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Antenatal Presentation of Bardet-Biedl Syndrome May Mimic Meckel Syndrome

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Bardet-Biedl syndrome (BBS) is a multisystemic disorder characterized by postaxial polydactyly, progressive retinal dystrophy, obesity, hypogonadism, renal dysfunction, and learning difficulty. Other manifestations include diabetes mellitus, heart disease, hepatic fibrosis, and neurological features. The condition is genetically heterogeneous, and eight genes (*BBS1–BBS8*) have been identified to date. A mutation of the *BBS1* gene on chromosome 11q13 is observed in 30%–40% of BBS cases. In addition, a complex triallelic inheritance has been established in this disorder—that is, in some families, three mutations at two *BBS* loci are necessary for the disease to be expressed. The clinical features of BBS that can be observed at birth are polydactyly, kidney anomaly, hepatic fibrosis, and genital and heart malformations. Interestingly, polydactyly, cystic kidneys, and liver anomalies (hepatic fibrosis with bile-duct proliferation) are also observed in Meckel syndrome, along with occipital encephalocele. Therefore, we decided to sequence the eight *BBS* genes in a series of 13 antenatal cases presenting with cystic kidneys and polydactyly and/or hepatic fibrosis but no encephalocele. These fetuses were mostly diagnosed as having Meckel or "Meckel-like" syndrome. In six cases, we identified a recessive mutation in a *BBS* gene (three in *BBS2*, two in *BBS4*, and one in *BBS6*). We found a heterozygous *BBS6* mutation in three additional cases. No *BBS1*, *BBS3*, *BBS5*, *BBS7*, or *BBS8* mutations were identified in our series. These results suggest that the antenatal presentation of BBS may mimic Meckel syndrome.

Introduction

Bardet-Biedl syndrome (BBS [MIM 209900]) is a multisystemic genetic disorder characterized by postaxial polydactyly, progressive retinal dystrophy, obesity, hypogonadism, learning difficulty, and renal dysfunction. Other manifestations include diabetes mellitus, neurological impairments (mainly ataxia), heart disease, dental malformations, and hepatic fibrosis. This condition is genetically heterogeneous, and six genes (*BBS1–BBS6*) were identified by genetic linkage studies (Katsanis et al. 2000; Slavotinek et al. 2000; Mykytyn et al. 2001, 2002; Nishimura et al. 2001; Chiang et al. 2004; Fan et al. 2004; Li et al. 2004). Two more genes (*BBS7* [Badano et al. 2003*a*] and *BBS8* [Ansley et al. 2003]) have been identified on the basis of their homology to previously identified *BBS* genes. The major locus, *BBS1*, is on chromosome 11q13. It is responsible for 30%–40% of BBS cases (Beales et al. 2001). In addition to genetic heterogeneity, a complex mode of inheritance called "triallelism" has been established for this disorder, since, at least in some families, three mutations at two *BBS* loci are necessary for the condition to be expressed (Katsanis et al. 2001, 2002).

Because of the late onset of symptoms, the diagnosis of BBS is usually made during childhood. For example, obesity appears around age 2–3 years, and retinal de-

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generation becomes clinically apparent only at age 8 years (Beales et al. 1999). The only features that may be present at birth are polydactyly, kidney anomaly, hepatic fibrosis, and genital or heart malformations. Interestingly, polydactyly and cystic kidneys are two malformations—along with occipital encephalocele—that characterize Meckel syndrome (MKS) (Mecke and Passarge 1971), a fetal-lethal autosomic recessive condition. Liver anomalies (hepatic fibrosis and bile-duct proliferation) are constant in MKS (Salonen 1984). On the basis of this phenotypic overlap between the two syndromes and the absence of major signs of BBS in the perinatal period, we hypothesized that fetuses presenting with cystic kidneys, polydactyly, and/or hepatic fibrosis but without encephalocele could be either misdiagnosed as MKS or referred to as "Meckel-like." Therefore, we decided to sequence the eight known *BBS* genes (*BBS1–BBS8*) in a series of 13 antenatal cases presenting with kidney anomaly, polydactyly, and/or hepatic fibrosis but not encephalocele. We identified a recessive mutation in a *BBS* gene in six cases and observed a heterozygous mutation in *BBS6* in three additional cases (fig. 1). In the present study, we describe the antenatal phenotype of patients with BBS and discuss the overlap with the clinical spectrum of MKS.

Material and Methods

Patients

A total of 13 patients, presenting with the association of kidney anomaly, polydactyly, and/or hepatic fibrosis, diagnosed prenatally, were included in the study. In 11 cases, pregnancy was terminated because of either severe renal dysfunction (oligohydramnios) or brain anomaly (corpus callosum agenesis/hypoplasia or Dandy-Walker malformation [DWM]), in accordance with French legislation. In the two postnatal cases (1 and 13b), the parents declined pregnancy termination, after genetic counseling. Chromosome analyses and clinicopathological examinations were performed in 11 cases after parental consent was obtained. Clinical and histological features are summarized in table 1.

Mutation Screening of BBS *Genes*

Genomic DNA was extracted from frozen fetal tissue in 11 cases and from peripheral blood samples in 2 postnatal cases, by use of standard procedures. Primers were designed using introns flanking the coding exons of the eight *BBS* genes and are available on request. Direct sequencing of both strands was performed using the Big Dye Terminator Cycle Sequencing kit (Applied Biosystems) and was analyzed on an ABI 3100 automated sequencer (Applied Biosystems).

Results

BBS2

Mutations were identified in three fetuses. Case 1 (in family FRA) was a 28-wk-old fetus presenting with enlarged hyperechogenic kidneys and unilateral foot polydactyly. After pregnancy termination, neuropathological study disclosed moderate cerebral ventricular dilatation with neuronal ectopias. Histological study of the kidneys showed preserved corticomedullar differentiation but the presence of multiple medullary cysts (fig. 2*E* and 2*F*). The liver was normal (fig. 2*G* and 2*H*). We identified two heterozygous truncating *BBS2* mutations: a 2-bp deletion in exon 15 (1909–1910delAT), resulting in a frameshift mutation (M637fsX648), which was inherited from the father, and a C→T transversion in exon 6, resulting in a nonsense mutation at codon 234 (R234X) (fig. 1*A*), which was inherited from the mother. In this fetus, a heterozygous 4-bp deletion was also detected in *BBS4* intron 7, potentially removing the lariat branch site. This mutation was inherited from the asymptomatic father. RNA was extracted from a blood sample, but RT-PCR failed to find an abnormal supernumerary transcript. This case is the only one of our series in which three *BBS* mutated alleles have been identified.

Case 2b (in family LER) was a *BBS2* compound heterozygote, 22-wk-old fetus (fig. 1*B*). He carried a paternally inherited nonsense mutation in exon 6 (R216X) and a 2-bp deletion in exon 15 (1808delAT), resulting in a frameshift mutation (Y603fsX612), which he inherited from his mother (fig. 1*B*). The pregnancy was terminated because of the presence, on ultrasound examination, of cystic kidneys associated with unilateral upper-limb and bilateral feet postaxial polydactyly. This case was first diagnosed as MKS, on the basis of kidney macroscopic and histological features showing severe disorganization of the renal parenchymal architecture, involving cortical and medullary layers (fig. 2*U* and 2*V*). However, the liver showed mild portal fibrosis but no bile-duct proliferation (fig. 2*W* and 2*X*). In this family, a previous child (case 2a) had died with hydrops at age 2 d (fig. 1*B*), and no autopsy was performed. She did not have polydactyly or brain anomaly, and the left kidney was slightly larger than normal on ultrasound examination. DNA analysis showed that she was heterozygous for the paternal R216X mutation.

Case 3 (in family KAY) was a 26-wk-old fetus of Turkish consanguineous descent. The pregnancy was terminated because the fetus presented with enlarged cystic kidneys, oligoamnios, and bilateral foot polydactyly. Histological examination of the liver showed mild portal fibrosis with no bile-duct proliferation (fig. 2*O* and 2*P*). The corticomedullary architecture of the enlarged kidneys was severely affected by numerous irregular cysts,

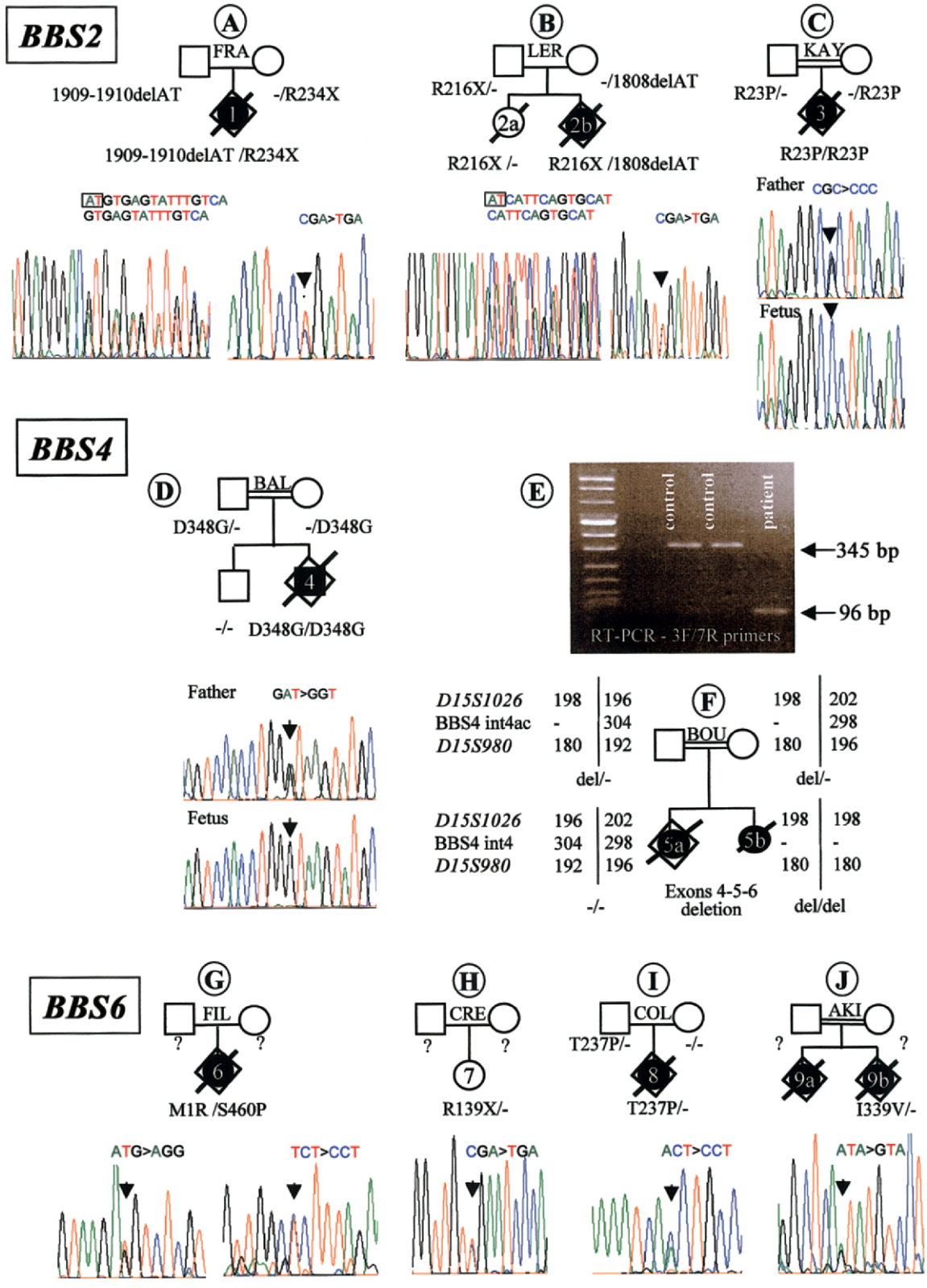

Figure 1 Results of the *BBS2*, *BBS4*, and *BBS6* mutation screening. The pedigrees and mutations are indicated. The black symbols indicate the affected cases. Below each pedigree, sequence chromatographs are shown. In family BOU, the results of the RT-PCR study confirming the deletion of three *BBS4* exons in proband 5b (*E*) and the results of haplotype analysis at the *BBS4* locus (*F*) are shown.

Table 1

Clinical and Pathological Findings Observed in Patients

Trait	Finding in Patient (Family)[a]																
	1 (FRA)	2a (LER)	2b (LER)	3 (KAY)	4 (BAL)	5a (BOU)	5b (BOU)	6 (FIL)	7 (CRE)	8 (COL)	9a (AKI)	9b (AKI)	10 (STA)	11 (AND)	12 (KAL)	13a (MOU)	13b (MOU)
Consanguinity	−	−	−	+	+	+	+	−	−	−	+	+	−	−	+	−	−
National origin	France	France	France	Turkey	Turkey	Tunisia	Tunisia	France	France	France	Turkey	Turkey	France	France	Algeria	France	France
Age[b]	28 wk	2 d	22 wk	26 wk	26 wk	26 wk	12 d	24 wk	12 years	32 wk	32 wk	?	27 wk	37 wk	25 wk	29 wk	18 wk
Brain:																	
Anomaly[c]	−	−	+	−	+	+	?	−	−	−	+	?	−	+	+	+	+
Supratentorial	VD				CCA						CCH, Arh						
Infratentorial	Nect		DWM			ME								DWM	DWM	ME, DWM	OD,DWM
Hand polydactyly	−/−	−/−	+/−	−/−	+/+	−/−	−/−	+/+	+/+	−/−	−/−	−/−	+/+	−/−	+/+	+/+	−/−
Foot polydactyly	+/−	−/−	+/+	+/+	+/+	−/−	+/−	+/+	+/−	+/+	−/−	−/−	+/−	−/−	+/+	−/−	−/−
Kidney anomaly[c]	+	Enlarged[d]	+	+	+	+	+	+	+	Enlarged	+	+	+	+	+	+	+
Pathology	MC	NA	MKL	MKL	MC	MKL	NA	MKS	Failure	Normal	MC	NA	MC	MC	MKL	MC	MC
Portal fibrosis	−	NA	+	+	−	+	NA	−	NA	−	+	NA	−	+	−	−	−
BDP	−	NA	−	−	−	+	NA	−	NA	−	+	NA	−	−	−	−	+/−
Heart defect	−	−	−	−	−	−	+	−	−	−	+	NA	−	−			
Other defects	−	−	+	−	−	+	NA	−	+	+	−	NA	−	−			
Initial diagnosis	BBS	?	MKS	MKL	MKL	MKS	MKS	MKL	BBS	BBS	MKS var	MKS var	BBS	Ago/Gold	MKS	Ago, MKS var	Ago, MKS var
BBS mutation(s)	2 Htz *BBS2* + 1 *BBS4*	1 Htz *BBS2*	2 Htz *BBS2*	1 Hmz *BBS2*	1 Hmz BBS4	None *BBS4*	1 Hmz *BBS4*	2 Htz *BBS6*	1 Htz *BBS6*	1 Htz *BBS6*	None *BBS6*	1 Htz *BBS6*					

[a] + = present; − = absent; ? = unknown; NA = not available; Ago = Agostino syndrome; Arh = arhinencephaly; BDP = bile-duct proliferation; CCA = corpus callosum agenesis; CCH = corpus callosum hypoplasia; Gold = Goldston syndrome; Htz = heterozygous mutation; Hmz = homozygous mutation; ME = meningocele; MC = medullary cysts; MKL = Meckel-like; Nect = neuronal ectopias; OD = occipital defect; var = variant; VD = ventricular dilatation.

[b] Wk indicates weeks of gestation.

[c] Detected on ultrasound examination.

[d] Enlarged left kidney.

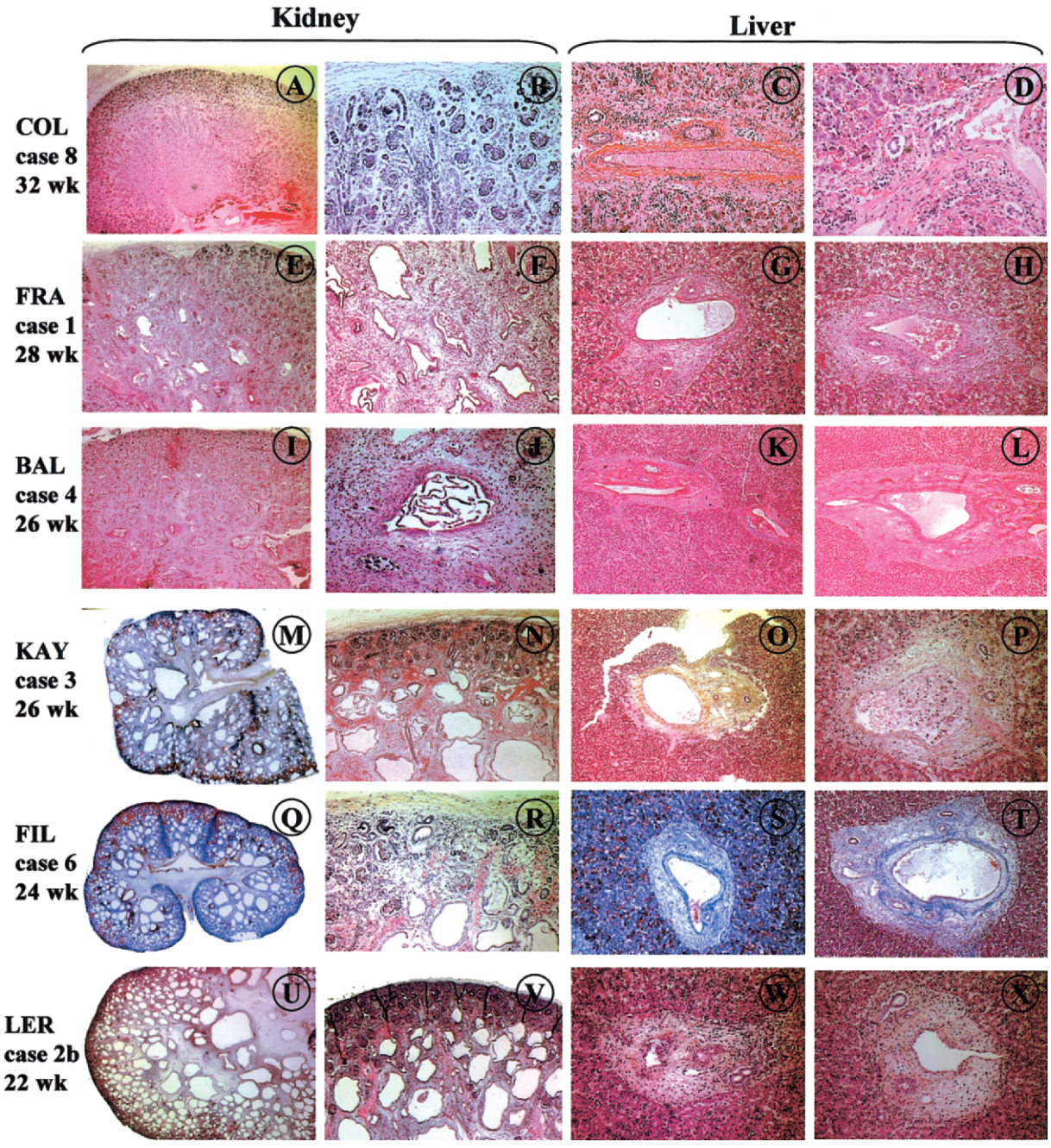

Figure 2 Histological sections (hematoxylin/eosin) of kidneys and livers of fetuses carrying *BBS* mutations. Case 8 shows normal kidney histology. Cases 1 and 4 show medullary cysts, whereas cases 3, 6, and 2b show kidneys "Meckel-like" lesions. The liver shows moderate portal fibrosis in cases 3 and 2b.

lined with a single cell layer. These cysts involved the entire renal parenchyma, with volume enlargement toward the medulla. Only one to two ranges of immature glomeruli were observed in the cortical nephrogenic zone (fig. 2*M* and 2*N*). There were no other visceral malformations, and examination of the CNS was unremarkable. In this case, a homozygous G→C transversion in exon 1 of the *BBS2* gene, leading to the substitution of an arginine with a proline at codon 23 (R23P), was identified. Both parents were heterozygous for this mutation (fig. 1*C*). This missense mutation concerned a conserved amino acid and was not detected in 100 control chromosomes.

BBS4

Mutations were identified in two fetuses. Case 4 (in family BAL) was a 26-wk-old fetus presenting with quadrilateral postaxial polydactyly and bilateral enlarged kidneys with cysts located in the deep cortex and the renal medulla (fig. 2*I* and 2*J*). The liver was normal (fig. 2*K* and 2*L*). Corpus callosum agenesis was observed on ultrasound examination and was confirmed at autopsy. No other malformation was observed. Sequence analysis of *BBS4* revealed a homozygous A→G transition in exon 13, resulting in a missense mutation (D348G) (fig. 1*D*). This mutation was inherited from consanguineous Turkish parents who were heterozygous for this mutation. A healthy brother did not carry this mutation and had inherited both wild-type alleles. This missense mutation involved a conserved amino acid and was not detected in 100 control chromosomes.

Case 5b (the proband in family BOU) was a girl who died at age 12 d. She had unilateral foot polydactyly, cystic kidneys, and endocardial cushion defects. No brain anomaly was apparent. Autopsy was refused. The absence of amplification of *BBS4* exons 4, 5, and 6 led to the suspicion of a homozygous deletion of these exons. The deletion was confirmed by RT-PCR analysis of RNA extracted from lymphoblastoid cells, by use of primers located in exons 3 and 7. The expected wild-type fragment was 345 bp in length, whereas the 96-bp amplification product (fig. 1*E*) observed in proband 5b corresponded to a lack of three exons, as confirmed by sequencing (data not shown). Haplotyping was performed using two flanking markers and one intragenic marker located in intron 4 of the *BBS4* gene. The absence of amplification of the intragenic marker in proband 5b and the hemizygosity observed in the parents are in accordance with both of the consanguineous parents being heterozygous for this deletion (fig. 1*F*). Interestingly, in this family, an earlier fetus (5a) presented with occipital meningocele, cystic kidneys, hepatic portal fibrosis, and bile-duct proliferation, a presentation considered characteristic of MKS. DNA was extracted from paraffin blocks, and haplotyping at the *BBS4* locus showed that sib 5a had a different haplotype from the proband and did not carry the *BBS4* deletion (fig. 1*F*).

BBS6

Mutations were identified in four fetuses. Case 6 (in family FIL) was a 24-wk-old fetus. The pregnancy was terminated after detection, on ultrasound examination, of enlarged and cystic kidneys, anamnios, and quadrilateral postaxial hexadactyly. Autopsy confirmed the absence of other malformations. Microscopic examination of the liver was normal (fig. 2*S* and 2*T*), but the kidneys showed histopathological changes reminiscent of MKS, with both cortical and medullar cystic formations. These cysts were larger in the medulla than in the cortex and were lined with a thin cuboidal epithelium. A thin cortical glomerular layer was present (fig. 2*Q* and 2*R*). Sequencing of the *BBS* genes revealed that this fetus was a *BBS6* compound heterozygote—the first missense mutation resulted in the substitution of the methionine initiator codon with an arginine (M1R), and the second change was a missense mutation in exon 6, resulting in the substitution of a serine with a proline at codon 460 (S460P) (fig. 1*G*). Unfortunately, DNA of the parents was not available to establish the inheritance of these mutations.

Case 7 (in family CRE) was a 12-year-old girl presenting with BBS. Enlarged kidneys, bilateral hand polydactyly, and left-foot polydactyly were detected antenatally. After a genetic-counseling discussion about the risk of MKS, the parents declined pregnancy termination. After birth, the size of the kidneys decreased to normal, whereas progressive renal failure appeared. Obesity started at age 3 years, and an electroretinogram examination established the diagnosis of BBS. At age 12 years, vision was normal. We found one heterozygous *BBS6* C→G transversion in exon 3 of the *BBS6* gene, resulting in a nonsense mutation (R139X) (fig. 1*H*). No other *BBS* mutations were identified in this patient.

In case 8 (in family COL), pregnancy was terminated at 32 wk of gestation because of enlarged kidneys and bilateral foot polydactyly detected on ultrasound examination. Autopsy and histological examination showed no other malformations. The CNS, liver, and kidneys were unremarkable (fig. 2*A*–2*D*). The diagnosis of BBS was suggested. We identified one heterozygous missense mutation in exon 3 of *BBS6,* resulting in the substitution of a threonine with a proline at codon 237 (T237P). This mutation was inherited from the father (fig. 1*I*) and was not observed in >100 control chromosomes. We failed to find any other change in the coding sequence of *BBS6* or the other *BBS* genes in this fetus.

In family 9 (AKI), a fetus (case 9a) presented with cystic kidneys and heart defect. Corpus callosum hypoplasia was detected on ultrasound examination, and

the parents elected to terminate the pregnancy at 32 wk of gestation. Brain examination showed absence of olfactory bulbs. Microscopical examination of the liver showed portal fibrosis and focal bile-duct proliferation and dilatation in some large portal areas. In the kidneys, medullary microcysts were noted. During the pregnancy that followed (proband 9b), abnormal kidneys were detected on ultrasound examination, and the pregnancy was terminated. The parents declined autopsy but agreed to molecular analysis of a blood sample. A heterozygous *BBS6* A→G transition was identified, resulting in the substitution of an isoleucine with a valine at codon 339 (I339V) (fig. 1*J*). This change was not observed in 100 control chromosomes and involved a conserved amino acid. No other *BBS6* coding-sequence mutations could be found in the fetus. Paraffin blocks were obtained from sib 9a, and DNA was extracted for molecular analysis, but we failed to find the same mutation.

No mutation was identified in the coding sequences of the *BBS1, BBS3, BBS5, BBS7,* and *BBS8* genes. Polymorphic changes observed in the *BBS* genes are summarized in table 2.

Table 2

Polymorphisms and Variants Observed in *BBS* Genes

Gene and Nucleotide Variation	Protein Change
BBS1:	
G379A	L126L
IVS6+55 C→T	
C684T	L228L
IVS8−8 G→C	
C1413T	L471L
IVS17+7 G→A	
BBS2:	
A367G	I123V
IVS5−54 G→C	
IVS6−34 C→T	
A1413C	V471V
BBS3:	
IVS4−18 T→C	
IVS5−49 A→G	
IVS8+75 A→G	
IVS8+80 A→G	
IVS8+82–86 del5	
BBS4:	
IVS1−17 C→T	
IVS1−38 C→A	
IVS2+19 G→T	
IVS2−6 A→G	
A137G	K46R
A180G	Q60Q
IVS6+7 C→T	
IVS7+23 G→C	
IVS10−17 G→C	
C1061T	T354I
BBS5:	
IVS1−40 G→C	
BBS6:	
C117T	P39P
C534T	I178I
IVS3+17 A→C	
IVS3+34 C→G	
G1595T	G532V
C1549T	R517C
BBS7:	
−133 C→G	
IVS3−45 C→T	
IVS9+32 A→G	
IVS9+32–34del4	
IVS14+24 C→A	
IVS17+16 G→A	
IVS17−12 C→A	
BBS8:	
IVS3+18 A→G	
IVS3+48 T→C	
IVS6+67 A→G	
IVS14−12 C→G	

Discussion

We sequenced the eight known *BBS* genes in 13 patients presenting prenatally with a kidney anomaly associated with polydactyly and/or hepatic fibrosis but with no encephalocele. Most of these cases were considered to be MKS or "Meckel-like" syndromes, on the basis of the presence of a CNS anomaly (cases 2b, 4, 9, 11, 12, and 13), kidney histology (cases 3 and 6), or MKS in the same family (case 5). We identified recessive mutations in *BBS* genes in six cases—*BBS2* in cases 1, 2b, and 3; *BBS4* in cases 4 and 5b; and *BBS6* in case 6—and identified a *BBS6* heterozygous mutation in cases 7, 8, and 9b. Since mutations in one of the eight known *BBS* genes are found in only 40% of BBS cases (Katsanis 2004), the diagnosis of BBS is not excluded in the remaining cases of our series.

Two mutations identified in our series have been reported elsewhere in patients with BBS. As in case 9b, the I339V *BBS6* mutation was reported in the heterozygous state in a patient with BBS in whom no other *BBS* gene mutations were identified (Slavotinek et al. 2002). Although this change may be a rare variant, neither Slavotinek et al. (2002) nor we found it in 100 controls, and it is not listed as a polymorphism in human SNP databases (see dbSNP and Ensembl Web sites). The R216X *BBS2* mutation identified in case 2b was reported in a BBS case carrying, in addition, a *BBS2* frameshift mutation and a *BBS6* missense mutation (Katsanis et al. 2001). This case presented a typical BBS phenotype with renal involvement.

No mutation in the *BBS1* gene, the major gene responsible for 30%–40% of postnatal BBS cases, was identified in our series. However, a single M390R mutation with a founder effect from Northern Europe accounts for 80% of cases with *BBS1* mutations (Beales et al. 2003; Mykytyn et al. 2003), and none of our cases was of North European extraction. In agreement with previous studies, a high rate of heterozygous *BBS6* mu-

Table 3

Syndromes Associated with or Occasionally Reported with Polydactyly, Cystic Kidney Dysplasia, and/or Brain Anomalies

		Clinical Findings[a]									
				Brain							
Syndrome	MIM	PD	CKD	DWM/VA	CCA/CCH	Other	Liver	Heart	Genital	Cleft	Other
MKS	249000	+	+	DWM	+	Occipital encephalocele	HF+BDP	+	+	+	Pancreas cysts
BBS	209900	+	+	DWM		Normal	HF+BDP	+	+		Obesity, diabetes, retinal dysplasia
Pallister-Hall	146510	+	+	−	+	Hamartoma		+		+	Imperforate anus, short limbs
Joubert	213300	+	+	DWM/VA		Occipital meningocele	HF				Coloboma,[b] retinal dystrophy, abnormal eye movements, tachypnea
Jeune	208500	+	+	−	−	−	HF+BDP				Short stature and ribs, retinal degeneration, pancreas
SLO	270400	+	+	DWM	−	Hydrocephaly, heterotopia		+	+	+	IUGR, microcephaly
CVA[c]	213010	+	+	VA	−	Occipital encephalocele	HF+BDP				Coloboma
OFDI	311200	+	+	−	+	Hamartoma, hydrocephaly, porencephaly				+	Syn-clino-brachy-dactyly, tongue anomalies, alopecia
Simpson-Golabi	312870	+	+	VA	+	Hydrocephaly		+	+	+	Pancreas and somatic overgrowth, macrocephaly, macroglossia
Miller-Diecker	247200	+	+	−	+	Lissencephaly, microcephaly		+		+	IUGR
DWM	220200	−	−	DWM			−				−
DWM with PD	220220	+	−	DWM							−
Goldston (1963)[d]		−	+	DWM			−				−
Goldston	267010	−	+	DWM			+				Pancreas
Scalp defects and PD	181250	+	+/−	DWM		Occiptial defect					Autosomic dominant
Mohr/OFDII	252100	+	+/−	DWM		Cerebellar defect				+	Lingual malformation, supernumerary sutures in skull, hearing loss, tachypnea
EVC	225500	+	+/−	DWM		Normal		+			Short limbs, ribs, nails, teeth
CDG	212065	−	+	DWM		Cerebellar defect	+				−
3C	220210	−		DWM				+		+	Coloboma
COACH	216360	−	+	VA		Occipital encephalocele					Coloboma, congenital ataxia
Hydrolethalus	236680	+	−	DWM	+	Hydrocephaly	−	+		+	−

[a] + = present; +/− = occasionally present; − = absent; PD = polydactyly; CKD = cystic kidney dysplasia; VA = vermis agenesis; CCA/CCH = corpus callosum agenesis or hypoplasia; HF = hepatic fibrosis; BDP = bile-duct proliferation.

[b] See MIM 243910.

[c] Cerebellar vermis aplasia with associated features suggesting SLO and MKS.

[d] See Goldston et al. (1963). Also reported by D'Agostino et al. (1963).

tations was observed (cases 7, 8, and 9b), and we failed to find any other *BBS* gene mutations in the three cases with a heterozygous *BBS6* mutation. These alleles might correspond to a "third allele," and further molecular analysis will be necessary to establish whether these cases carry a recessive mutation at another as-yet-unidentified *BBS* gene. In case 1, two *BBS2* mutations were identified, and, in addition, a 4-bp deletion was identified in *BBS4* intron 7, potentially located in the lariat branch site. As mentioned above, this is the only case in our series in which three *BBS* mutations were identified.

In the present study, polydactyly and cystic kidneys were the only features observed in seven fetuses on prenatal ultrasound examination (cases 1, 3, 5b, 6, 7, 8, and 10). In one of them (case 3), mild liver portal fibrosis without bile-duct proliferation was found on histological examination. A *BBS* mutation was identified in 6/7 of these cases. In two of them (cases 3 and 6), the kidney histopathological changes were reminiscent of MKS, and, interestingly, the occurrence of such severe cystic kidneys in a sib with BBS has been reported elsewhere (Gershoni-Baruch et al. 1992). The association of polydactyly and cystic kidneys is not reported as a single entity in OMIM but is observed in numerous syndromes, such as BBS, MKS, and Pallister-Hall syndrome (table 3). In addition, these features have been reported in patients with Joubert, Jeune, Smith-Lemli-Opitz, oro-facio-digital I (OFDI), and Simpson-Golabi syndromes. However, in all these syndromes, other clinical features can be detected antenatally. Cassart et al. (2004) already suggested that BBS was a possible diagnosis for cases in which polydactyly and enlarged kidneys were observed antenatally. We demonstrate that 6/7 of cases presenting this association, with or without liver portal fibrosis but with no other findings, are cases of BBS. In the absence of polydactyly, other congenital hepatorenal fibrocystic syndromes can be discussed (Johnson et al. 2003).

To our knowledge, corpus callosum agenesis has never been reported in patients with BBS. In the present study, a homozygous *BBS4* mutation was found in one patient (case 4) with corpus callosum agenesis associated with polydactyly and cystic kidneys. These data suggest that corpus callosum agenesis might be associated with the antenatal presentation of BBS. Interestingly, hypoplasia of the corpus callosum was also present in patient 9a, in addition to cystic kidneys and a heart defect. Portal fibrosis and focal bile-duct proliferation and dilatation in some large portal areas were noted on histological examination. The pregnancy that followed (case 9b) was terminated for cystic kidneys, and the fetus was found to carry a heterozygous I339V *BBS6* mutation, previously identified in a patient with BBS (Slavotinek et al. 2002). However, analysis of DNA from paraffin blocks of fetus 9a failed to find the same *BBS6* mutation. Either this change is a rare variant or this "third" *BBS* mutated allele not shared by the sibs—who may still share another homozygous *BBS* gene mutation—acts as a modifier and modulates the phenotype, as reported elsewhere in some families with BBS and a third mutation present in the more severely affected sib but not the other (Badano et al. 2003*b*).

The association of DWM with either polydactyly (Hart et al. 1972; Tal et al. 1980) or cystic kidney dysplasia (D'Agostino et al. 1963; Goldston et al. 1963) has been reported. In addition, DWM, cystic kidneys, and hepatic fibrosis have been documented in several cases (Kudo et al. 1985; Gloeb et al. 1989; Pierquin et al. 1989; Hunter et al. 1991; Walpole et al. 1991; Gulcan et al. 2001) and have been recorded as Goldston syndrome. Despite the lack of bile-duct proliferation, Goldston syndrome has been suggested to be a variant of MKS (Walpole et al. 1991; Gulcan et al. 2001). Furthermore, the association of DWM, cystic kidneys, and hepatic fibrosis with polydactyly (as observed in case 2b) has been reported several times; most authors considered these patients as having MKS (Summers and Donnenfeld 1995; Cincinnati et al. 2000), suggesting that DWM belongs to the spectrum of MKS brain malformations. By other authors, these cases were classified as "Meckel-like," in the context of the cerebro-reno-digital syndrome (Lurie et al. 1991; Genuardi et al. 1993). In these reports, however, hepatic fibrosis but no bile-duct proliferation was present (Genuardi et al. 1993; Summers and Donnenfeld 1995; Cincinnati et al. 2000). Although a molecular study is necessary to establish whether these patients had BBS, these findings suggest that they did not have MKS. Finally, the present study shows that infratentorial malformations should be added to the spectrum of malformations observed in BBS. Along this line, vermis agenesis and mega cisterna magna have been reported once in BBS (Baskin et al. 2002).

Other syndromes constantly or occasionally associating DWM with cystic kidneys and/or polydactyly—namely, MKS, Goldston, Joubert, hydrolethalus (Morava et al. 1996), Ellis-Van Creveld (EVC), SLO, congenital disorder of glycosylation (CDG), OFDII, and scalp defects with polydactyly—are summarized in table 3. In all these syndromes (except Joubert and CDG), other clinical signs, such as intrauterine growth retardation (IUGR) (in SLO), short ribs (in EVC), and tongue anomalies (in OFDII), are observed antenatally. In the present report, three cases presented with this association, but no *BBS* mutation was detected. Although other *BBS* genes could be mutated, some cases could also correspond to prenatal cases of Joubert syndrome.

Several patients with Goldston syndrome, MKS, or Joubert syndrome have been reported to have both

DWM and an occipital meningocele (Miranda et al. 1972; Malpuech et al. 1979; Walpole et al. 1991; Moerman et al. 1993; Piantanida et al. 1993; Al-Gazali et al. 1996; Yapar et al. 1996). This raised the possibility of a common mechanism for both malformations, even though discordant sibs with either encephalocele or DWM have been reported (Blankenberg et al. 1987; Moerman et al. 1993). In most cases, however, the so-called DWM was diagnosed on the basis of brain-imaging criteria alone, and one can postulate that the occipital meningo encephalocele may interfere with brainstem and cerebellum development, leading to an infratentorial dysplasia mimicking DWM. Only a neuropathological examination could help distinguish these two entities.

In view of the results of the present study, the question of whether MKS and BBS are allelic disorders arose. First, MKS is a genetically heterogeneous condition. Three loci have been mapped on 17q23 (*MKS1* [Paavola et al. 1995]), 11q14 (*MKS2* [Roume et al. 1998]), and 8q24 (*MKS3* [Morgan et al. 2002]), but no gene has been identified yet. One locus is common to both MKS and BBS, since both *BBS1* and *MKS2* map on chromosome 11q13-q14. Although the *BBS1* gene is located almost 10 cM centromeric to the *MKS2* locus, we sequenced the *BBS1* gene in 17 MKS cases, including the familial cases linked to 11q13 (Roume et al. 1998), and identified a heterozygous *BBS1* mutation in two cases: the recurrent M390R mutation and a new G559D mutation. No other *BBS* gene mutation could be identified in these two cases. These results may suggest genetic interactions between BBS and MKS. However, although renal histological features in some cases are very similar to those observed in MKS (fig. 2*M,* 2*N,* and 2*Q*), the typical liver ductal plate anomaly, considered a constant in MKS, was absent from cases in the present study. Finally, other malformations frequently found in MKS, such as cleft lip/palate and pancreatic and epidydymal cysts, are not observed in patients with BBS (Fraser and Lytwyn 1981). These observations argue against the hypothesis that the two disorders are allelic. Also, in the family in which a homozygous *BBS4* deletion was found in one sib presenting with severe BBS (case 5b), the sib born earlier (case 5a) with an MKS phenotype did not carry this deletion. Therefore, it is likely that, in this consanguineous family, two different recessive disorders—both characterized by the association of polydactyly and cystic kidneys—were segregating. Indeed, both BBS and MKS are frequently found in consanguineous populations (Teebi 1994; Zlotogora 1997). Here, also, one can hypothesize that an as-yet-unidentified MKS allele may be shared between sibs and may add to the severity of the BBS phenotype in case 5b. Interestingly, family 5 illustrates how the clinical spectrum of a genetic disorder might be extended wrongly when two different disorders segregate in consanguineous families.

In conclusion, our study shows that the association of DWM, cystic kidneys, and hepatic fibrosis without bile-duct proliferation, reported as Goldston syndrome or as "Meckel-like," belongs to the clinical spectrum of BBS. Although BBS and MKS kidney histopathological findings may be similar, the present study suggests that, although genetic interaction may exist between BBS and MKS genes, the two disorders are not caused by the same gene mutations. This hypothesis can be definitively established when MKS genes are identified. The recent demonstration of the role of BBS proteins in ciliary function and the clinical overlap between BBS and MKS will hopefully open the way to discovery of the MKS disease-causing genes.

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Electronic-Database Information

The URLs for data presented herein are as follows:

dbSNP, http://www.ncbi.nlm.nih.gov/SNP/
Ensembl, http://www.ensembl.org/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

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