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McKusick-Kaufman Syndrome

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Summary

Clinical characteristics

McKusick-Kaufman syndrome (MKS) is characterized by the combination of postaxial polydactyly (PAP), congenital heart disease (CHD), and hydrometrocolpos (HMC) in females and genital malformations in males (most commonly hypospadias, cryptorchidism, and chordee). HMC in infants usually presents as a large cystic abdominal mass arising out of the pelvis, caused by dilatation of the vagina and uterus as a result of the accumulation of cervical secretions from maternal estrogen stimulation. HMC can be caused by failure of the distal third of the vagina to develop (vaginal agenesis), a transverse vaginal membrane, or an imperforate hymen. PAP is the presence of additional digits on the ulnar side of the hand and the fibular side of the foot. A variety of congenital heart defects have been reported including atrioventricular canal, atrial septal defect, ventricular septal defect, or a complex congenital heart malformation.

Diagnosis/testing

The clinical diagnosis of MKS can be established in a proband based on clinical diagnostic criteria of HMC and PAP in the absence of clinical or molecular genetic findings suggestive of an alternative diagnosis. The molecular diagnosis can be established in proband with suggestive findings and biallelic pathogenic variants in *MKKS* identified by molecular genetic testing. However, care must be taken to ensure that the proband does not have Bardet-Biedl syndrome, an allelic condition with considerable clinical overlap and age-dependent features including retinal dystrophy, obesity, and intellectual disability.

Management

Treatment of manifestations: Surgical repair of the obstruction causing HMC and drainage of the accumulated fluid. Treatment for polydactyly and congenital heart defects and any other anomalies is standard.

Surveillance: Watch for recurrent later complications of surgery for HMC; ongoing surveillance for manifestations of BBS including growth and developmental assessments, ophthalmologic examination, and

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electroretinogram, renal anomaly complications and development of severe constipation (which raises the possibility of Hirschsprung disease).

Agents/circumstances to avoid: Care with anesthesia in the neonatal period as severe HMC can cause diaphragmatic compression.

Genetic counseling

MKS is inherited in an autosomal recessive manner. If both parents of an individual with MKS are known to be heterozygous for an *MKKS* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. (Note: Genetic counseling should encourage caution regarding premature diagnosis of MKS [i.e., a diagnosis made before age 5 years] because of the possibility of manifestations of Bardet-Biedl syndrome appearing at a later age.) Carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible if the *MKKS* pathogenic variants have been identified in the family. Although HMC, PAP, and CHD can be detected by prenatal ultrasound examination, the reliability of prenatal ultrasound as a method of prenatal diagnosis of MKS is unknown because these findings are variable and may not be apparent in an individual until after birth.

Diagnosis

No consensus clinical diagnostic criteria for McKusick-Kaufman syndrome (MKS) have been published.

Suggestive Findings

Diagnosis of McKusick-Kaufman syndrome (MKS) should be suspected in individuals with the following features.

In females

- Hydrometrocolpos (HMC) *
- Postaxial polydactyly (PAP) **
- Congenital heart disease (CHD)

In males

- Genital malformations (most commonly hypospadias, cryptorchidism, and chordee)
- PAP **
- CHD

In all

- Insufficient manifestations of overlapping syndromes, such as Bardet-Biedl syndrome (BBS) for a diagnosis of this syndrome or another condition
- Family history typically consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity and unaffected parents). Absence of a known family history does not preclude the diagnosis.

* Hydrometrocolpos (HMC) in infants is dilatation of the vagina and uterus caused by the accumulation of cervical secretions as a result of maternal estrogen stimulation. HMC can be caused by:

- Failure of the distal third of the vagina to develop (vaginal atresia or agenesis);
- A transverse vaginal membrane;

- Imperforate hymen; in rare cases, HMC and polydactyly may be associated with an imperforate hymen, but many individuals reported with these findings were described at young ages and it is thus not known if the actual diagnosis was MKS or BBS.

HMC often presents at birth as a large, cystic abdominal mass arising out of the pelvis, which can be sufficiently large to be clinically obvious and is verified using an ultrasound scan. The mass can be large enough to cause intestinal obstruction, urinary outflow obstruction leading to dilatation of the ureter (hydroureter) and kidneys (hydronephrosis), obstruction of the inferior vena cava, and/or elevation of the diaphragm resulting in breathing difficulties.

** Postaxial polydactyly (PAP) is the presence of additional digits on the ulnar side of the hand and the fibular side of the foot.

- The additional digit can be fully formed or can be a rudimentary skin tag (often called a "minimus").
- If clinical examination is insufficient, radiographs may be used to determine whether the polydactyly is postaxial or mesoaxial (also known as insertional polydactyly); that is, the presence of an extra digit or digits between the thumb and fifth finger. Mesoaxial polydactyly is much less common than postaxial polydactyly.

Establishing the Diagnosis

The clinical diagnosis of McKusick-Kaufman syndrome (MKS) can be **established** in a proband based on clinical diagnostic criteria of HMC and postaxial polydactyly in the absence of clinical or molecular genetic findings suggestive of an alternative diagnosis in an individual age five years or older. Evidence of likely autosomal recessive inheritance can be a supporting factor. A molecular diagnosis can be **established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *MKKS* (also known as *BBS6*) identified by molecular genetic testing (see Table 1).

Clinical Diagnosis

MKS was first described by McKusick in 1978 in the Amish population as a triad of HMC, postaxial polydactyly, and congenital heart disease. For females without a family history and who are not part of the Amish population, HMC with distal vaginal agenesis or a transverse vaginal membrane and postaxial polydactyly have been considered sufficient for a clinical diagnosis MKS [Slavotinek & Biesecker 2000, Schaefer et al 2011, Mallmann et al 2019]. As HMC and polydactyly typically present in the newborn period, the diagnosis of MKS is usually made at birth. However, discrimination between MKS and BBS in the neonatal period is challenging, as the age-dependent features of BBS (including retinal dystrophy, obesity, and intellectual disability) have not developed [Slavotinek & Biesecker 2000]. The clinical diagnosis of MKS is thus not confirmed until the individual has reached age five years without fulfilling the diagnostic criteria for BBS, or manifesting additional findings of an alternative diagnosis. In addition, MKS is relatively rare compared to BBS outside the Amish population.

Molecular Diagnosis

The molecular diagnosis of MKS **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *MKKS* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *MKKS* variants of uncertain significance (or identification of one known *MKKS* pathogenic variant and one *MKKS* variant of uncertain significance) does not establish or rule out the diagnosis.

Because the phenotype of MKS is indistinguishable from BBS through early childhood, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *MKKS*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A multigene panel** that includes *MKKS* and other genes of interest, including the genes for BBS (see Differential Diagnosis) is likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in McKusick-Kaufman Syndrome (MKS)

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
MKKS	Sequence analysis [3]	~100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

McKusick-Kaufman syndrome (MKS), defined as hydrometrocolpos (HMC) and postaxial polydactyly (PAP) without the development of the age-dependent features of BBS, was first diagnosed in a large Amish family [Stone et al 1998]. Although the MKS phenotype is very rare, it has been presumed to be pan ethnic following descriptions of HMC in association with polydactyly in numerous ancestries. In the Amish population, variable expressivity for MKS has been described: 70% of affected females have HMC, 60% of affected individuals of both sexes have PAP, and 15% of affected individuals of both sexes have congenital heart disease (CHD) [Slavotinek & Biesecker 2000]. Of note, many individuals with HMC and PAP diagnosed as having MKS have been reported at

an age too young to manifest the age-dependent features of BBS [Mallmann et al 2019]. The true incidence of physical findings associated with the MKS phenotype alone is therefore unknown.

Table 2 shows the most frequent associated features in 49 individuals of Amish and non-Amish ethnicity who were diagnosed with MKS; 75% were diagnosed at birth and 98% by age six months [Slavotinek & Biesecker 2000]. Of these individuals, 44 were female and five were male. No similar large studies have been realized more recently and the majority of recent case reports have comprised single individuals with HMC reported in the first year of life [Adam et al 2017, Halim et al 2018]. The degree of similarity of the phenotype between the Amish and non-Amish population is unclear and has not been systematically studied; in addition, it is not known if these individuals would have developed manifestations of BBS as they aged.

The incidence of genital findings in males has also been difficult to establish outside the Amish population due to the rarity of the condition, but in 11 males who had affected sisters or other female relatives diagnosed with MKS, polydactyly was present in all cases and only one had genital abnormalities comprising cryptorchidism and hypospadias [Chitayat et al 1987]; however, the incidence of BBS among these individuals is not known.

Table 2. Phenotypic Features of Individuals with McKusick-Kaufman Syndrome (MKS)

Finding		# of Individuals (%)
Genitourinary malformations in females	HMC	42/44 (95%)
	Vaginal agenesis	26/44 (59%)
	Urogenital sinus	16/44 (36%)
	Ectopic urethra	8/44 (18%)
	No urethral opening	6/44 (14%)
	No vaginal opening	4/44 (9%)
	Genitourinary tract fistulae	6/44 (14%)
PAP – limbs affected	Hands only	12/42 (29%)
	Feet only	6/42 (14%)
	Hands & feet [1]	11/42 (26%)
	Four-limb polydactyly [1]	11/42 (26%)
Other digital anomalies	Syndactyly	12/49 (24%)
	Metacarpal/tarsal anomalies	8/49 (16%)
	Postaxial minimus	6/49 (12%)
	Brachydactyly	3/49 (6%)
	Absent phalanges	2/49 (4%)
	Interstitial polydactyly	0/48 (0%)
	Heptadactyly	2/48 (4%)
Cardiac malformations	Various (See Cardiovascular Malformations.)	7/49 (14%)

Table 2. continued from previous page.

Finding		# of Individuals (%)
Renal anomalies	Hydronephrosis	31/49 (63%)
	Hydroureter	12/49 (24%)
	Renal cysts	2/49 (4%)
	Calyceal dilatation	7/49 (14%)
	Renal atrophy/ hypoplasia [2]	2/49 (4%)
	Corticomedullary dysplasia [3]	3/46 (6%)
	Nonfunctioning kidney	2/49 (4%)
GI malformations	Imperforate anus	4/49 (8%)
	Anal atresia	1/49 (2%)
	Hirschsprung disease	6/49 (12%)
	Anteriorly placed anus	2/49 (4%)

From Slavotinek & Biesecker [2000]
GI = gastrointestinal; PAP = postaxial polydactyly
1. Four-limb polydactyly involves both hands and both feet; polydactyly of the hands and feet means that both upper and lower limbs are affected, but not every limb.
2. Renal dysplasia is a histologic diagnosis that describes abnormal differentiation of the renal parenchyma.
3. Corticomedullary dysplasia is abnormal differentiation of both the cortex and the medulla of the kidney. If focal, renal function may be preserved; if bilateral and extensive, renal failure can result.

Cardiovascular Malformations

Congenital heart defects comprising: atrioventricular canal defect; atrial septal defect; ventricular septal defect; complex congenital heart disease with an atrioventricular canal defect, small aorta, and hypoplastic left ventricle; tetralogy of Fallot; and a patent ductus arteriosus have been reported in individuals with an MKS phenotype [Slavotinek & Biesecker 2000, Tsai et al 2014].

Renal Anomalies and GI Malformations

Although both renal anomalies and GI malformations have been identified in those with a clinical diagnosis of MKS, not all of these individuals have had molecular genetic testing nor were they followed to an age in which an eye exam could exclude the diagnosis of BBS. Since these physical findings are more common in those with a molecularly confirmed diagnosis of BBS, they should prompt screening for other clinical manifestations of BBS or molecular genetic testing for BBS.

Other Findings Associated with MKS

Development. Developmental delay was present in 3/37 individuals (14%) in one study [Slavotinek & Biesecker 2000], but this figure may have been influenced by the inclusion of individuals who later developed manifestations typical of BBS.

Gynecologic issues. Fertility has been described; one female age 16 years gave birth to a healthy son [Cohen & Javitt 1998]. However, molecular genetic testing was not reported in this individual. Fertility is likely dependent on the extent of the genitourinary malformations, but has not been systematically studied.

Prognosis. Studies on life span have not been performed on individuals with MKS, but life span is not known to be reduced apart from the morbidity and mortality that can be associated with HMC [Mallmann et al 2019] and congenital heart disease.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *MKKS* have been identified.

Penetrance

Non-penetrance has been estimated to occur in at least 9% of affected Amish males and 3% of affected Amish females [Stone et al 1998].

Determination of penetrance in the non-Amish population has not yet been possible due to the rarity of the syndrome.

Nomenclature

MKS was first described as HMC and PAP in the Amish population.

Prevalence

More than 100 individuals with the MKS phenotype from different ethnic groups have been reported. The majority were reported at birth or in the neonatal period because of HMC; thus, BBS was frequently not excluded. The true prevalence of MKS is unknown, and the incidence of MKS has not been estimated in the non-Amish population.

Stone et al [2000] estimated a heterozygote frequency of 1%-3% for MKS in the Amish population or an incidence of approximately 1:10,000 [Scott et al. 2017].

Genetically Related (Allelic) Disorders

Bardet-Biedl syndrome (BBS). A substantial and prognostically significant clinical overlap between MKS and BBS has long been noted. The close relationship between BBS and MKS has been further complicated by the demonstration of disease-causing sequence alterations in *MKKS* in both MKS and in an estimated 6% of unselected individuals with BBS. See Bardet-Biedl Syndrome Overview.

It therefore becomes pertinent to consider whether MKS should continue to remain a separate entity or henceforth be considered as belonging to the wider phenotypic spectrum that includes BBS (see Differential Diagnosis). However, as retinal disease, obesity, and developmental disabilities have classically been absent in MKS, there is support for a distinct clinical entity. In addition, cardiovascular and genital anomalies may be more frequently associated with variants in *MKKS* compared to other BBS genes (see BBS Overview). In support of continued consideration of a phenotypic separation, studies in zebrafish have shown that BBS6 is actively transported between the cytoplasm and the cell nucleus, and this interaction is perturbed in MKS, but not in BBS [Scott et al 2017].

Retinitis pigmentosa (RP) and polydactyly without other findings of BBS or MKS. A female age 13 years and her brother age 18 years were reported to have retinitis pigmentosa (RP) and four-limb postaxial polydactyly with a homozygous pathogenic variant in *MKKS* [Hulleman et al 2016]. There were no additional clinical findings suggestive of MKS or BBS, although the older sib was described as having poor scholastic performance [Hulleman et al 2016]. Similarly, a family with four-limb polydactyly and RP, but without other manifestations of MKS or BBS, was found to harbor a homozygous pathogenic variant in *MKKS* that segregated with the disease in three affected individuals [Goyal et al 2020].

Differential Diagnosis

Bardet-Biedl syndrome (BBS) is a multisystem non-motile ciliopathy primarily characterized by retinal rod-cone dystrophy, truncal obesity and related complications, postaxial polydactyly, cognitive impairment, hypogonadotropic hypogonadism and/or genitourinary malformations, and renal malformations and/or renal parenchymal disease (for overview, see Bardet-Biedl Syndrome Overview). Overlap with MKS occurs due to the finding of HMC (in females), genital malformations in males, and postaxial polydactyly and congenital heart disease in both conditions.

At least 26 genes are known to be associated with BBS. Pathogenic variants in *MKKS* (see Genetically Related Disorders) account for an estimated 6.3% of all BBS (see BBS Overview).

The genital malformations associated with MKS, including HMC, vaginal atresia, and cryptorchidism, have also been associated with BBS-related genes including *BBS2*, *BBS6*, *BBS10*, and *BBS12*, suggesting that these features are not *MKKS*/*BBS6* specific [Deveault et al 2011, Schaefer et al 2011].

Note: Although several reports have described BBS phenotypes with three pathogenic variants and at least one variant involving the *MKKS* locus [Hjortshøj et al 2010], triallelic inheritance has been refuted in other studies and is not currently considered a typical inheritance pattern for either MKS or BBS [Abu-Safieh et al 2012].

Table 3 illustrates the phenotypic overlap between MKS and BBS [Schaefer et al 2011] (+ = major feature; ± = minor feature).

Table 3. Phenotypic Overlap Between McKusick-Kaufman Syndrome and Bardet-Biedl Syndrome

Clinical Feature	MKS	BBS
Hydrometrocolpos in females	+	±
Congenital heart disease	+	±
Polydactyly	+	+
Retinitis pigmentosa		+
Obesity		+
Renal anomalies		+
Developmental disabilities		+

+ = major feature; ± = minor feature
BBS = Bardet-Biedl syndrome; MKS = McKusick-Kaufman syndrome

Other Disorders with Overlapping Clinical Features

Hydrometrocolpos and postaxial polydactyly (PAP)

- **Ellis-van Creveld syndrome (EVC).** Cardinal phenotypic features of EVC comprise chondrodysplasia with acromelic growth restriction, polydactyly, ectodermal dysplasia with dystrophy of the nails, and congenital heart disease [Ruiz-Perez et al 2000, Ruiz-Perez et al 2003]. Although individuals reported as having HMC and PAP have had clinical features consistent with EVC [Digilio et al 2004], genetic testing should differentiate these conditions. EVC is an autosomal recessive disorder known to be associated with pathogenic variants in *EVC* or *EVC2*.
- A woman age 19 years with lack of müllerian fusion, vaginal agenesis, a unicornuate uterus, postaxial polydactyly, brachydactyly, and tetralogy of Fallot had normal development, normal weight, and no evidence of retinal dystrophy. No *MKKS* sequence variants were identified by sequence analysis; thus, it is unknown if the individual has a variant form of MKS or a new syndrome [Slavotinek et al 2004].

- **Pallister-Hall syndrome (PHS).** Overlap of MKS with PHS has been described due to HMC and postaxial polydactyly [Kos et al 2008]. PHS is characterized by a spectrum of anomalies ranging from polydactyly, asymptomatic bifid epiglottis, and hypothalamic hamartoma at the mild end to laryngotracheal cleft with neonatal lethality at the severe end. Individuals with mild PHS may be incorrectly diagnosed as having isolated postaxial polydactyly type A. Individuals with PHS can have pituitary insufficiency and may die as neonates from undiagnosed adrenal insufficiency. PHS is caused by pathogenic variants in *GLI3* and is inherited in an autosomal dominant manner.

Hydrometrocolpos with preaxial polydactyly. HMC has also been reported in one case in association with preaxial, "mirror" polydactyly [Traisrisilp et al 2021], but genetic testing in this individual did not confirm either MKS or BBS.

HMC can be a feature of several malformation syndromes (see Mallmann et al [2019]) including:

- Mayer-Rokitansky-Küster-Hauser syndrome
- Herlyn-Werner-Wunderlich syndrome
- Intraabdominal teratoma
- VACTERL association. VACTERL is an acronym for an association of physical findings that comprises *v*ertebral anomalies, *a*nal atresia, *c*ardiac malformations, *t*racheo*e*sophageal fistula, *r*enal abnormalities, and *l*imb anomalies including hexadactyly (OMIM 192350).
- Trichorhinophalangeal syndrome. HMC is a rare finding in trichorhinophalangeal syndrome II (Langer-Giedion syndrome) [Schinzel et al 2013].

Vaginal agenesis. Rarely, vaginal agenesis can be described with chromosome aberrations (e.g., see Anant et al [2020]).

Management

No clinical practice guidelines for MKS have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with McKusick-Kaufman syndrome (MKS), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with McKusick-Kaufman Syndrome (MKS)

System/Concern	Evaluation	Comment
Genitourinary malformations	Pelvic ultrasound	In females; in males, inspection of the genitalia should be performed.
Polydactyly & syndactyly	Skeletal radiographs to detect osseous polydactyly & syndactyly	Provide referral to surgical specialist as needed.
Cardiac malformation	Echocardiogram	Specialist referral as appropriate

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Possible Bardet-Biedl syndrome (BBS) [2]	Assessment of height, weight, & head circumference & initiation of a carefully maintained growth chart to document obesity	If obesity or short stature present, this may indicate a diagnosis of BBS
	Determination of developmental status by standard screening tools to detect DD	If present, this may indicate a diagnosis of BBS.
	Ophthalmologic exam & ERG to evaluate for manifestations of retinal dystrophy	Specialist referral to ophthalmologist for monitoring is frequently recommended.
	Renal ultrasound	To detect pelvicalyceal abnormalities, renal hypoplasia, or cystic dysplasia of the kidneys
	Rectal biopsy in those w/severe constipation to exclude Hirschsprung disease	
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of MKS to facilitate medical & personal decision making

DD = developmental delay; ERG = electroretinogram; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse
2. A subset of those with a diagnosis of MKS as infants may with age develop findings that lead to a revised diagnosis of BBS.

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with McKusick-Kaufman Syndrome (MKS)

Manifestation/Concern	Treatment	Considerations/Other
Hydrometrocolpos	Prompt surgical repair of obstruction & drainage of accumulated fluid	Hydrometrocolpos can also present after neonatal period.
Polydactyly & syndactyly	Standard treatment	
Congenital heart defects		
Renal anomalies		
Anal anomalies & Hirschsprung disease		

Surveillance

Table 6. Recommended Surveillance for Individuals with McKusick-Kaufman Syndrome (MKS)

System/Concern	Evaluation	Frequency
Hydrometrocolpos	Watch for later complications of surgery for HMC, incl recurrent urinary tract infections & re-stenosis & infection of vaginal tract.	No monitoring; prompt eval of symptoms & signs of abdominal distention

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Possible Bardet-Biedl syndrome [1] (BBS)	Serial growth measurement to track height & weight to document obesity that can occur w/BBS	Annually until at least age 5 yrs
	Developmental assessments to detect developmental disabilities that can occur w/BBS	
	Regular ophthalmologic exam & ERG (if appropriate) to evaluate for visual signs & symptoms of RP	Annually after age 5 yrs
	If renal anomaly present, monitor renal function & blood pressure.	Frequency of follow up of renal anomalies per specialist
	Monitor for development of severe constipation w/referral for rectal biopsy to exclude Hirschsprung disease.	Review at well child health exams

ERG = electroretinogram; RP = retinitis pigmentosa

1. A subset of those with a diagnosis of MKS as infants may with age develop findings that lead to revision of the diagnosis to BBS.

Agents/Circumstances to Avoid

In the newborn with severe HMC, care with anesthesia in the neonatal period is appropriate, as HMC can cause diaphragmatic compression [Tekin et al 2003].

Evaluation of Relatives at Risk

It is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

- If the pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known:
  - **Sisters of females with MKS.** Examination of the external genitalia for vaginal membranes or an imperforate vagina, and of the hands and feet for polydactyly; echocardiogram for the congenital heart defects associated with MKS
  - **Brothers of affected females.** Examination of the external genitalia for hypospadias, cryptorchidism, and chordee; and of the hands and feet for polydactyly; echocardiogram for cardiac manifestations of MKS

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

McKusick-Kaufman syndrome (MKS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *MKKS* pathogenic variant based on family history).
- If a molecular diagnosis has been established in the proband, molecular genetic testing of the parents is recommended to confirm that both parents are heterozygous for an *MKKS* pathogenic variant and to allow reliable recurrence risk assessment. (In rare families, only one parent of a proband with an autosomal recessive disorder is heterozygous and the proband is affected as the result of either (1) one pathogenic variant inherited from the heterozygous parent and a second pathogenic variant that occurred *de novo* in the proband or (2) uniparental isodisomy and consequent homozygosity for the pathogenic variant transmitted by a heterozygous parent [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents of an individual with MKS are known to be heterozygous for an *MKKS* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Intrafamilial clinical variability has been observed in sibs with biallelic pathogenic *MKKS* variants [Manara et al 2019].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- The offspring of an individual with MKS are obligate heterozygotes (carriers) for a pathogenic variant in *MKKS*.
- The heterozygote frequency of MKS in the Amish population is estimated to be 1%-3% (see Prevalence), increasing the risk that an affected individual may have a reproductive partner who is heterozygous for the specific *MKKS* variant allele found in the Amish population (see Molecular Pathogenesis). The offspring of an affected individual and a heterozygous reproductive partner are at 50% risk of being affected and 50% risk of being heterozygous.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *MKKS* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *MKKS* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

MKS vs Bardet-Biedl syndrome. Genetic counseling should encourage caution regarding premature diagnosis of MKS (i.e., a diagnosis made before age 5 years) because of the possibility of manifestations of Bardet-Biedl syndrome appearing at a later age.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *MKKS* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for MKS are possible.

Ultrasound examination. The manifestations of MKS, including hydrometrocolpos (HMC), postaxial polydactyly (PAP), and congenital heart disease, can be detected by prenatal ultrasound examination. If present, these findings may not be identified until late second trimester or third trimester, or may not be apparent until after birth. Given the variability in findings of MKS, the reliability of prenatal ultrasound as a method of diagnosing MKS is unknown.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  McKusick-Kaufman syndrome

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. McKusick-Kaufman Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MKKS	20p12.2	Molecular chaperone MKKS	MKKS database	MKKS	MKKS

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for McKusick-Kaufman Syndrome (View All in OMIM)

236700	MCKUSICK-KAUFMAN SYNDROME; MKKS
604896	MKKS CENTROSOMAL SHUTTLING PROTEIN; MKKS

Molecular Pathogenesis

McKusick-Kaufman syndrome (MKS), like Bardet-Biedl syndrome (BBS) is part of a group of disorders known as ciliopathies. At least 26 different genes are associated with BBS and it has long been recognized that pathogenic variants in *MKKS* (also known as *BBS6*) have been associated with both MKS and BBS.

In the Old Order Amish kindred in which MKS was first described, the phenotype was recorded as due to homozygosity for two pathogenic variants, p.His84Tyr and p.Ala242Ser, inherited *in cis* (i.e., p.[His84Tyr, Ala242Ser]; [His84Tyr, Ala242Ser]). The p.[His84Tyr, Ala242Ser] allele, with both variants, is present in approximately 2% of the Amish population, but is very rare outside of this ancestry. To date, very few individuals outside the Amish population diagnosed clinically with MKS have been found to have biallelic pathogenic variants in *MKKS*.

The proteins encoded by the genes that cause BBS form two main complexes: the BBSome (a multi-protein complex) and the BBS chaperonin complex [Scott et al 2017]. The BBSome, consisting of eight proteins (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9, and BBS18) is involved in ciliary function by transporting ciliary cargo destined for the plasma membrane of the cell, whereas the BBS chaperonin complex, comprising MKKS/BBS6, BBS10, and BBS12, functions as a scaffold for assembly of the BBSome complex [Scott et al 2017]. Other BBS-related genes have also been identified.

Wild type MKKS protein binds SMARCC1 and is actively transported between the cytoplasm and nucleus, whereas the MKKS protein resulting from the MKS-associated allele, *MKKS/BBS6* p.[His84Tyr, Ala242Ser] found in the Amish population, binds to SMARCC1, but is defective in its ability to enter the cell nucleus [Scott et al 2017]. Other variants in *MKKS* associated with BBS were not found to alter nuclear import. The *MKKS/BBS6* p.[His84Tyr, Ala242Ser] allele was shown not to impair cilia-related processes and this may explain the milder phenotype associated with MKS compared to BBS [Scott et al 2017].

Mechanism of disease causation. MKS occurs via a loss-of-function mechanism consistent with autosomal recessive conditions.

Table 7. Notable *MKKS* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_018848.3 NP_061336.1	c.250C>T	p.His84Tyr	Amish founder variant [Stone et al 2000]; assoc w/altered nuclear import of *MKKS*/*BBS6* [Scott et al 2017]
	c.724G>T	p.Ala242Ser	Amish founder variant [Stone et al 2000]; assoc w/altered nuclear import of *MKKS*/*BBS6* [Scott et al 2017]

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Dr Slavotinek received her medical degree from the University of Adelaide and her PhD from Flinders University in South Australia. She trained in Clinical Genetics in the United Kingdom and subsequently did a Genetics Fellowship at the National Institutes of Health to become Board certified in Clinical Genetics in the USA. She joined the Department of Pediatrics at UCSF in 2002 and is now a Professor of Clinical Pediatrics. Dr Slavotinek is an author on more than 195 peer-reviewed publications in addition to book chapters and reviews.

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References

Literature Cited

Abu-Safieh L, Al-Anazi S, Al-Abdi L, Hashem M, Alkuraya H, Alamr M, Sirelkhatim MO, Al-Hassnan Z, Alkuraya B, Mohamed JY, Al-Salem A, Alrashed M, Faqeih E, Softah A, Al-Hashem A, Wali S, Rahbeeni Z, Alsayed M, Khan AO, Al-Gazali L, Taschner PE, Al-Hazzaa S, Alkuraya FS. In search of triallelism in Bardet-Biedl syndrome. Eur J Hum Genet. 2012;20:420–7. PubMed PMID: 22353939.

Adam A, Hellig J, Mahomed N, Lambie L. Recurrent urinary tract infections in a female child with polydactyly and a pelvic mass: consider the McKusick-Kaufman syndrome. Urology. 2017;103:224–6. PubMed PMID: 28153592.

Anant M, Raj N, Yadav N, Prasad A, Kumar S, Saxena AK. Two distinctively rare syndromes in a case of primary amenorrhea: 18p deletion and Mayer-Rokitansky-Kuster-Hauser syndromes. J Pediatr Genet. 2020;9:193–7. PubMed PMID: 32714621.

Chitayat D, Hahm SY, Marion RW, Sachs GS, Goldman D, Hutcheon RG, Weiss R, Cho S, Nitowsky HM. Further delineation of the McKusick-Kaufman hydrometrocolpos-polydactyly syndrome. Am J Dis Child. 1987;141:1133–6. PubMed PMID: 3631003.

Cohen E, Javitt MC. Term pregnancy in a patient with McKusick-Kaufman syndrome. AJR Am J Roentgenol. 1998;171:273–4. PubMed PMID: 9648816.

Deveault C, Billingsley G, Duncan JL, Bin J, Theal R, Vincent A, Fieggen KJ, Gerth C, Noordeh N, Traboulsi EI, Fishman GA, Chitayat D, Knueppel T, Millán JM, Munier FL, Kennedy D, Jacobson SG, Innes AM, Mitchell GA, Boycott K, Héon E. BBS genotype-phenotype assessment of a multiethnic patient cohort calls for a revision of the disease definition. Hum Mutat. 2011;32:610–9. PubMed PMID: 21344540.

Digilio MC, Torrente I, Goodship JA, Marino B, Novelli G, Giannotti A, Dallapiccola B. Ellis-van Creveld Syndrome with hydrometrocolpos is not linked to chromosome arm 4p or 20p. Am J Med Genet A. 2004;126A:319–23. PubMed PMID: 15054850.

Goyal S, Singh IR, Vanita V. Novel mutation in MKKS/BBS6 linked with arRP and polydactyly in a family of North Indian origin. Clin Exp Ophthalmol. 2020;48:343–55. PubMed PMID: 31989739.

Halim A, Afzal T, Fatima S, Riaz S. A newborn with rare McKusick syndrome. J Coll Physicians Surg Pak. 2018;28:S140–2. PubMed PMID: 29866251.

Hjortshøj TD, Grønskov K, Philp AR, Nishimura DY, Riise R, Sheffield VC, Rosenberg T, Brøndum-Nielsen K. Bardet-Biedl syndrome in Denmark-report of 13 novel sequence variations in six genes. Hum Mutat. 2010;31:429–36. PubMed PMID: 20120035.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Hulleman JD, Nguyen A, Ramprasad VL, Murugan S, Gupta R, Mahindrakar A, Angara R, Sankurathri C, Mootha VV. A novel H395R mutation in MKKS/BBS6 causes retinitis pigmentosa and polydactyly without other findings of Bardet-Biedl or McKusick-Kaufman syndrome. Mol Vis. 2016;22:73–81. PubMed PMID: 26900326.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Kos S, Roth K, Korinth D, Zeilinger G, Eich G. Hydrometrocolpos, postaxial polydactyly, and hypothalamic hamartoma in a patient with confirmed Pallister-Hall syndrome: a clinical overlap with McKusick-Kaufman syndrome. Pediatr Radiol. 2008;38:902–6. PubMed PMID: 18478223.

Mallmann MR, Reutter H, Mack-Detlefsen B, Gottschalk I, Geipel A, Berg C, Boemers TM, Gembruch U. Prenatal diagnosis of hydro(metro)colpos: a series of 20 cases. Fetal Diagn Ther. 2019;45:62–8. PubMed PMID: 29478043.

Manara E, Paolacci S, D'Esposito F, Abeshi A, Ziccardi L, Falsini B, Colombo L, Iarossi G, Pilotta A, Boccone L, Guerri G, Monica M, Marta B, Maltese PE, Buzzonetti L, Rossetti L, Bertelli M. Mutation profile of BBS genes in patients with Bardet-Biedl syndrome: an Italian study. Ital J Pediatr. 2019;45:72. PubMed PMID: 31196119.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Ruiz-Perez VL, Ide SE, Strom TM, Lorenz B, Wilson D, Woods K, King L, Francomano C, Freisinger P, Spranger S, Marino B, Dallapiccola B, Wright M, Meitinger T, Polymeropoulos MH, Goodship J. Mutations in a new gene in Ellis-van Creveld syndrome and Weyers acrodental dysostosis. Nat Genet. 2000;24:283–6. PubMed PMID: 10700184.

Ruiz-Perez VL, Tompson SW, Blair HJ, Espinoza-Valdez C, Lapunzina P, Silva EO, Hamel B, Gibbs JL, Young ID, Wright MJ, Goodship JA. Mutations in two nonhomologous genes in a head-to-head configuration cause Ellis-van Creveld syndrome. Am J Hum Genet. 2003;72:728–32. PubMed PMID: 12571802.

Schaefer E, Durand M, Stoetzel C, Doray B, Viville B, Hellé S, Danse JM, Hamel C, Bitoun P, Goldenberg A, Finck S, Faivre L, Sigaudy S, Holder M, Vincent MC, Marion V, Bonneau D, Verloes A, Nisand I, Mandel JL, Dollfus H. Molecular diagnosis reveals genetic heterogeneity for the overlapping MKKS and BBS phenotypes. Eur J Med Genet. 2011;54:157–60. PubMed PMID: 21044901.

Schinzel A, Riegel M, Baumer A, Superti-Furga A, Moreira LM, Santo LD, Schiper PP, Carvalho JH, Giedion A. Long-term follow-up of four patients with Langer-Giedion syndrome: clinical course and complications. Am J Med Genet A. 2013;161A:2216–25. PubMed PMID: 23913778.

Scott CA, Marsden AN, Rebagliati MR, Zhang Q, Chamling X, Searby CC, Baye LM, Sheffield VC, Slusarski DC. Nuclear/cytoplasmic transport defects in BBS6 underlie congenital heart disease through perturbation of a chromatin remodeling protein. PLoS Genet. 2017;13:e1006936. PubMed PMID: 28753627.

Slavotinek AM, Biesecker LG. Phenotypic overlap of McKusick-Kaufman syndrome with bardet-biedl syndrome: a literature review. Am J Med Genet. 2000;95:208–15. PubMed PMID: 11102925.

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;129A:69–72. PubMed PMID: 15266619.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Stone DL, Agarwala R, Schaffer AA, Weber JL, Vaske D, Oda T, Chandrasekharappa SC, Francomano CA, Biesecker LG. Genetic and physical mapping of the McKusick-Kaufman syndrome. Hum Mol Genet. 1998;7:475–81. PubMed PMID: 9467007.

Stone DL, Slavotinek A, Bouffard GG, Banerjee-Basu S, Baxevanis AD, Barr M, Biesecker LG. Mutation of a gene encoding a putative chaperonin causes McKusick-Kaufman syndrome. Nat Genet. 2000;25:79–82. PubMed PMID: 10802661.

Tekin I, Ok G, Genc A, Tok D. Anaesthetic management in McKusick-Kaufman syndrome. Paediatr Anaesth. 2003;13:167–70. PubMed PMID: 12562491.

Traisrisilp K, Nunthapiwat S, Luewan S, Tongsong T. Fetal hydrometrocolpos with pre-axial mirror polydactyly as a new variant of McKusick-Kaufman syndrome. J Clin Ultrasound. 2021;49:62–5. PubMed PMID: 32537787.

Tsai HF, Wu MH, Cheng YC, Chang CH, Chang FM. Prenatal ultrasonography and postnatal follow-up of a case of McKusick-Kaufman syndrome. Taiwan J Obstet Gynecol. 2014;53:241–4. PubMed PMID: 25017277.

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