Bardet-Biedl syndrome (BBS) is a genetically heterogeneous disorder characterised by the primary features of obesity, retinal dystrophy, polydactyly, renal malformations, mental retardation, and hypogonadism. Patients with BBS also have an increased risk for developing diabetes mellitus, hypertension, and congenital heart disease. Seven loci have been mapped with evidence of at least one additional locus: 11q13 (BBS1), 16q21 (BBS2), 3p13 p12 (BBS3), 1p22.3q23 (MKKS), 2p12 (BBS5), 20p12 (BBS6), and 4q27 (BBS7). Five genes have been cloned so far: BBS1, BBS2, BBS4, MKKS, and BBS7. The function of these genes and the disease mechanism remain unclear. Whereas the BBS6 protein has similarity to a bacterial chaperonin, the other BBS proteins have no significant similarity to archebacterial chaperonins or other known proteins.

Before the BBS1 gene had been cloned, a report had suggested that three mutated alleles (two at one locus, and a third at a second locus) may be required for manifestation of BBS, a so called triallelic inheritance. Also, many cases with only one mutant allele suggested an unusual mechanism of inheritance.

In this study, we have analysed whether there is evidence for multi-allelic inheritance in patients with BBS by sequencing the complete coding region and exon-intron boundaries of four cloned BBS genes (BBS1, BBS2, BBS4, and MKKS) which represent most of the mapped loci. Twenty one unrelated European patients were studied.

* Mutations were identified in the BBS1 gene in five (24%) patients, two novel mutations were found in BBS2 and BBS6 (MKKS), and one mutation in BBS4. Overall, mutations were found in nine (43%) patients suggesting that either a large number of cryptic mutations are present in these genes or a sizeable proportion of genes have yet to be identified.

* Five patients had mutations in BBS1 and each had at least one M390R mutant allele in combination with a second mutation. This confirms that mutations in BBS1 account for most cases of BBS among the mapped loci. No support for the involvement of BBS1 in triallelic inheritance was found.

* The remaining four patients had mutations in BBS2, BBS4, or MKKS. However, in three of these four patients, two mutant alleles were not present in the same gene. Two patients had one mutation in two different BBS genes (BBS2 and BBS4), one patient had only one mutated allele, in MKKS. This strongly supports a digenic diallelic pattern of inheritance in two if not three patients. This phenomenon would also be expected if a three allele hypothesis were correct. These data add to the increasing evidence that BBS has a complex mode of inheritance.
identified in the patient with the D492N mutation. In two patients, mutations occur at highly conserved residues and were not found in 60 controls. Eight out of 21 patients had the I123V polymorphism. In one of these patients, two mutant alleles were not present in the same gene. Two patients had one mutant allele in two genes (BBS2 and BBS4), suggesting a digenic diallelic mode of inheritance. If in one of these cases the K46R (BBS4) mutation is considered a non-disease causing sequence change, then this patient would harbour only one mutant allele in four BBS genes. Another patient was identified with only one mutant allele in MKKS. The detection of only one mutant allele was reported in 10 cases in MKKS. One possibility is that additional mutations were not detected with the methodology used. These mutations would include changes in the promoter region, in introns, or in additional exons. But additional unidentified mutations would not account for the fact that patients were found with two mutations in two different genes associated with BBS. Although these data do not support triallelic inheritance per se, they strongly support multiallelic inheritance. It provides good evidence for digenic diallelic inheritance in BBS. This phenomenon would also be expected if the three allele hypothesis were correct. Particularly, the patient with the two significant mutations R143X (BBS2) and P503L (BBS4) would be a strong indication for diallelic digenic inheritance.

Another interesting finding is the relatively high percentage of patients with no mutations. At least one mutation was found in nine out of 21 patients (43%). The two remaining mapped loci (BBS3 and BBS5) should only account for a very small percentage of cases. Either a large number of cryptic mutations are present in the five known genes or additional unidentified loci are mutated in most cases.

There is increasing evidence that BBS is involved in a complex mode of inheritance. This is confirmed by the results of our study, which support a digenic mode of inheritance. Experiments of gene interactions will be required to understand the exact mechanism of the disease.

**References**


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**Table 1** Mutations found in BBS1, BBS2, BBS4, and MKKS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gene</th>
<th>Exon</th>
<th>Nucleotide change</th>
<th>Predicted effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BBS1</td>
<td>12</td>
<td>1169T&gt;G</td>
<td>M390R</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>BBS1</td>
<td>15</td>
<td>1152T&gt;C</td>
<td>L518F</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>BBS1</td>
<td>10</td>
<td>IVS10+1G&gt;A</td>
<td>Splice site</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>BBS1</td>
<td>9</td>
<td>IVS9+1G&gt;A</td>
<td>Splice site</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>BBS1</td>
<td>3</td>
<td>436C&gt;T</td>
<td>R146X</td>
<td>17</td>
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<tr>
<td>6</td>
<td>BBS1</td>
<td>12</td>
<td>1169T&gt;G</td>
<td>M390R</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>BBS1</td>
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<td>9</td>
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<tr>
<td>8</td>
<td>MKKS</td>
<td>3</td>
<td>541G&gt;C</td>
<td>A181P</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>MKKS</td>
<td>3</td>
<td>541G&gt;C</td>
<td>A181P</td>
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</tbody>
</table>

**Table 2** Evolutionary conservation of BBS genes surrounding mutation sites showing local alignment of amino acid sequence A, BBS2, B, BBS4, C, MKKS (the number indicates the position of the missense mutation)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Exon</th>
<th>Amino Acid</th>
<th>BBS2</th>
<th>HS</th>
<th>MM</th>
<th>DR</th>
<th>B</th>
<th>BBS4</th>
<th>HS</th>
<th>MM</th>
<th>DR</th>
<th>C</th>
<th>MKKS</th>
<th>HS</th>
<th>MM</th>
<th>DR</th>
<th>C</th>
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unaffected family members of three patients were either heterozygous for a mutant allele or had wild type alleles. An affected sister of one patient showed the same mutations as her sib.

In BBS2, two novel mutations were found and in both cases only one mutant allele was identified. The two mutations were R643H and R413X. One of the mutations introduces a stop codon, the other one changes a highly conserved amino acid (table 2) and was not found among 60 controls. The R643H mutation occurred in combination with the sequence change K46R in BBS4. K46R was suggested to be a polymorphism. The other patient was a compound heterozygote for R143X (BBS2) and P503L (BBS4). P503L is a highly conserved residue and was not found in 60 controls. Eight out of 21 patients had the II23V polymorphism. In BBS4, two polymorphisms were found: V284A and T354I. In MKKS two novel mutations were found, a homozygous A181P mutation and a heterozygous D492N mutation. Both mutations occur at highly conserved residues and were not present among 60 controls. No second mutation was identified in the patient with the D492N mutation. In two patients, two polymorphisms (R517C and G532V) were found in MKKS.


Further support for digenic inheritance in Bardet-Biedl syndrome

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