with 18p deletion syndrome
9	Smol T, 2020 [83]	Microdeletion in 2q12.1q14.1 (involving <i>PAX8</i>) and microdeletion of <i>SHOX</i> locus ($n = 1$)	Case Report: a MRKH patient with congenital hypothyroidism
10	Herlin M K, 2019 [71]	Variants of <i>GREB1L</i> ($n = 4$)	A three-generation family with CUAs
11	Backhouse B, 2019 [35]	Variants ($n = 6$) and a deletion (affecting <i>TBX6</i>) ($n = 1$) of 16p11.2	8 MRKH and MURCS individuals
12	Pan H X, 2019 [84]	De novo changes in <i>BAZ2B</i> , <i>KLHL18</i> , <i>PIK3CD</i> , <i>SLC4A10</i> and <i>TNK2</i>	9 MRKH I individuals and their parents
13	Tewes A C, 2019 [37]	Variants and substitution of <i>TBX6</i> ($n = 4$)	125 MRKH individuals: 26 MRKH I, 27 MRKH II and 72 individuals with Müllerian ducts fusion anomalies 135 individual controls
14	Chunfang Chu, 2019 [38]	Deletion of the 16p11.2 (affecting <i>TBX6</i>) ($n = 1$)	5 individuals with distal vaginal atresia
15	Eggermann T, 2018 [85]	Failing to identify altered imprinting marks of differentially methylated regions <i>PLAGL1</i> , <i>GRB10</i> and <i>MEST</i> , <i>H19</i> and <i>KCNQ1OT1</i> , <i>MEG3</i> , <i>SNRPN</i> , <i>DIRAS</i> , <i>NESPAS</i> and <i>GNAS</i>	53 MRKH I individuals and 52 patients with a MRKH II individuals
16	AlSubaihin A, 2018 [57]	Tetrasomy of the pericentromeric region of chromosome 22 ($n = 1$)	Case Report: a MRKH individual with CES

Table A1. Cont.

No.	1st Author Date of Publication Reference	Main Results	Group of Patients
17	Takahashi K, 2018 [86]	De novo variants of <i>MYCBP2</i> , <i>NAV3</i> , and <i>PTPN3</i> ($n = 3$ families) and a variant of <i>MYCBP2</i> ($n = 1$)	10 MRKH individuals, including three MRKH individuals from trio-based families and 7 unaffected individuals
18	Demir Eksi, 2018 [36]	Variants of <i>BM8A</i> , <i>CMTM7</i> , <i>CCR4</i> , <i>TRIM71</i> , <i>CNOT10</i> , <i>TP63</i> , <i>EMX2</i> , and <i>CFTR</i> ($n = 4$)	19 MRKH individuals
19	Ledig S, 2018 [46]	Microdeletions and microduplications in 17q12, 22q11.21, 9q33.1, 3q26.11 and 7q31.1. ($n = 8$)	103 individuals with CUAs
20	Brucker SY 2017 [87]	Variants of <i>OXTR</i> ($n = 18$) and <i>ESR1</i> ($n = 1$)	93 MRKH individuals (68 type I and 25 type II)
21	Williams L S, 2017 [51]	Copy number variants of <i>WNT4</i> , <i>HNF1B</i> , or <i>LHX1</i> ($n = 6$), but no point change ($n = 100$)	147 MRKH individuals and their families 80 North American MRKH individuals, 58 with other family members and 22 singletons 67 Turkish MRKH individuals, (41 with family members and 26 singletons.)
22	Xing Q, 2016 [88]	Missense change of <i>DACT1</i> ($n = 1$)	100 individuals with Müllerian duct anomalies 200 individual controls
23	Waschk D E J, 2016 [47]	Variant of <i>WNT9B</i> ($n = 5$)	226 individuals with Müllerian duct anomalies, including 109 MRKH individuals 135 individual controls
24	Wenqing Ma, 2015 [89]	Polymorphisms in <i>WNT9B</i> and <i>PBX1</i> Epistatic effect of <i>AMH</i> , <i>PBX1</i> , <i>WNT7A</i> and <i>WNT9B</i>	182 unrelated Chinese MRKH individuals (155 type I and 27 type II) and 228 individual controls
25	Rall K, 2015 [16]	Duplication of <i>MMP14</i> and <i>LRP10</i> ($n = 1$ affected twin)	5 MRKHS-discordant monozygotic twin pairs
26	Tewes A C, 2015 [30]	Variants of <i>RBM8A</i> ($n = 13$) <i>TBX6</i> ($n = 5$)	167 individuals with CUAs: 116 MRKH and 51 with other anomalies of the Müllerian ducts 94 individual control
27	Liu S, 2015 [90]	Novel nonsense variants of <i>EMX2</i> ($n = 1$)	517 individuals with incomplete Müllerian fusion 563 individual controls
28	Murry, 2015 [91]	No pathogenic CNCs ($n = 20$)	20 individuals with CUA
29	McGowan R, 2015 [27]	Microdeletion and microduplication 1q21.1, 7p14.3, 16p11.2, 17q12, and 22q11.21-q11.23 and possibly implicating several genes (<i>LHX1</i> , <i>BBS9</i> , <i>HNF1β</i> , and <i>TBX6</i>) ($n = 9$)	35 individuals with Müllerian disorders
30	Chen M J, 2015 [92]	Deletions at 15q11.2 (80%), 19q13.31 (40%), 1p36.21 (40%) and 1q44 (40%) ($n = 5$), 1q21.1 ($n = 2$) Damaging variants of <i>HNRNPCL1</i> , <i>OR2T2</i> , <i>OR4M2</i> , <i>ZNF816</i> and <i>PDE11A</i>	7 MRKH I individuals
31	Nodale C, 2014 [93]	Upregulation of <i>MUC1</i> ($n = 8$) and significant upregulation of <i>HOXC8</i> ($n = 3$) Downregulation of <i>HOXB2</i> ($n = 7$) and <i>HOXB5</i> ($n = 7$) and Notch ligands <i>JAG1</i> ($n = 6$) and <i>DLL1</i> ($n = 5$)	8 out of 16 MRKHS individuals underwent reconstruction of neovagina with an autologous vaginal tissue and 5 individual controls

Table A1. Cont.

No.	1st Author Date of Publication Reference	Main Results	Group of Patients
32	Wang M, 2014 [94]	Variants of <i>WNT9B</i> ($n = 1$)	42 Chinese MRKH individuals and 42 individual controls
33	Deqiong Ma, 2014 [95]	Deletion at 2q13q14.2 (including <i>PAX8</i>) ($n = 1$)	Case Report: 1 individual with Müllerian agenesis and hypothyroidism
34	Sandbacka M, 2013 [34]	Variations including 16p11.2 and 17q12 deletions (8/50) or variations in <i>TBX6</i> or <i>LHX1</i> in MA patients (30/112)	112 MRKH I individuals
35	Ekici AB, 2013 [96]	Variations <i>HOXA10</i> and <i>HOXA13</i>	20 MRKH individuals, 7 non-MRKH individuals with genital tract anomalies and 53 individual control
36	Ledig S, 2012 [44]	No changes in <i>HNF1B</i> Variants of <i>LHX1</i> ($n = 1/62$)	62 MRKH individuals (23 MRKH I and 39 MRKH II)
37	Chang X, 2012 [97]	No perturbation that indicates significance of <i>WNT4</i>	189 Chinese individuals with CUAs (10 MRKH, 5 Müllerian aplasia and 174 incomplete Müllerian fusion)
38	Ravel C, 2012 [98]	No significant changes were observed between the MRKH individuals and control group for <i>LAMC1</i> and <i>DLGH1</i> gene polymorphisms.	12 MRKH individuals
39	Mingdi Xia, 2012 [52]	No significant variants ($n = 0/96$) but a rare polymorphism of <i>LHX1</i> ($n = 1/77$)	For variants of <i>LHX</i> : 96 individuals with CUAs and 105 individual controls
40	Wang P, 2012 [99]	Variant of <i>PAX2</i> ($n = 1$)	192 Chinese individuals with CUAs (15 with uterine aplasia and 177 with incomplete Müllerian fusion) and 192 ethnic-matched individual controls
41	Hinkes B, 2012 [45]	Microdeletion in 17q12 (involving <i>HNF1β</i> and <i>LHX1</i>) ($n = 1$)	Case Report: 1 MRKH individual with right kidney aplasia
42	Rall K, 2011 [23]	293 genes with altered expression and 194 genes differentially methylated	8 MRKH individuals and 8 individual controls
43	Morcel K, 2011 [55]	Deletion in 4q34-qter, 8p23.1, 10p14 and 22q11.2 ($n = 4$)	57 MRKH individuals
44	Philibert P, 2011 [66]	Variants of <i>WNT4</i> ($n = 1$)	4 individuals with Müllerian duct abnormalities and hyperandrogenism
45	Nik-Zainal S, 2011 [33]	Microdeletion at 16p11.2 ($n = 4$), microdeletion at 17q12 ($n = 4$), 22q11.2 ($n = 1$)	38 MRKH I individuals and 25 MRKH II individuals
46	Sandbacka M, 2011 [100]	No association between hypomethylation of the <i>H19</i> imprinted control region but aberrant methylation ($n = 3/16$)	83 individuals with CUAs
47	Jinlong Ma, 2011 [101]	Polymorphisms in <i>PBX1</i> ($n = 2$)	192 Chinese individuals with CUAs
48	Ledig S, 2011 [25]	Microdeletions and -duplications in 1q21.1, 17q12, and 22q11.21 involving <i>LHX1</i> and <i>HNF1B</i> gene ($n = 48$)	56 MRKH individuals
49	Gervasini C, 2010 [102]	Partial duplication of <i>SHOX</i> ($n = 5$)	30 MRKH individuals 53 individual controls
50	Acién P, 2010 [103]	No microdeletions in 17q12 and 22q11.21 ($n = 1$)	Case Report: 1 MRKH individual with pulmonary hypoplasia

Table A1. Cont.

No.	1st Author Date of Publication Reference	Main Results	Group of Patients
51	Liatsikos S A, 2010 [58]	No causative variants of <i>HOX A10</i> and <i>HOX A11</i>	30 individuals with MDAs 100 individual controls
52	Richard A Oram, 2010 [104]	Variants or deletion of <i>HNFB1B</i> ($n = 9/50$ individuals with both CUAs and renal abnormalities)	50 individuals with both CUAs and renal abnormalities 58 individuals with isolated CUAs
53	Bernardini L, 2009 [43]	Deletion in 17q12 (involving <i>TCF2</i> and <i>LHX1</i> genes) ($n = 2$)	22 MRKH individuals
54	Ravel C, 2009 [105]	Variants of <i>WNT4</i> , <i>WNT5A</i> , <i>WNT7A</i> , and <i>WNT9B</i>	11 MRKH individuals
55	Hofstetter G, 2008 [106]	No major deletions or duplications in 22q11.1 12q24.1. and 3q27 ($n = 1$)	Case report: 1 MURCS individual
56	Mencarelli M A, 2008 [48]	Deletions in 7q31, 14q21.1, Xq25 and duplications in 12p11.22, 12q21.31, 13q31.1, 17q12, Xp22.31, Xq28	84 individuals with mental problems and congenital anomalies (including CUAs)
57	Philibert P, 2008 [65]	Variants of <i>WNT4</i> gene	28 individuals with CUAs 100 individual controls
58	Drummond JB, 2008 [107]	No variants of the <i>GSK-3beta</i> phosphorylation sites on exon 3 of <i>beta-catenin</i> gene ($n = 12$)	12 MRKH patients
59	Lalwani S, 2008 [108]	No <i>HOXA10</i> gene variants	26 individuals with CUAs 30 individual controls
60	Sundaram U T, 2007 [54]	Deletion in 22q11.2 ($n = 2$)	2 individuals with absent uterus and unilateral renal agenesis
61	Cheroki C, 2007 [26]	Submicroscopic genomic imbalances in 1q21.1, 17q12, 22q11.21, and Xq21.31	14 MRKH II individuals
62	Biason-Lauber A, 2007 [64]	Variants of <i>WNT4</i> ($n = 1$)	Case report: 1 MRKH individual
63	Burel A, 2006 [109]	No variants of <i>HOXA7-HOXA13</i> region ($n = 6$)	6 MRKH individuals
64	Cheroki C, 2006 [56]	Deletion in 22q11 (excluding <i>WNT-4</i> , <i>RARGamma</i> , <i>RXR-alpha</i>) ($n = 1$)	25 MRKH individuals
65	Oppelt P, 2005 [110]	<i>AMH</i> promoter sequence variations cannot the cause of aberrant <i>AMH</i> expression leading to Müllerian duct formation disorders	30 MRKH individuals 48 individual controls
66	Clément-Ziza Mi, 2005 [111]	No significant variations of <i>WNT4</i> ($n = 19$)	19 MRKH individuals
67	Zenteno J C, 2004 [112]	No significant difference in Polymorphisms <i>AMH</i> and <i>AMHR</i> genes between MRKH individuals and controls	15 individuals with Mullerian agenesis 25 individual controls
68	Biason-Lauber A, 2004 [63]	Variants of the <i>WNT4</i> ($n = 1$)	Case Report: 1 MRKH individual
69	Plevraki E, 2004 [113]	Positive <i>TSPY</i> gene ($n = 2$)	6 MRKH individuals
70	Klipstein S, 2003 [114]	<i>GALT</i> enzyme do not affect PMD formation	32 individuals with CUAs 138 individual controls
71	Aydos S, 2003 [115]	Deletion of Xq ($n = 1$)	Case Report: 1 MRKH individual with gonadal dysgenesis
72	Timmreck LS, 2003 [116]	Variants of <i>CFTR</i> ($n = 2$)	25 individuals with CUAs

Table A1. Cont.

No.	1st Author Date of Publication Reference	Main Results	Group of Patients
73	Bingham C, 2002 [49]	Changes in <i>HNF-1beta</i> gene ($n = 2$ families)	9 families with renal abnormalities and a personal or family history of female genital tract malformations, but no history of diabetes
74	Resendes D L, 2001 [117]	No changes or rare polymorphism in <i>AMH</i> and the <i>AMHR</i> genes ($n = 22$)	22 individuals with CUAs 96 individual controls
75	Lindner T H, 1999 [50]	Deletion in <i>HNF-1beta</i> gene	1 Norwegian family, N5, with a syndrome of mild diabetes, progressive non-diabetic renal disease and severe genital malformations
76	Cramer D W, 1996 [118]	Carriers for the <i>N314D</i> variants of <i>GALT</i> ($n = 6/13$ individuals with Müllerian agenesis and 16/113 individual controls)	13 individuals with vaginal agenesis and their mothers 113 individual controls

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