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McKusick-Kaufman Syndrome

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Summary

Disease characteristics. McKusick-Kaufman syndrome (MKS) is characterized by the triad 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 and is 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. Cardiac malformations that have been described at least once in individuals with MKS include atrioventricular (AV) communis with a left-sided superior vena cava, atrial septal defect, ventricular septal defect, AV canal, small aorta and hypoplastic left ventricle, tetralogy of Fallot, and patent ductus arteriosus.

Diagnosis/testing. Diagnosis of MKS is based on clinical findings. The diagnosis of MKS in a female with HMC and PAP cannot be made until at least age five years and requires absence of features of Bardet-Biedl syndrome (BBS). *MKKS* is the only gene currently known to be associated with MKS. Molecular genetic testing of the *MKKS* gene is available on a research basis only.

Management. Treatment of MKS includes surgical repair of the obstruction causing hydrometrocolpos and drainage of the accumulated fluid. Treatment for polydactyly, syndactyly, and congenital heart defects is standard. Routine surveillance for manifestations of BBS includes growth and developmental assessments, ophthalmologic examination, and electroretinogram (ERG).

Genetic counseling. MKS is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Heterozygous (carriers) are asymptomatic. Prenatal testing may be available through laboratories offering custom prenatal testing for families in which the disease-causing mutations have been identified in an affected family member. Although HMC, PAP, and CHD can be detected by prenatal ultrasound examination, the reliability of prenatal ultrasound scanning is unknown because the degree of PAP in individuals with MKS is variable and HMC may not be apparent until after birth.

Diagnosis

Clinical Diagnosis

Formal clinical diagnostic criteria for McKusick-Kaufman syndrome (MKS) have not been published.

- **The diagnosis of MKS in females** is based on the triad of hydrometrocolpos (HMC), postaxial polydactyly (PAP), and congenital heart disease (CHD) without manifestations of overlapping syndromes such as Bardet-Biedl syndrome (BBS).
- **The diagnosis of MKS is males** is based on genital malformations (most commonly hypospadias, cryptorchidism, and chordee), PAP, and CHD.

Hydrometrocolpos (HMC) in infants is dilatation of the vagina and uterus caused by 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
- Imperforate hymen; however, in the child with this finding reported by El-Messidi & Fleming (2006), it was too early to know if the actual diagnosis is 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), inferior vena caval obstruction, 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) (i.e., the presence of an extra digit or digits between the thumb and fifth finger). Mesoaxial polydactyly is less common than postaxial polydactyly.

Congenital heart disease (CHD). Cardiac malformations that have been described at least once in individuals with MKS are atrioventricular (AV) communis with a left-sided superior vena cava, atrial septal defect, ventricular septal defect, AV canal, small aorta and hypoplastic left ventricle, tetralogy of Fallot, and patent ductus arteriosus [Slavotinek & Biesecker 2000]. Because of the limited number of individuals with MKS and cardiac malformations, the relative incidences are unknown.

Note: (1) Hydrometrocolpos and PAP in a non-Amish female without evidence of overlapping syndromes (see Differential Diagnosis) are sufficient for a clinical diagnosis of MKS [Stone et al 1998, Slavotinek & Biesecker 2000].
(2) Because HMC and PAP can also be found in female infants with Bardet-Biedl syndrome (BBS), the diagnosis of MKS in a female with HMC and PAP must be delayed until at least age five years and requires absence of features of BBS such as rod-cone dystrophy, developmental delay or mental retardation, and morbid obesity [David et al 1999, Slavotinek & Biesecker 2000].
3) Males with one or more features of the MKS triad should have at least one affected female relative to establish the clinical diagnosis of MKS.

4) Other physical findings in addition to the characteristic phenotypic triad associated with MKS are listed in Table 2. Although these features are nonspecific and have not been used to establish the diagnosis of MKS, the presence of renal anomalies may also prove useful in establishing the diagnosis of MKS.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *MKKS* is the only gene currently known to be associated with McKusick-Kaufman syndrome (MKS).

Other loci. Although genetic heterogeneity has not been demonstrated for the MKS phenotype and linkage to alternative loci or mutations in other Bardet-Biedel syndrome (BBS) genes (see Allelic Disorders) has not been reported [Katsanis et al 2000; Mykytyn et al 2001; Nishimura et al 2001; Mykytyn et al 2002; Ansley et al 2003; Li et al 2004], the possibility of genetic heterogeneity remains.

Molecular genetic testing: Research. Mutations in *MKKS* have been found to date in the following:

- Individuals with MKS within the Amish population, in which all affected individuals are homozygous for the mutations H84Y or A242S [Stone et al 2000]. The frequency of the individual mutations is unknown.

  Note: Both mutations were present in *cis* configuration on one chromosome from an apparently normal, "unrelated" Amish individual.
- One other non-Amish female with HMC and PAP who was an infant at the time of her molecular genetic studies. The phenotype in this child thus remains undetermined.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Direct DNA [1]	*MKKS* mutations	Unknown	Research only

1. Direct DNA methods may include mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with MKS.

Genetically Related (Allelic) Disorders

Bardet-Biedl syndrome (BBS) (see Differential Diagnosis). A substantial and prognostically significant clinical overlap between MKS and BBS has been noted [David et al 1999, Slavotinek & Biesecker 2000]. The close relationship between BBS and MKS has been further complicated by the demonstration of disease-causing sequence alterations in the *MKKS* gene in both MKS and in an estimated 4%-6% of unselected individuals with BBS [Beales et al 2001, Hichri et al 2005, Moore et al 2005]. 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. Of note, rare features associated with *MKKS* mutations and a BBS phenotype (not an MKS phenotype) include phimosis, urethral strictures, posterior urethral valves, and hypoplasia of the labia minora [Moore et al 2005].

Note: Sequencing of the *MKKS* gene in individuals with BBS and phenotypic features found in MKS (such as HMC) does not increase the mutation detection rate in the *MKKS* gene compared to other genes causing BBS [Slavotinek et al 2002].

Nonsyndromic obesity. Although five variants in *MKKS* (p.P39P, p.I178I, p.A242S, p.R517C, p.G532V) were identified in a cohort of 744 Danish men with juvenile-onset obesity, Andersen et al (2005) concluded that it is unlikely that *MKKS* variants play a major role in the pathogenesis of nonsyndromic obesity.

Clinical Description

Natural History

The Amish form of McKusick-Kaufman syndrome (MKS) (HMC and PAP without age-dependent features of BBS) can be considered to be clinically and prognostically distinct from the BBS phenotype. In the Amish population, variable expressivity 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 CHD [Stone et al 1998, Slavotinek & Biesecker 2000]. Of note, many individuals with HMC and PAP diagnosed as having MKS were reported at an age too young to observe the age-dependent features of BBS [David et al 1999, Slavotinek & Biesecker 2000]. The true incidence of physical findings associated with the MKS phenotype is therefore unknown.

Table 2 shows the most common associated features in a series of 49 individuals with the MKS phenotype [Slavotinek & Biesecker 2000]; 75% were diagnosed at birth and 98% by age six months.

Table 2. Phenotypic Features of Individuals with MKS

Finding	Number of Individuals	Percent of Individuals
Genitourinary malformations		
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 and 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%
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

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.

Other findings associated with MKS. Developmental delay was present in 3/37 (14%) of survivors in one study [Slavotinek & Biesecker 2000]. Normal development has also been described at age five years [Gilli et al 1981], six years [Lurie & Wulfsberg 1994], and 14 years [Hamel & ter Haar 1984].

Height ranges from the 25th centile to below the third centile.

Fertility has been described; one 16-year-old girl gave birth to a healthy son [Cohen & Javitt 1998].

Three young women required hysterectomy at puberty for complications of endometriosis [Paredes Esteban et al 1996].

Findings of unknown significance. Findings that may be either part of the MKS phenotype or coincidental occurrences include cleft palate, high palate, small umbilical herniae, seizures and EEG abnormalities, hearing impairment, albinism, bifid manubrium, supernumerary nipple, single palmar crease [Siala-Giagi et al 1996], sacral dimple, talipes [Siala-Giagi et al 1996], distal tracheo-esophageal fistula, esophageal atresia, and somatic asymmetry.

Genotype-Phenotype Correlations

No genotype-phenotype correlation has been reported for mutations in the *MKKS* gene and either the MKS or the BBS phenotype [Moore et al 2005].

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].

The penetrance in the non-Amish population has not yet been determined.

Nomenclature

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

Prevalence

More than 90 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.

In the Amish, one allele with the sequence alterations H84Y and A242S was found in 100 'control chromosomes' from individuals apparently not closely related to individuals with MKS [Stone et al 2000]. This finding implies a carrier frequency of 1%-3% for MKS in the Amish population [Stone et al 2000], or an incidence of approximately 1:10,000.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Disorders in which Hydrometrocolpos (HMC) and Postaxial Polydactyly (PAP) Occur

Bardet-Biedl syndrome (BBS) (see Allelic Disorders) is characterized by rod-cone dystrophy, early childhood onset truncal obesity, postaxial polydactyly, mild cognitive impairment, male hypogonadotrophic hypogonadism, complex female genitourinary malformations, and renal dysfunction, which is a major cause of morbidity and mortality. Night blindness is usually evident by age seven to eight years; the mean age of legal blindness is 15.5 years.

Eleven genes are known to be associated with BBS: *BBS1*, *BBS2*, *ARL6/BBS3*, *BBS4*, *BBS5*, *MKKS/BBS6*, *BBS7*, *TTC8/BBS8*, *B1/BBS9*, *BBS10*, and *TRIM32/BBS11*.

Ellis van Creveld syndrome (EVC) [OMIM 225500]. The cardinal phenotypic features of EVC are chondrodysplasia with acromelic growth retardation, polydactyly, ectodermal dysplasia with dystrophy of the nails, and congenital heart disease, most commonly an atrial septal defect [Ruiz-Perez et al 2000, Al-Khenaizan et al 2001]. Several individuals reported as having MKS based on the findings of HMC and PAP had clinical features consistent with EVC [Arcellana et al 1996, Yapar et al 1996]. The two genes known to be associated with EVC and the allelic disorder Weyers acrodental dysostosis [OMIM 193530] are *EVC* [Ruiz-Perez et al 2000] and *EVC2* [Galdzicka et al 2002, Ruiz-Perez et al 2003]; however, further locus heterogeneity is suggested by the lack of linkage to either the *EVC* loci or the *MKKS* locus in one individual with an EVC phenotype and hydrometrocolpos [Digilio et al 2004].

Other. A 19-year-old woman with lack of müllerian fusion, vaginal agenesis, a unicornuate uterus, postaxial polydactyly, brachydacytly, 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].

Disorders in which PAP Occurs

Mesoaxial polydactyly is less common than postaxial polydactyly in individuals with MKS and is more likely to indicate an underlying genetic syndrome such as MKS, BBS, Ellis-van Creveld syndrome, or Pallister-Hall syndrome.

VACTERL association. VACTERL is an acronym for an association of physical findings that comprises vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula, renal abnormalities, and limb anomalies including hexadactyly [OMIM 192350]. Clinical similarity between MKS and VACTERL association has been noted on the basis of tracheal abnormalities in individuals with HMC.

Pallister-Hall syndrome (PHS) [OMIM 146510]. Overlap of MKS with PHS has been described [el Hammar et al 1998, McCann et al 2006]. Pallister-Hall syndrome 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 PHS can have pituitary insufficiency and may die as neonates from undiagnosed adrenal insufficiency. The diagnosis of Pallister-Hall syndrome is based on clinical findings of hypothalamic hamartoma, central and postaxial polydactyly, bifid epiglottis, imperforate anus and renal abnormalities, and family history. *GLI3* gene is the only gene known to be associated with Pallister-Hall syndrome. Molecular genetic testing of the *GLI3* gene is clinically available. PHS is inherited in an autosomal dominant manner.

Disorders in which HMC Occurs

Interstitial deletion of chromosome 8q21.11-q24.13 was reported in three female children with HMC who had multiple exostoses that appeared after age three years and craniofacial features consistent with trichorhinophalangeal syndrome type 2 (Langer-Giedion syndrome) [Fryns 1997].

No other cytogenetic abnormalities have been associated with HMC, although two chromosome abnormalities have been associated with vaginal agenesis:

- *De novo* translocation [46,XX, t(8;13)(q22.1;q32.1)] in a female with vaginal agenesis and congenital amastia [Amesse et al 1999]
- Chromosome 13 variant with double satellite stalks on the short arm 46,XX,13pstk +) in a female with vaginal agenesis, posterior displacement of the urethra, small uterus, absent cervix, and bilateral absence of the radii, but no polydactyly [Behera et al 2005]

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Pelvic ultrasound examination to detect genitourinary malformations (Table 2)
- Skeletal radiographs to detect osseous polydactyly and syndactyly
- ECG, echocardiogram, and a renal imaging study to detect congenital heart defects
- Renal ultrasound examination and a renal imaging study to detect pelvicalyceal abnormalities, renal hypoplasia, or cystic dysplasia of the kidneys
- Assessment of height, weight, and head circumference and initiation of a carefully maintained growth chart to document obesity that may indicate BBS

- Determination of developmental status by standard screening tools to detect developmental delay that may indicate BBS. If delays are identified, a more detailed assessment of developmental and cognitive abilities is indicated.
- In children with weight greater than the 90th centile and/or short stature and/or developmental delay or mental retardation, ophthalmologic examination and electroretinogram to evaluate for manifestations of BBS

Treatment of Manifestations

Prompt surgical repair of the obstruction causing hydrometrocolpos and drainage of the accumulated fluid can be curative.

Standard treatment is indicated for the following:

- Polydactyly and syndactyly
- Congenital heart defects
- Anal anomalies and Hirschsprung disease (surgical treatment)

Prevention of Secondary Complications

Recurrent urinary tract infections and restenosis of the vaginal orifice are the most common complications in individuals with MKS following surgical drainage of the HMC [Slavotinek & Biesecker 2000].

Care should be taken with anesthesia in the neonatal period if severe hydrometrocolpos causing diaphragmatic compression is present. Gastric decompression and preoxygenation prior to tracheal intubation were used in the anesthetic management of one neonate with severe hydrometrocolpos compressing the diaphragm [Tekin et al 2003].

Surveillance

- In individuals with renal abnormalities, monitoring of blood pressure and renal function, although no individual with MKS has developed renal failure to date [Slavotinek & Biesecker 2000]
- In individuals with interim history of constipation, rectal biopsy to exclude Hirschsprung disease
- Continuing surveillance for manifestations that would establish the diagnosis of Bardet-Biedl syndrome including the following:
  - Serial growth measurements to track height and weight until at least age five years to document obesity that can occur with BBS
  - Developmental assessments until at least age five years to detect developmental disabilities that can occur with BBS
  - Regular ophthalmologic examination and electroretinogram (ERG) (if appropriate) after age five years to evaluate for visual signs and symptoms of retinitis pigmentosa [A Verloes, personal communication]
  - As diabetes mellitus is a rare complication of BBS, measurement of blood glucose as appropriate
  - Investigations for rarer complications of BBS, including hearing assessment, dental assessment, electroencephalogram, and thyroid function tests as appropriate

Therapies Under Investigation

Search ClinicalTrials.gov 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.
- *De novo* mutations in the *MKKS* gene have not been observed.

Sibs of a proband

- At conception, each sib of an affected individual has 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.
  - Sisters of females with MKS should have a careful examination of the external genitalia for vaginal membranes or an imperforate vagina and of the hands and feet for polydactyly, and an echocardiogram for the congenital heart defects associated with MKS.
  - Brothers of affected females should have an examination of the external genitalia for hypospadias, cryptorchidism, and chordee and of the hands and feet for polydactyly, and an echocardiogram for cardiac manifestations of MKS.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with MKS are obligate heterozygotes (carriers) for a disease-causing mutation in the *MKKS* gene.

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

Carrier Detection

Carrier testing using molecular genetic techniques is not offered because it is not clinically available.

Related Genetic Counseling Issues

MKS vs BBS. Genetic counseling should encourage caution regarding premature diagnosis of MKS because of the possibility of complications of BBS appearing at a later age.

Triallelic inheritance. Although triallelic inheritance has not been established for the original Amish MKS pedigree (see Molecular Genetic Pathogenesis; Nakane & Biesecker 2005), several reports describe BBS phenotypes with three mutant alleles with at least one allele involving the *MKKS* locus [Badano et al 2003; Beales et al 2003]. The finding of three mutant alleles has also been associated with a more severe BBS phenotype than in family members with two mutant alleles [Beales et al 2003]. However, triallelic inheritance appears to be less common than autosomal recessive inheritance in BBS and has not clearly been established for the MKS phenotype.

Note: In triallelic inheritance, the phenotype is dependent on the inheritance of two mutant alleles at one locus and another mutant allele at a separate locus.

Family planning. The optimal time for discussion of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. No laboratories offering molecular genetic testing for prenatal diagnosis of MKS are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering custom prenatal testing, see 

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Ultrasound examination. The manifestations of MKS (HMC, PAP, and CHD) can be detected by prenatal ultrasound examination. The reliability of prenatal ultrasound scanning is unknown because the degree of PAP in individuals with MKS is variable and HMC may not be apparent until after birth. Cardiac defects may also not be present. The most accurate period for ultrasound examination is at 16-20 weeks' gestation; the earliest time at which the manifestations of MKS can be detected by ultrasound examination is unknown and the hydrometrocolpos can develop over time.

It is worth noting that two initial prenatal sonograms at ten and 19 weeks' gestation were normal in a female baby who was later found to have an ill-defined lower abdominal mass and bilateral mild hydronephrosis by sonogram in labor at 42 weeks [Khatwa et al 2005]. Ultrasound guided decompression of hydrometrocolpos in a fetus has also been reported [Chen et al 1996].

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see 

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Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of McKusick-Kaufman Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
MKKS	20p12	McKusick-Kaufman/Bardet-Biedl syndromes putative chaperonin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for McKusick-Kaufman Syndrome

236700	MCKUSICK-KAUFMAN SYNDROME; MKKS
604896	MKKS GENE; MKKS

Table C. Genomic Databases for McKusick-Kaufman Syndrome

Gene Symbol	Entrez Gene	HGMD
MKKS	8195 (MIM No. 604896)	MKKS

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

The molecular basis for the differences in phenotype between MKS and BBS remains undetermined. It was first postulated that the differences between the MKS and BBS phenotypes were the result of quantitative or qualitative differences in the protein encoded by *MKKS* [Katsanis et al 2001, Slavotinek & Biesecker 2001]. It is interesting that mice with a targeted mutation to remove exon 3, which contains the start codon of the murine *mkks* gene [Fath et al 2005], have a phenotype that more closely resembles BBS than MKS: the mice develop obesity with high leptin levels and photoreceptor degeneration and have lower levels of social dominance than heterozygotes and wild-type controls. In addition, the males show an absence of flagella in the seminiferous tubules at all ages [Fath et al 2005].

However, it is also plausible that the MKS phenotype could be inherited in an autosomal recessive manner, whereas the BBS phenotype could be inherited in a triallelic manner (i.e., resulting from inheritance of mutations at two separate loci) with the third mutant allele modifying the phenotype to increase clinical severity [Badano et al 2003]. Triallelic inheritance has been demonstrated in families with the BBS phenotype who have affected individuals with three mutations in two different genes associated with BBS [Badano et al 2003; Li et al 2004]. Individuals from the same family with two mutations in a single gene associated with BBS may be clinically unaffected [Badano et al 2003].

Triallelic inheritance has not been demonstrated for the MKS phenotype. In a study on the original Amish family with MKS, in which three affected children were homozygous for both the H84Y and A242S mutations, sequencing of the genes *BBS1, BBS2, BBS3, BBS4, BBS5*, and *BBS7* in the parents failed to identify any mutations in the coding sequence or splice sites [Nakane & Biesecker 2005]. Involvement of the *BBS8* gene in triallelic inheritance for this family was excluded by genotyping [Nakane & Biesecker 2005]. However, this study could not exclude possible triallelic inheritance resulting from a mutation present in a regulatory region or deep within an intron, a microdeletion of a BBS gene not detectable by genotyping, or a mutation in a BBS gene that was not sequenced [Nakane & Biesecker 2005].

Normal allelic variants: The *MKKS* gene has six exons. The start codon of the gene is in exon 3. Two alternatively spliced 5' exons (exon 1A and exon 1B) are not translated [Stone et al 2000]. See Table 3 (pdf).

Pathologic allelic variants: Mutations have been identified in all of the coding exons of the gene; see Table 4 (pdf). No known mutation 'hot spot' exists. A high frequency of 'isolated' sequence alterations is observed in the *MKKS* gene [Beales et al 2001, Katsanis et al 2001]. Possible explanations other than the failure of sequencing strategies to detect cryptic mutations include triallelic inheritance or autosomal recessive inheritance with a modifying locus [Katsanis et al 2001].

Click here for more detailed information on mutations in *MKKS*.

Normal gene product: The protein encoded by *MKKS* is a 570-amino acid protein that has the greatest similarity to the Group II chaperonins (archebacterial chaperonins and eukaryotic T complex-related proteins [Slavotinek & Biesecker 2001]). Chaperonins are members of the chaperone protein family or heat shock proteins and stabilize nonnative or unfolded proteins during heat shock or cellular stress. Group I chaperonins (e.g., GroEL in *E. coli*) are composed of seven identical subunits of 57 kd arranged in two rings stacked back to back. Each subunit has an apical domain, an intermediate domain, and an equatorial domain. The apical domain has hydrophobic residues that bind to nonnative substrate. After binding of the unfolded protein, a co-chaperonin or capping molecule (GroES), and ATP, the chaperonin complex can undergo a conformational change that allows the nonnative protein to be folded in a protected cellular environment [Shtilerman et al 1999].

Note: Another BBS gene, *BBS10*, also encodes a protein related to the group II chaperonins [Stoetzel et al 2006].

Abnormal gene product: In the Amish, H84Y is predicted to affect ATP hydrolysis in the equatorial domain of the protein encoded by *MKKS*, and thus to disrupt protein function. The functional effect of A242S on the protein encoded by *MKKS* is not known.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

No specific resources exist for McKusick-Kaufman Syndrome.

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

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