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ORIGINAL INVESTIGATION

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Mutation analysis of the *MKKS* gene in McKusick-Kaufman syndrome and selected Bardet-Biedl syndrome patients

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Abstract McKusick-Kaufman syndrome comprises hydrometrocolpos, polydactyly, and congenital heart defects and overlaps with Bardet-Biedl syndrome, comprising retinitis pigmentosa, polydactyly, obesity, mental retardation, and renal and genital anomalies. Bardet-Biedl syndrome is genetically heterogeneous with three cloned genes (*BBS2*, *BBS4*, and *MKKS*) and at least three other known loci (*BBS1*, *BBS3*, and *BBS5*). Both McKusick-Kaufman syndrome and Bardet-Biedl syndrome are inherited in an autosomal recessive pattern, and both syndromes are caused by mutations in the *MKKS* gene. However, mutations in *MKKS* are found in only 4%–11% of unselected Bardet-Biedl syndrome patients. We hypothesized that an analysis of patients with atypical Bardet-Biedl syndrome and McKusick-Kaufman syndrome (Group I; 15 probands) and patients with Bardet-Biedl syndrome who had linkage results inconsistent with linkage to the other loci (Group II; 12 probands) could increase the *MKKS* mutation yield. Both mutant alleles were identified in only two families in Group II. Single (heterozygous) sequence variations were found in three Group I families and in two Group II families. Combining these results with previously published data showed that only one mutant allele was detected in nearly half of all patients screened to date, suggesting that unusual mutational mechanisms or patterns of inheritance may be involved. However, sequencing of the *BBS2* gene in these patients did not provide any evidence of digenic or "triallelic" inheritance. The frequency of detected mutations in *MKKS* in Group II patients was 24%, i.e., six times higher than the published rate for unselected BBS patients, suggesting that small-scale linkage analyses may be useful in suitable families.

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Introduction

McKusick-Kaufman syndrome (MKS) is a rare syndrome inherited in an autosomal recessive pattern with a phenotypic triad comprising hydrometrocolpos (HMC), post-axial polydactyly (PAP), and congenital cardiac disease (McKusick et al. 1964; Kaufman et al. 1972; Lurie and Wulfsberg 1994; Slavotinek and Biesecker 2000). Bardet-Biedl syndrome (BBS) is a genetically heterogeneous disorder inherited in an autosomal recessive pattern characterized by retinitis pigmentosa (RP), PAP, truncal obesity,

Table 1 Phenotypic features of Group I and Group II patients (*M* McKusick-Kaufman syndrome, *B* Bardet-Biedl syndrome, *U* unknown diagnosis, *RP* retinitis pigmentosa, *PAP* postaxial polydactyly, *Insert. PD* insertional polydactyly, *Dev* developmental, *HMC* hydrometrocolpos, *VA/TM* vaginal agenesis/transverse membrane of vagina, *UGS* urogenital sinus, *NIDDM* non-insulin dependent diabetes mellitus, + yes, – no)

Feature	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Sex	F	F	F	F	F	M	M	F	F	F	F	F	F	F	F	M	M	M	M	F	M	M	F	F	F	F	F
Age <5 years	–	–	+	–	+	–	–	+	+	+	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
Family history	+	+	–	+	+	+	+	+	–	+	–	–	+	–	–	+	+	+	+	+	–	+	+	+	+	+	–
Consanguinity	+	+	–	+	+	–	+	+	+	+	–	–	–	–	–	+	–	+	–	+	–	–	–	–	–	–	–
Diagnosis	M	M	U	U	U	B	B	U	U	B	U	B	U	U	B	B	B	B	B	B	B	B	B	B	B	B	B
Ocular findings																											
RP	–	–	–	–	–	+	+	–	–	–	–	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Myopia	–	–	–	+	–	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
Digital anomalies																											
PAP hands	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	–	–	+	+	+	+	+	+	–	+	+	+
PAP feet	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	–	–	+	+	–	+	–
Insert. PD	–	–	–	+	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–
Brachydactyly	–	–	–	–	–	+	+	–	–	–	–	–	–	–	+	+	+	+	+	+	+	–	+	+	+	+	–
Syndactyly	–	–	+	+	–	+	–	–	+	+	–	–	+	–	+	+	–	–	–	–	–	–	–	+	–	+	–
Weight																											
<90th centile	–	–	–	–	–	+	–	–	–	–	+	+	–	–	+	+	+	–	+	+	+	+	+	+	+	–	–
Neurologic																											
Dev. delay	–	–	–	–	–	+	–	–	–	–	+	+	–	–	+	+	+	+	+	+	+	+		+	–	–	+
Seizures	–	–	–	–	–	–	–	–	+	–	+	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
Genitalia																											
HMC	+	+	+	+	+	–	–	+	+	–	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
VA/TM	–	–	–	–	–	–	–	–	+	–	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
UGS	–	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Absent uterus	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Micropenis	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	+	+	–	+	–	+	+	–	–	–	–	–
Renal anomalies																											
Hydronephrosis	–	–	–	–	+	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	+	+	–	–
Renal cysts	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Renal failure	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Small kidneys	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–
Other																											
Hypothyroidism	–	–	–	–	–	–	+	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
NIDDM	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–
Hirschsprung disease	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

mental retardation, genital hypoplasia, and renal anomalies (Green et al. 1989; Schachat and Maumenee 1982; Beales et al. 1999). Hydrometrocolpos and congenital heart defects can also occur in BBS (Green et al. 1989; Beales et al. 1999), and there is significant clinical overlap between MKS and BBS.

There are at least six known loci for BBS. BBS1–5 were discovered through linkage analysis (Kwitek-Black et al. 1993; Leppert et al. 1994; Sheffield et al. 1994; Carmi et al. 1995; Woods et al. 1999), and the genes for BBS2 (Nishimura et al. 2001) and BBS4 (Mykytyn et al. 2001) have been cloned. For BBS6, the causative *MKKS* gene was identified following positional cloning of the *MKKS* gene in Amish MKS patients (Stone et al. 1998, 2000; Katsanis et al. 2000; Slavotinek et al. 2000). The *MKKS* gene is mutated in 4%–11% of unselected BBS patients (Beales et al. 2001). In patients with either MKS or BBS with HMC, abnormalities of the female genital tract have been associated with cardiac malformations, imperforate anus, Hirschsprung disease, and osseous syndactyly (data not shown). We hypothesized that the frequency of *MKKS* mutations could be increased by sequencing patients with these phenotypic features and by sequencing patients in whom linkage studies had failed to identify linkage to the other known BBS loci.

Materials and methods

Gene mutation nomenclature used in this article follows the recommendations of den Dunnen and Antonarakis (2001). Gene symbols used in this article follow the recommendations of the HUGO Gene Nomenclature Committee (Povey et al. 2001).

Human subjects use was approved by the Institutional Review Board at the National Institutes of Health in Bethesda and collaborating institutions. Samples were received as genomic DNA or as whole blood, and DNA was isolated from peripheral blood lymphocytes according to established techniques. Mutation detection for the *MKKS* gene was performed by direct sequencing of polymerase chain reaction (PCR) products as previously described (Stone et al. 2000). In patients in whom mutations did not alter a restriction enzyme site, sequence alterations were verified by cloning amplified PCR products by using standard techniques (TOPOII Cloning kit, Invitrogen). Control samples were taken from the parents of children with sporadic multiple congenital malformations (Rosenberg et al. 2000). For *BBS2* mutation detection, sequencing was performed as described by Nishimura et al. (2001).

The clinical features of the patients in both groups are summarized in Table 1. In the first patient group (MKS and atypical BBS; patients 1–15), there were two adult MKS patients with HMC and PAP without RP, obesity, or developmental delay (patients 1 and 2). Four patients also had MKS but were too young to exclude later development of BBS features (patients 3, 5; Arena et al. 1999; and patients 13 and 14). Four patients had BBS and HMC (patients 4, 9; Cantani et al. 1991; and patients 11 and 12), one patient was a female with HMC who had an affected sib who had BBS (patient 8), and one patient was a member of a family in which affected females have had BBS and HMC (patient 10; Kumar et al. 1998). One patient had BBS and Hirschsprung disease (patient 6), and another had BBS and hypothyroidism (patient 7; Capellini and Barba 1991). One patient had BBS with a bifid epiglottis (patient 15). There were 12 probands (patients 16–27) from BBS families in whom previous linkage studies had failed to identify linkage to BBS1–BBS5 loci (Group II patients, also summarized in Table 1). Linkage to BBS6 at chromosome 20p12 had not been studied in these patients. We used the published diagnostic criteria for BBS in all cases (Beales et al. 1999).

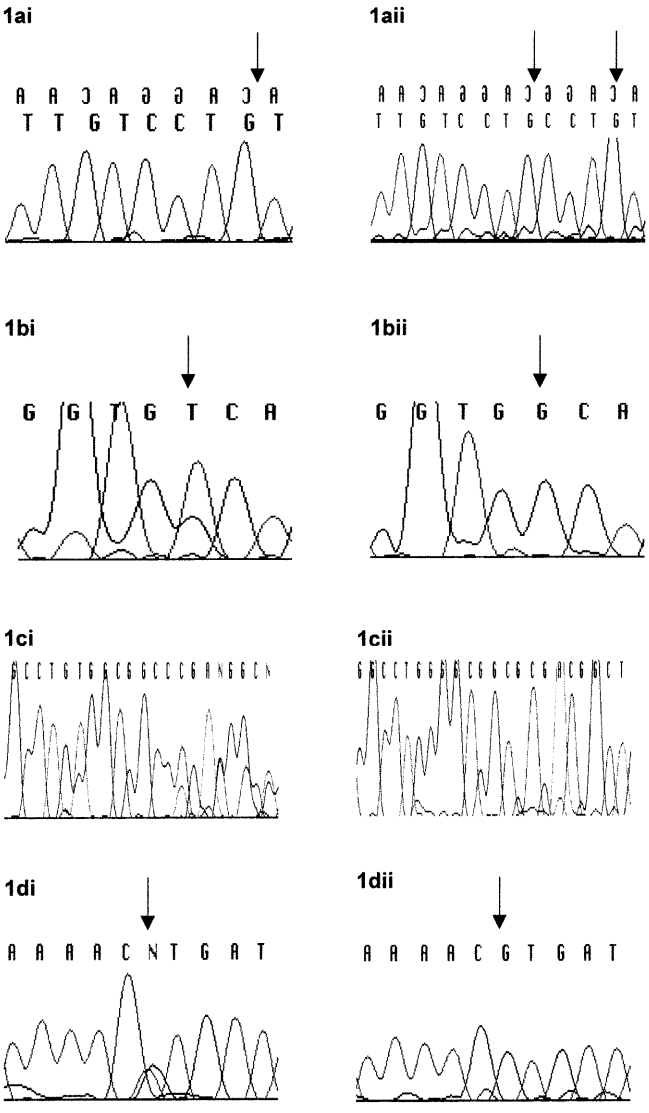

Fig. 1 **a** *Left* (*i*) Chromatograph of exon 3 from patient 6, *arrows* site of the 4-bp insertion (c.876_877insCCTG). *Right* (*ii*) Chromatograph of wild type sequence. **b** *Left* (*i*) Chromatograph of exon 3 from patient 7, *arrow* c.724G→T transversion resulting in p.A242S. *Right* (*ii*) Chromatograph of wild type sequence. **c** *Left* (*i*) Chromatograph of exon 1A from patient 11, *arrow* site of the 10-bp insertion (c.-674_675insGTGGCGGCCT). *Right* (*ii*) Chromatograph of wild type sequence. **d** *Left* (*i*) Chromatograph of exon 3 from patient 14, arrow site of the c.-74G→A transition, resulting in an in frame start sequence. *Right* (*ii*) Chromatograph of wild type sequence

Results

Among the 15 probands in Group I, we detected one mutant allele in two patients, a 5' non-coding polymorphism and a de novo in frame start codon of uncertain significance (Fig. 1). Patient 6 was heterozygous for a 4-bp insertion in exon 3 (c.876_877insCCTG), predicting a

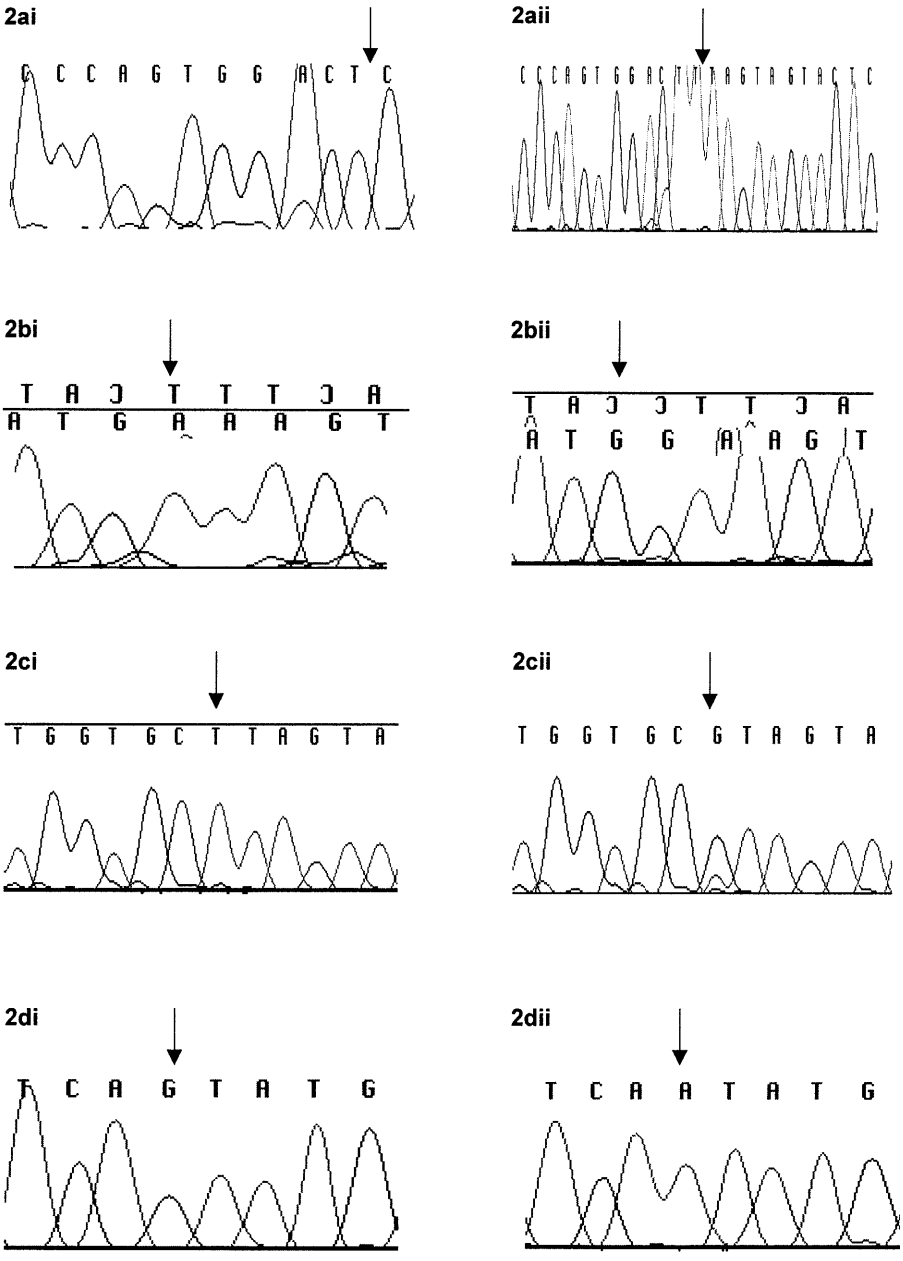

Fig. 2 **a** *Left* (*i*) Chromatography of exon 3 from patient 18, *arrows* site of the 11-bp deletion (c.431_441del TTAGTAGTACT). *Right* (*ii*) Chromatograph of wild type sequence. **b** *Left* (*i*) Chromatograph of exon 4 from patient 27, *arrow* site of the c.1034G→A transition resulting in p.G345E. *Right* (*ii*) Chromatograph of wild type sequence. **c** *Left* (*i*) Chromatograph of exon 3 from patient 19, arrow site of the c.463G→T transversion resulting in p.R155L. *Right* (*ii*) Chromatograph of wild type sequence. **d** *Left* (*i*) Chromatograph of exon 4 from patient 25, *arrow* site of the c.1015A→G transition resulting in p.I339 V. *Right* (*ii*) Chromatograph of wild type sequence

frameshift at amino acid 292 and a premature stop codon at amino acid 327. The insertion was present in the father but not the mother of the proband and was not found by sequencing 100 ethnically matched control chromosomes. In patient 7, a previously described *MKKS* sequence alteration, viz., c.724G>T (p.242A>S), was found in heterozygous form. A second sequence alteration was not detected in either patient. This alteration was reported in homozygous form in *cis* with p.H84Y in the Amish population (Stone et al. 2000) and identified in a heterozygous form in an unselected BBS patient (Beales et al. 2001). The p.A242S sequence variation may therefore be causally related to the BBS phenotype. We conclude that these are pathologic mutations.

There were also a number of sequence differences that were judged not to be pathologic or were not conclusive. Patient 11 had a 10-bp insertion in the 5' untranslated region (UTR; exon 1A). This sequence alteration was also present in patients 20, 21, and 24. Sequencing of ethnically matched controls showed this alteration in 2.25% of control chromosomes, establishing it as a polymorphism. Patient 14 had a c.-74G→A alteration resulting in a premature in-frame start codon in exon 3. The new start site was in a good Kozak consensus sequence (data not shown). The alteration was not found in 94 control chromosomes of Caucasian ethnicity. This proband was of Haitian ethnicity, and control chromosomes from this population were not available. The present data did not allow us to determine whether this alteration was benign or pathogenic.

Among the patients in Group II, we found two patients who had mutations on both chromosomes and two patients

who had a sequence alteration on only one chromosome (Fig. 2). Patient 18 was homozygous for c.431_441delTTAGTAGTACT in exon 3. This deletion predicts a frameshift at amino acid 144 and a premature stop codon at amino acid 152. It was not found in 110 Caucasian control chromosomes. Both parents were heterozygous for the same mutation (data not shown). Patient 27 was homozygous for c.1034G→A in exon 4, predicting p.G345E. This mutation was also present in homozygous form in one affected and one unaffected sib and in heterozygous form in both parents (data not shown). The alteration was not found in 102 Caucasian control chromosomes. In patient 19, a c.463G→T transversion was found. This predicts the amino acid substitution p.R155L. This mutation was present in the mother of the patient and absent in 108 ethnically matched control chromosomes (data not shown). A second mutation was not identified in this patient. In patient 25, a missense alteration c.1015G→A predicting p.I339 V was identified. This mutation was not accompanied by any other coding sequence alterations and was not found in an affected sibling or two unaffected siblings (data not shown). DNA from the parents was not available. This sequence alteration was not present in 100 ethnically matched control chromosomes.

Both groups of patients were sequenced for alterations in the *BBS2* gene, and no pathogenic mutations were identified (data not shown). However, several individuals had p.I123 V in homozygous (patient 24) or heterozygous (patients 11, 14, 20; data not shown) form, a sequence alteration that has been considered to be a polymorphism (data not shown).

Discussion

Among these 27 families, we identified both mutant alleles in two out of 27 patients (7%), consistent with previous estimates of the *MKKS* mutation frequency (4%–11%) in unselected BBS patients (Katsanis et al. 2000; Slavotinek et al. 2000; Beales et al. 2001). However, we detected a number of sequence alterations that were found without alterations of a second allele. When these results are combined with previously published studies, there are ten distinct sequence variations that have been described in isolation without the identification of a second mutation in affected persons (Table 2). This high frequency of single alterations is unexpected and suggests that the mechanism of *MKKS* mutations may be unusual or that unusual patterns of inheritance may be important in these phenotypes. We consider that the isolated sequence alterations are significant, as some predict premature protein truncation (for example, c.876_877insCCTG as identified

Table 2 Mutations in *MKKS* ordered according to patient

Phenotype	Mutation	Exon	Reference
MKS	p.H84Y Homozygote	3	Stone et al. 2000
	p.A242S Homozygote	3	
MKS/BBS	p.Y37C	3	Stone et al. 2000
	c.1215_1216delGG	5	
BBS	p.Y37C Homozygote	3	Katsanis et al. 2000
BBS	c.280_281delT	3	Katsanis et al. 2000
	c.429_430delCT;433_434delAG[a]	3	
BBS	c.280_281delT Homozygote	3	Katsanis et al. 2000; Slavotinek et al. 2000
BBS	c.429_430delCT;433_434delAG[a] Homozygote	3	Katsanis et al. 2000; Slavotinek et al. 2000
BBS	c.429_430delCT;433_434delAG[a]	3	Katsanis et al. 2000
	p.L227P	3	
BBS	p.T57A	3	Katsanis et al. 2000
BBS	p.G52D	3	Slavotinek et al. 2000
	p.Y264X	3	
BBS	p.I32 M	3	Beales et al. 2001
	p.S235P	3	
BBS	p.A242S	3	Beales et al. 2001; this paper
BBS	p.Q147X	3	Beales et al. 2001
BBS	p.D285A	3	Beales et al. 2001
BBS	p.R518H	6	Beales et al. 2001
BBS	p.C499S	6	Beales et al. 2001
BBS	p.S511A	6	Beales et al. 2001
BBS	c.431_441delTTAGTAGTACT Homozygote	3	This paper
BBS	c.876_877insCCTG	3	This paper
BBS	p.G345E Homozygote	4	This paper
BBS	p.R155L	3	This paper
BBS	p.I339 V	4	This paper

[a]c.429_430delCT;433_434delAG is the alternative nomenclature for 1316delC,1324_1326delGTA

in patient 6 in this study). We suggest three mechanisms that are not mutually exclusive to explain these results. First, the *MKKS* gene may have a high frequency of cryptic mutations that would not be detected by the methods used in this and other studies. These include mutations in the promoter, enhancer, or distal locus control regions of the gene, intronic mutations, or deletions of an entire allele. Second, *MKKS* may act as a modifier gene in conjunction with other BBS genes. The modifier hypothesis is attractive as the MKKS protein is a putative chaperonin and therefore likely to be involved in the folding and structural modification of other proteins (Slavotinek and Biesecker 2001). Third, BBS and/or MKS may be inherited in some families in a digenic pattern. This hypothesis would be consistent with the small but persistent number of patients who do not map to the known loci and with the non-penetrance that has previously been described in MKS (Stone et al. 2000). Recently, Katsanis et al. (2001) hypothesized that the inheritance of BBS was triallelic following the identification of one BBS family in which two mutations at one BBS locus (BBS2) was insufficient to generate the BBS phenotype. In this family, a single mutation at BBS6 was present in an affected family member in addition to the two other BBS2 mutations, implying that three altered alleles are necessary for the BBS phenotype (Katsanis et al. 2001). We therefore sequenced the *BBS2* gene in our patients. However, no pathogenic alterations were detected, and thus our data do not support or refute digenic inheritance or the "triallelic" hypothesis.

In addition to the high frequency of isolated sequence alterations in the MKS and BBS phenotypes, patients 1 and 2 had HMC and hexadactyly without other features of BBS in the third decade of life. The absence of *MKKS* mutations in these patients suggests either that they have cryptic mutations or that the MKS phenotype is genetically heterogeneous.

We have sequenced the entire coding region and part of the UTR of the *MKKS* gene in 27 patients. Fifteen patients had MKS or atypical BBS and 12 patients were unlinked to any of the other known BBS loci. These results support previous work by showing that *MKKS* mutations are an infrequent cause of BBS and that, at present, phenotypic screening cannot be used to enrich the yield of *MKKS* mutations. A high frequency of single mutations in BBS implies that the *MKKS* gene may act as a modifier, as a digenic locus, or that the gene has a high frequency of mutations outside the coding region. The frequency of detected mutations in *MKKS* in Group II patients was 24%, six times higher than the published rate for unselected BBS patients, suggesting that small-scale linkage analyses may be useful.

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