Title: Mutations in *MKKS,* supplemental to McKusick-Kaufman Syndrome *GeneReview*
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McKusick-Kaufman Syndrome, Molecular Genetics

Mutations in *MKKS*

- ***MKKS*, H84Y.** This mutation was found in homozygous form together with A242S in all affected Amish individuals with MKS. Both mutations were also present in three apparently normal Amish relatives of the affected individuals. This mutation has been predicted to interfere with ATP hydrolysis in the equatorial domain of the protein encoded by *MKKS*, and thus to disrupt protein function. The functional significance of p.A242S is unknown [Stone et al 2000].
- ***MKKS*, A242S.** See *MKKS*, H84Y. This mutation has not been predicted to disrupt protein function. The mutation has been found in one unaffected Newfoundland control [Beales et al 2001] and in heterozygous form in an individual with BBS who also had hypothyroidism [Slavotinek et al 2002] and in affected and unaffected sibs from a Newfoundland kindred later suspected of displaying triallelic inheritance [Katsanis et al 2001].
- ***MKKS*, Y37C.** This mutation has been found in homozygous form in an individual with BBS [Katsanis et al 2001] and also in homozygous form in an individual with BBS who had a third mutation in the *BBS2* gene [Katsanis et al 2001]. The mutation has been identified in compound heterozygous form in a female infant with HMC, PAP, an atrioventricular septal defect, cystic dysplasia of the kidneys, and microtia [Stone et al 2000].
- ***MKKS*, del2111GG.** This 2-bp deletion in exon 5 of the *MKKS* gene was found with a missense mutation in exon 3 in a female infant with HMC, PAP, an atrioventricular septal defect, cystic dysplasia of the kidneys, and microtia [Stone et al 2000] as described in *MKKS*, Y37C.
- ***MKKS*, G52D.** This missense mutation in exon 3 of the *MKKS* gene was identified in a 13-year-old female of Hispanic ethnicity who had severe retinitis pigmentosa (RP), PAP, mental retardation, and obesity (body mass index >40) [Slavotinek et al 2000].
- ***MKKS*, Y264X.** This nonsense mutation in exon 3 of the *MKKS* gene was identified as the second mutation in a 13-year-old female of Hispanic ethnicity with severe RP, PAP, mental retardation, and obesity (see *MKKS*, G52D) [Slavotinek et al 2000].

- ***MKKS*, 280delT.** This mutation has been described in homozygous form in at least two families with BBS from Newfoundland; haplotype analysis showed that the deleted allele was likely to have been transmitted from a common ancestor [Slavotinek et al 2000, Katsanis et al 2001]. Affected individuals in one family had reduced visual acuity, PAP, obesity, and cystic kidneys; a male individual had hypospadias [Slavotinek et al 2000]. Affected individuals in the second family had severe RP, PAP, obesity, lobulated cystic kidneys, and diabetes mellitus [Slavotinek & Biesecker 2001].

  This mutation has also been seen in compound heterozygous form in an individual with BBS from Newfoundland [Katsanis et al 2001]. The other mutation was a missense mutation, L277P [Katsanis et al 2001].

- ***MKKS*, L277P.** This mutation has also been seen in compound heterozygous form with a 280delT (see *MKKS*, 280delT) [Katsanis et al 2001].

- ***MKKS*, 429delCT, 433delAG; also described as MKKS 1316delC, 1324-1326delGTA.** This mutation is a complex deletion that predicts premature termination of the protein encoded by *MKKS* at amino acid 157 [Katsanis et al 2001]. The mutation was identified in two sibs with RP, PAP, obesity, lobulated kidneys with prominent calyces, diabetes mellitus, and mild mental retardation [Slavotinek et al 2000]. In another family member who was deceased, phenotypic features included vaginal atresia and syndactyly [Slavotinek et al 2000]. This mutation has also been described with F94fsX103 in a proband with Laurence-Moon syndrome and clinical findings of retinal dystrophy, spasticity, ataxia, hypogenitalism, mild mental retardation, and no polydactyly [Moore et al 2005].

- ***MKKS*, T57A.** This missense mutation in exon 3 was identified as an isolated sequence alteration in an individual with BBS [Katsanis et al 2001].

- ***MKKS*, Q147X.** This nonsense mutation in the *MKKS* gene was identified with two other nonsense mutations in *BBS2* in an individual with BBS [Katsanis et al 2001].

- ***MKKS*, C499S.** This missense mutation was present with two nonsense mutations in the *BBS2* gene in an individual with BBS [Katsanis et al 2001].

- ***MKKS*, S236P.** This missense mutation was reported in a BBS proband with two mutations in BBS1, Q291X and M390R.

- ***MKKS*, T325P.** This missense substitution has been reported with two *BBS1* mutations, M390R and L548fsX549, in an individual with BBS who had a more severe phenotype (earlier-onset maculopathy and obesity, severe developmental delay and hypotonia) than other family members with only two *BBS1* mutations [Badano et al 2003, Beales et al 2003].

- ***MKKS*, T327P.** This allele was found as a heterozygous alteration in a fetus with a prenatal ultrasound presentation of BBS comprising renal anomalies and postaxial polydactyly [Hichri et al 2005].