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Delineation of the Critical Interval of Bardet-Biedl Syndrome 1 (*BBS1*) to a Small Region of 11q13, through Linkage and Haplotype Analysis of 91 Pedigrees

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Summary

Bardet-Biedl syndrome (BBS) is a genetically heterogeneous recessive disease characterized primarily by atypical retinitis pigmentosa, obesity, polydactyly, hypogenitalism, and mental retardation. Despite the presence of at least five loci in the human genome, on chromosomes 2q, 3p, 11q, 15q and 16q, as many as 50% of the mutations appear to map to the *BBS1* locus on 11q13. The recessive mode of inheritance and the genetic heterogeneity of the syndrome, as well as the inability to distinguish between different genetic loci by phenotypic analyses, have hindered efforts to delineate the 11q13 region as a first step toward cloning the mutated gene. To circumvent these difficulties, we collected a large number of BBS pedigrees of primarily North American and European origin and performed genetic analysis, using microsatellites from all known BBS genomic regions. Heterogeneity analysis established a 40.5% contribution of the 11q13 locus to BBS, and haplotype construction on 11q-linked pedigrees revealed several informative recombinants, defining the *BBS1* critical interval between *D11S4205* and *D11S913,* a genetic distance of 2.9 cM, equivalent to ~2.6 Mb. Loss of identity by descent in two consanguineous pedigrees was also observed in the region, potentially refining the region to 1.8 Mb between *D11S1883* and *D11S4944.* The identification of multiple recombinants at the same position forms the basis for physical mapping efforts, coupled with mutation analysis of candidate genes, to identify the gene for *BBS1.*

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Introduction

Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder characterized primarily by retinal pigmentary dystrophy, obesity, postaxial polydactyly, hypogenitalism, and mental retardation, as well as by a range of other clinical findings such as renal dysplasia, hepatic fibrosis, diabetes mellitus, hearing loss, developmental delay, and speech impairment. The frequency of BBS varies between populations, from an estimated 1/150,000 in Europe to 1/13,500 in the Middle East (Farag and Teebi 1988; Beales et al. 1997). The nature of the genetic defect and the underlying pathophysiological basis for BBS are unknown. To delineate the cause of this disease, a positional cloning approach has been undertaken to identify the defective gene(s). Five loci have been identified to date: *BBS1* (MIM 209901) on 11q13 (Leppert et al. 1994), *BBS2* (MIM 209900) on 16q21 (Kwitek-Black et al. 1993), *BBS3* (MIM 600151) on 3p12-p13 (Sheffield et al. 1994), *BBS4* (MIM 600374) on 15q22.22-q23 (Carmi et al. 1995*b*), and *BBS5* (MIM 603650) on 2q31 (Young et al. 1998*a*). Data from additional families, with BBS not linked to these loci, suggest the existence of at least one more locus in the human genome (Anderson 1996; Bruford et al. 1997; authors' unpublished data).

The inherent complexity of genetic analysis in recessive disorders, due to the scarcity of large pedigrees, is exacerbated in the case of BBS by the presence of genetic locus heterogeneity. Furthermore, despite efforts to distinguish clinically between the different loci in this variable phenotype, data addressing correlations of specific phenotypic features with distinct *BBS* genes have proved inconclusive. Thus, in the absence of large families or pedigrees from population isolates, genetic analysis of unrelated families remains the only reliable means to differentiate loci to which the phenotype is linked (Carmi et al. 1995*a;* Beales et al. 1997; Bruford et al. 1997; Young et al. 1998*b*).

Previous studies suggest that *BBS1* is the most common locus, accounting for as many as 50% of BBS cases

(Leppert et al. 1994; Beales et al. 1997; Bruford et al. 1997). However, since the first linkage report of *BBS1* to 11q13 (Leppert et al. 1994), little progress has been made in defining the critical region. This is mainly because the locus has been described only in small, nonconsanguineous pedigrees for which confident assignment to *BBS1* is difficult. In contrast, the other BBS loci have been mapped in large consanguineous Bedouin or Canadian pedigrees, and the critical region has been defined by means of shared marker homozygosity in the affected individuals (Kwitek-Black et al. 1993; Sheffield et al. 1994; Carmi et al. 1995*b;* Young et al. 1998*a,* 1998*b*). We have sought to delineate the 11q13 critical interval by linkage and haplotype analysis of 91 pedigrees of primarily North American or European origin, using markers spanning 32 cM on 11q. Genetic data from this large number of individuals have enabled us to identify multiple recombination events and thus to define the *BBS1* critical interval, an important first step in the effort to isolate the *BBS1* gene.

Patients and Methods

A total of 91 families comprising 561 individuals, 168 of whom were affected, were enrolled in this study. With the exception of four pedigrees (AR-062, AR-074, AR-084, and PB-010) that were consanguineous, the remaining pedigrees were nonconsanguineous. One pedigree was from South Africa (AR-287) and one pedigree was from Iran (PB-010); the remaining families were of northern European descent. Individuals diagnosed with BBS were ascertained by R.A.L., P.L.B., or the referring regional physician. Diagnosis of BBS was based on previously established criteria (Leppert et al. 1994). For all kindreds, personal interviews were conducted and family histories were collected and evaluated. With informed consent, all available medical records were obtained and reviewed.

DNA was extracted from venous lymphocytes, as described elsewhere (Lewis et al. 1990). A total of 31 microsatellite markers were subsequently evaluated in each family. For chromosome 11q, microsatellites *D11S905, D11S903, D11S1298, D11S4191, D11S4076, D11S1765, D11S480, D11S4205, D11S1883, PYGM, D11S4944, D11S913, D11S1889, D11S4113, D11S916, D11S1902,* and *D11S901* were tested. Microsatellites used from the other BBS loci were as follows: *BBS5—D2S1353* and *D2S1776; BBS3—D3S1285, D3S1566, D3S1271,* and *D3S1278; BBS4—D15S117, D15S153, D15S131,* and *D15S205;* and *BBS2—D16S411, D16S415, D16S503,* and *D16S515.* Fluorescent markers were either obtained from the ABI linkage mapping set I (Applied Biosystems) or custom synthesized by Genosys Biotechnologies. Primer sequences, expected-size information, and allele frequencies were obtained from either The Genome Database or the Whitehead Institute for Biomedical Research/MIT Center for Genome Research. DNA sample concentration was adjusted to 20 ng/μl, and amplification was performed on a 9600 or 9700 thermal cycler (PE Biosystems). Alleles were resolved on an ABI 377 automated sequencer and were analyzed with the GENESCAN version 2.0 and GENOTYPER version 2.1 software (Applied Biosystems).

Linkage analysis was performed with the MLINK, ILINK, and LINKMAP programs from the FASTLINK version 4.0 software package (Stockton et al. 1998). Genetic locus heterogeneity was assessed by means of the HOMOG program (Ott 1983). A disease-allele frequency of .005 was used, with penetrance set at 95%. Marker alleles were assumed to be of equal frequency, and the number of alleles was estimated either on the basis of information from The Genome Database, if available, or from the number of alleles observed in the study samples.

Physical and genetic mapping data for markers used are expressed in megabases or centimorgans, respectively, depending on the availability of such data. Genetic mapping data were obtained from The Genome Database or from the Généthon website. Physical mapping data and estimated marker distances were obtained from The Genome Database or from the long-range restriction map of the 11q13 region as reported by Kitamura et al. (1997).

Results

Identification of Pedigrees with Likely Linkage to the BBS1 *Locus on 11q13*

To ascertain which pedigrees were likely to carry a *BBS1* mutation, we genotyped all available individuals for six markers (*D11S4076, D11S1765, D11S4205, D11S1883, D11S1889,* and *D11S4113*) surrounding the *PYGM* locus on 11q13 and performed two-point linkage analysis. However, the small size of the majority of the pedigrees precluded statistically significant mapping to (LOD score $\geq$3.0) or exclusion from (LOD score ≤ -2.0) 11q13. We therefore constructed haplotypes for all individuals, thus increasing our ability to eliminate pedigrees not linked to 11q13 by demonstrating the inheritance of either different chromosomal fragments in affected family members or the same chromosomal fragment in both affected and unaffected members of the same kindred. This analysis provided evidence that there is no linkage to 11q13 in 30 of the families with BBS. An additional 21 pedigrees were not informative and were also eliminated from the study. Double-recombinant chromosomes or other inconsistent marker genotype data suggesting either sample contamination or sub-

microscopic chromosomal rearrangements were not seen, except in pedigree AR-013, which was also eliminated from further analysis. On completion of this portion of our study, we had identified 39 kindreds whose genotypes were consistent with mapping to the *BBS1* locus.

Heterogeneity Analysis

To assess the contribution of the *BBS1* locus in BBS, we performed a test of genetic heterogeneity (HOMOG) on 80 of 91 pedigrees. Since linkage to 11q had been reported previously for 11 pedigrees (Beales et al. 1997), those pedigrees were not used in this analysis, to prevent skewing of the data. We found that linkage to chromosome 11 is likely in 40.5% of our pedigrees, with a likelihood ratio of 125.5 ($\chi^2 = 9.66$; $P < 10^{-3}$). This is slightly lower than the 44%–50% figure quoted previously. Nevertheless, it is likely to be a more accurate representation of the mutation distribution in the population tested, since our sample is significantly larger than those in previous reports (Leppert et al. 1994; Beales et al. 1997; Bruford et al. 1997).

Before further evaluation of the 39 pedigrees whose haplotypes were consistent with mapping to *BBS1,* an independent test of genetic heterogeneity was also performed to confirm our initial linkage observations. We found no evidence for genetic heterogeneity, with a likelihood ratio of 1.413×10^6 ($\chi^2 = 28.3$; $P < 10^{-7}$), suggesting linkage to 11q13 in all 39 pedigrees.

Multipoint and Haplotype Analysis

To substantiate these findings and to delineate the critical interval, we genotyped all 39 pedigrees, using an additional 11 microsatellites from 11q13. Twenty-five kindreds showed no recombinations >35 cM around *PYGM,* where the maximum LOD score for *BBS1* has been observed (Leppert et al. 1994; Bruford et al. 1997), and were therefore excluded from further analysis. For the remaining 14 pedigrees, we compiled all the genotype data and performed multipoint analysis across 11q13. Figure 1 shows the plot for the compound multipoint LOD scores generated from two pedigrees, AR-037 and AR-062, which gave the highest LOD scores for 11q13 markers. These data suggest that *BBS1* most likely lies between *D11S4191* and *D11S1889*. However, the only reliable means of defining the critical interval is the identification of historical recombinants in the pedigrees with linkage to 11q. To achieve this, we constructed detailed haplotypes spanning a 32-cM region on 11q13. This enabled us to identify recombinations in 13 pedigrees (fig. 2). A schematic drawing of the positions of the recombinations is shown in figure 3.

To further confirm that BBS in these pedigrees maps to 11q13 and thus to use the observed recombinations

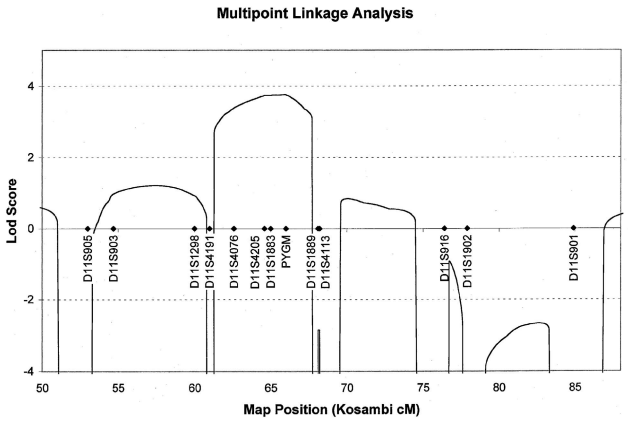

Figure 1 Plot of the compound multipoint LOD scores generated for pedigrees AR-037 and AR-062 by means of a series of microsatellite markers on 11q13.

to define the critical interval, we analyzed the 13 recombinant-containing families for the presence of other *BBS* loci. Because of the limited power of the pedigrees in linkage analysis, we constructed haplotypes across the previously reported critical intervals. The results from these analyses are summarized in table 1. Eight of 14 pedigrees could be excluded from all other *BBS* loci, and, in several cases, exclusion by haplotyping was possible even when a nonsignificant LOD score was obtained. This is particularly relevant when the size of the critical region is large (the critical interval for *BBS5,* for example, spans 6 cM) and the LOD scores become nonsignificant with greater recombination fraction (θ) values, leaving haplotype analysis as the only effective means of exclusion.

Delineation of the BBS1 *Critical Interval*

Haplotype analysis revealed two types of genetic events that defined the critical interval for *BBS1:* informative recombinants and ancestral recombinants, demonstrated through loss of identity by descent (IBD) in two consanguineous pedigrees. As shown in figure 3, several recombinations define the proximal boundary. Six recombinations were seen distal to *D11S1765,* including one in individual AR-062-10. The haplotypes for this pedigree are shown in figure 4*B*. Pedigree AR-062 generates a LOD score of 2.18 with *D11S1889* at $\theta = 0$. Given that the theoretical maximum LOD score for this pedigree is 2.19 and that AR-062 can be excluded from all the other *BBS* loci (table 1), this finding supports linkage to Hsa11 in this pedigree. Consequently, the observed recombination places *BBS1* distal to *D11S1765*.

In five cases, further analysis of the recombinant chromosomes does not decrease the critical interval. The hap-

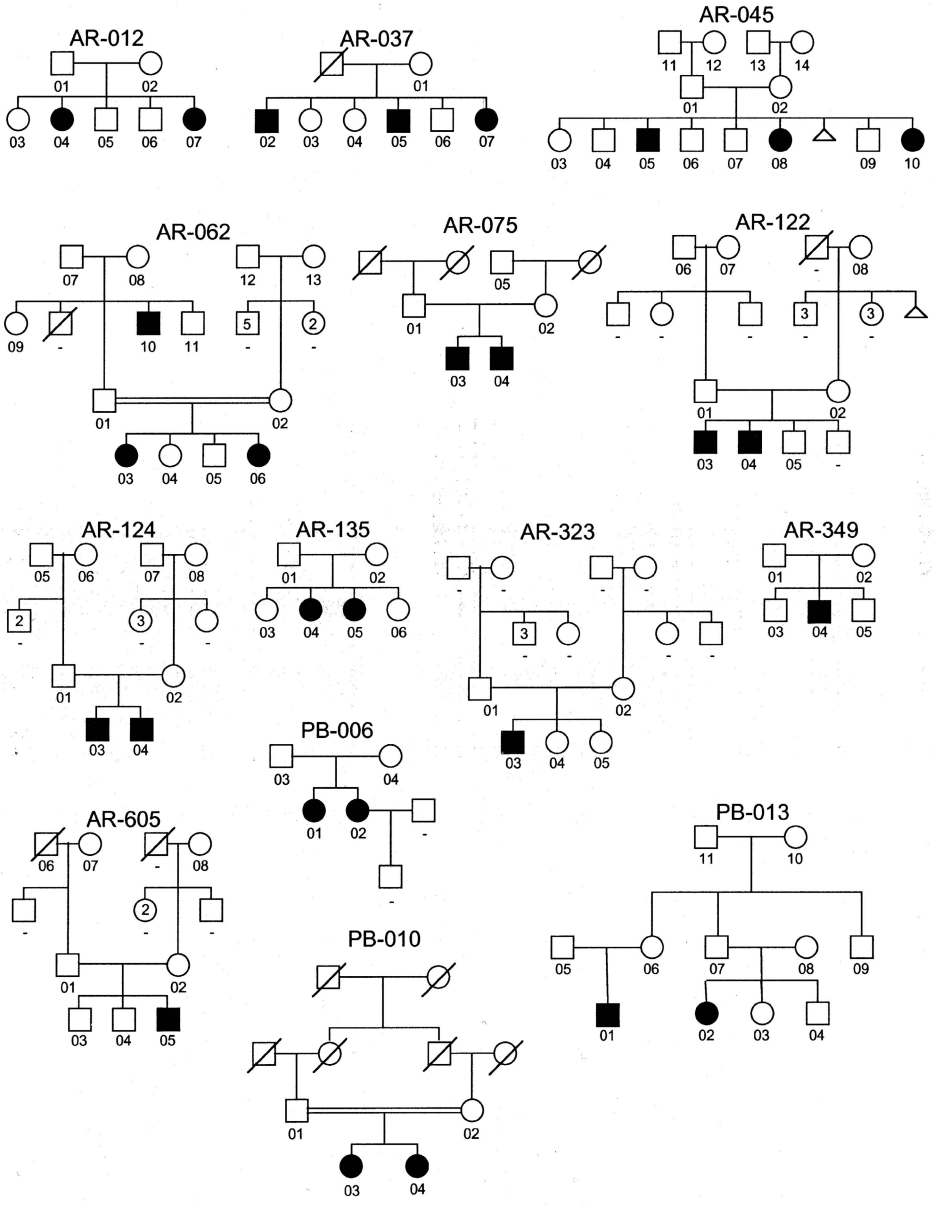

Figure 2 Thirteen 11q13 recombinant pedigrees. The inbred loop in AR-062 is not shown; consanguinity was established through interview, but ancestral records were not retrieved.

lotype of PB-006-02, however, narrows the proximal border to *D11S4205*. PB-006 has been excluded from all other *BBS* loci and generates a LOD score of 0.6 with *D11S1889,* at $\theta = 0$ (the theoretical maximum LOD score for this pedigree is 0.68), consistent with it mapping to 11q13.

The distal boundary is defined by three recombinations proximal to *D11S1889* in pedigrees AR-037, AR-605, and PB-013. The strongest evidence supporting this boundary comes from AR-037 (fig. 4*A*), in which a LOD score of 1.58 was generated with *D11S1883,* at $\theta = 0$, a figure close to the 1.63 theoretical maximum LOD score possible for this pedigree. Furthermore, AR-037 was excluded from having all other known *BBS* loci. Thus, the likelihood that the observed recombination has no bearing on the affection status of individual AR-037-05 is small; the identification of recombinants at that position in three more pedigrees further supports *D11S1889* as the distal boundary.

Haplotype analysis of pedigrees AR-605 and PB-013 further refines this boundary, through two recombinations proximal to *D11S913* (fig. 3). However, since neither of these families can be excluded unequivocally from all other known *BBS* loci (table 1), this boundary

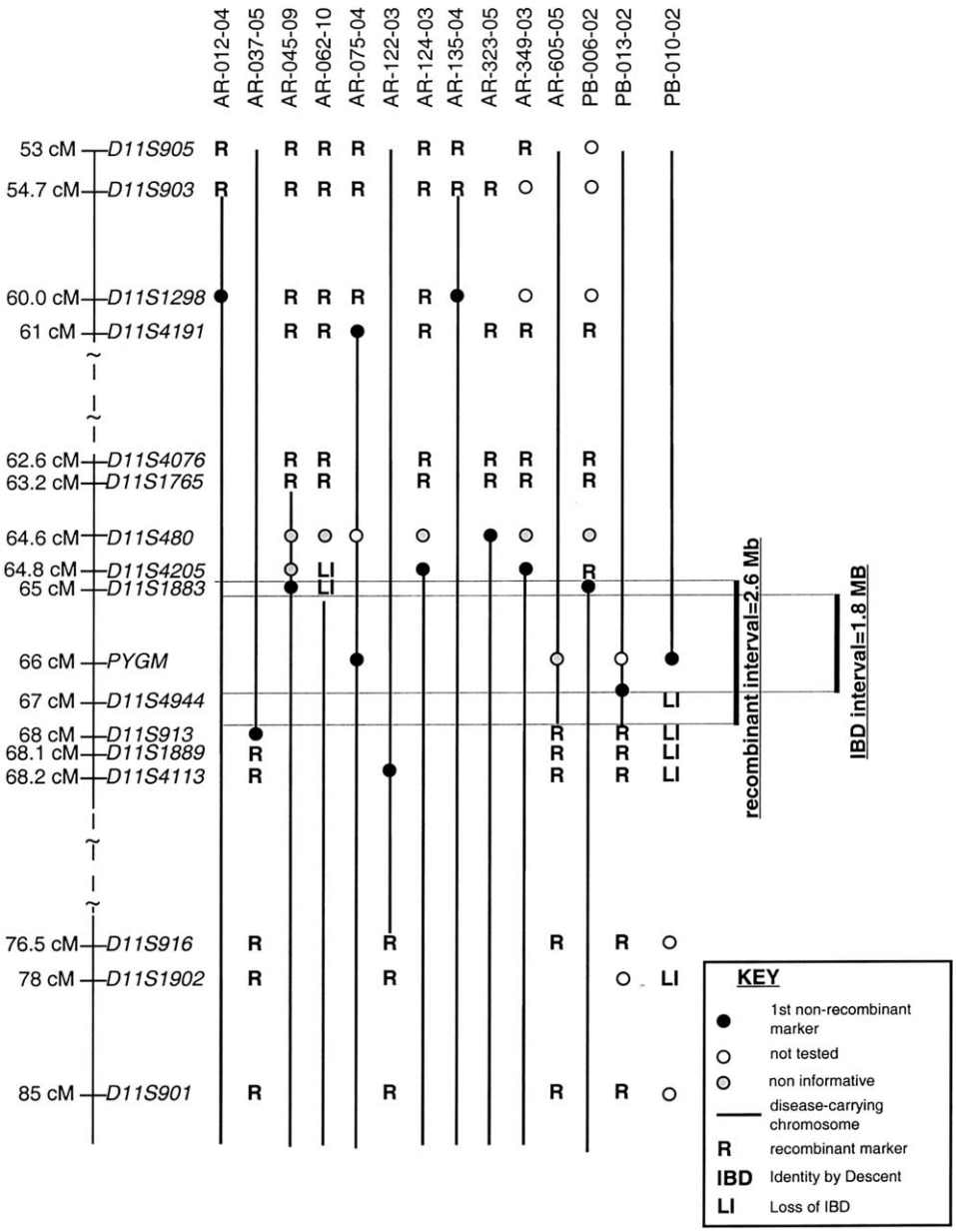

Figure 3 Haplotype analysis of 14 pedigrees, using 15 microsatellites from 11q that span a genetic distance of ~32 cM. The chromosome is illustrated on the left, with markers placed at approximate centimorgan positions as found in the Généthon, Genome Database integrated, and Marshfield genetic maps. Vertical solid black lines represent the portion of the disease chromosome carried by the individuals listed at the top of the figure. All individuals listed are affected, as diagnosed by standard criteria (Leppert et al. 1994), except for AR-045-09, who is unaffected (in this case, the minimal unaffected chromosomal region is illustrated).

is useful to set priorities in the examination of transcripts until additional recombinants can be identified with this marker.

Four of the families in our cohort are consanguineous: the offspring in PB-010 are the result of first-cousin mating. In the case of AR-062, interviews with family members revealed common ancestry between the two branches of the pedigree, although the precise structure of the tree cannot be extended to the common ancestor. As a result, we expect the same ancestral mutation–carrying chromosome to be present in both parents and all markers to be reduced to homozygosity in the vicinity of the *BBS1* gene in the affected siblings. Examination of the haplotypes of pedigrees AR-062 and PB-010 revealed that several markers are heterozygous. Specifically, heterozygosity was observed with *D11S4205* and *D11S1883* in AR-065 and with markers distal to and including *D1S4944* in PB-010 (figs. 3 and

Table 1

Summary of Haplotype Data for All *BBS* Loci in 14 Pedigrees in Which 11q13 Recombinations Were Detected

	Status of Locus[a]				
Pedigree	Hsa2	Hsa3	Hsa15	Hsa16	Hsa11
AR-12	U	X	X	X	Prox
AR-037	X	X	X	X	Dist
AR-045	X	X	X	X	Prox
AR-062	X	X	X	X	Prox
AR-075	X	X	X	X	Prox
AR-122	U	X	U	X	Dist
AR-124	X	U	U	X	Prox
AR-135	X	X	X	X	Prox
AR-323	U	X	X	X	Prox
AR-349	X	X	X	X	Prox
AR-605	U	X	X	X	Dist
PB-006	X	X	X	X	Prox
PB-010	X	X	X	X	Dist
PB-013	X	U	X	X	Dist

[a] X = excluded by haplotyping; U = unable to exclude; Prox = proximal recombinant; and Dist = distal recombinant.

4). From these data we concluded that *BBS1* may lie between *D11S1883* and *D11S4944,* a distance of ~1.8 Mb. However, as with the recombinant critical interval, caution must be exercised until either loss of IBD or recombinants are found at these positions in additional pedigrees. Nevertheless, the facts that the non-IBD markers are located within the recombinant interval and that the regions of IBD extend over contiguous portions of the chromosome provide independent corroborative evidence for the delineation of the *BBS1* critical interval.

Discussion

Despite an original expectation that, because of its relatively uniform clinical presentation, BBS may be caused by a defect at a single locus, it has proved to be a genetically heterogeneous disease with at least six loci in the human genome (Kwitek-Black et al. 1993; Leppert et al. 1994; Sheffield et al. 1994; Carmi et al. 1995*b;* Bruford et al. 1997; Young et al. 1998*a*). We have found the 11q13 locus to account for 40.5% of BBS cases in our population sample, a figure similar to those reported elsewhere (Leppert et al. 1994; Beales et al. 1997; Bruford et al. 1997). Despite this, *BBS1* has remained the most poorly refined locus to date. We have chosen a strategy of large-scale genotyping, followed by linkage and haplotype analysis, to delineate the *BBS1* critical region. On analysis of 91 pedigrees, we identified multiple recombinants that allowed us to delineate the *BBS1* critical region in two ways: a 2.6-Mb interval between *D11S4205* and *D11S913,* determined on the basis of recombination events, and a 1.8-Mb interval between *D11S1883* and *D11S4944,* determined on the basis of loss of IBD in two consanguineous pedigrees. A similar critical interval for *BBS1* has been identified independently on the basis of both historical recombinants and linkage disequilibrium in large Newfoundland families (Young et al. 1999 [in this issue]).

Our strategy relies on the analysis of a large number of small pedigrees and is in sharp contrast to the approaches that have delineated the critical interval in other *BBS* loci. Such studies have typically been based on large consanguineous pedigrees from distinct population isolates (Kwitek-Black et al. 1993; Sheffield et al. 1994; Carmi et al. 1995*b;* Bruford et al. 1997; Young et al. 1998*a*). In rare, recessive, genetically heterogeneous disorders such as BBS, and in the absence of large pedigrees or founder populations, our approach may be the only feasible means to analyze the critical region, since large pedigrees are either scarce or unavailable.

Small pedigree size often renders linkage analysis ineffective, leaving haplotype construction as the only means to evaluate a candidate critical interval. Such a strategy is not error proof, especially where haplotypes are constructed over large regions, in which case rare double recombinants cannot be detected. The only means to ameliorate this is to increase both the number of unrelated families studied and the density of the markers examined. Nevertheless, the limit of resolution of this approach is lower than that for genetically homogeneous disorders, since the inability to independently map a single family to any given locus decreases the usefulness of single, rare recombination events that cannot be confirmed independently in unrelated kindreds.

The data presented here substantially advance the positional cloning effort for the *BBS1* gene. The critical region extends from a maximum of 2.6 Mb to a minimum of 1.8 Mb. Given the high gene density of 11q13, 1.8 Mb remains a significant interval, with as many as 150 transcripts to assess for candidacy (authors' unpublished data). However, a plethora of physical reagents is available because of the *MEN1* and Best macular dystrophy positional cloning efforts. Thus, several megabase-scale BAC/PAC contigs are available (Cooper et al. 1997; Guru et al. 1997; Kitamura et al. 1997), and portions of the critical interval have been or are in the process of being sequenced. Furthermore, the construction of a radiation-hybrid map of the human genome, containing >30,000 expressed sequence tags (ESTs) has identified ⩾100 ESTs overlapping the critical interval, presenting many new candidate genes for analysis (Deloukas et al. 1998).

Overall, our approach illustrates the need for substantial numbers of pedigrees, to refine the genetic interval for rare genetically heterogeneous diseases, even though the power that these pedigrees have for statistically significant linkage may be low. It is difficult to predict where the limit of genetic resolution is reached. We were able to identify a critical interval of 1.8 Mb

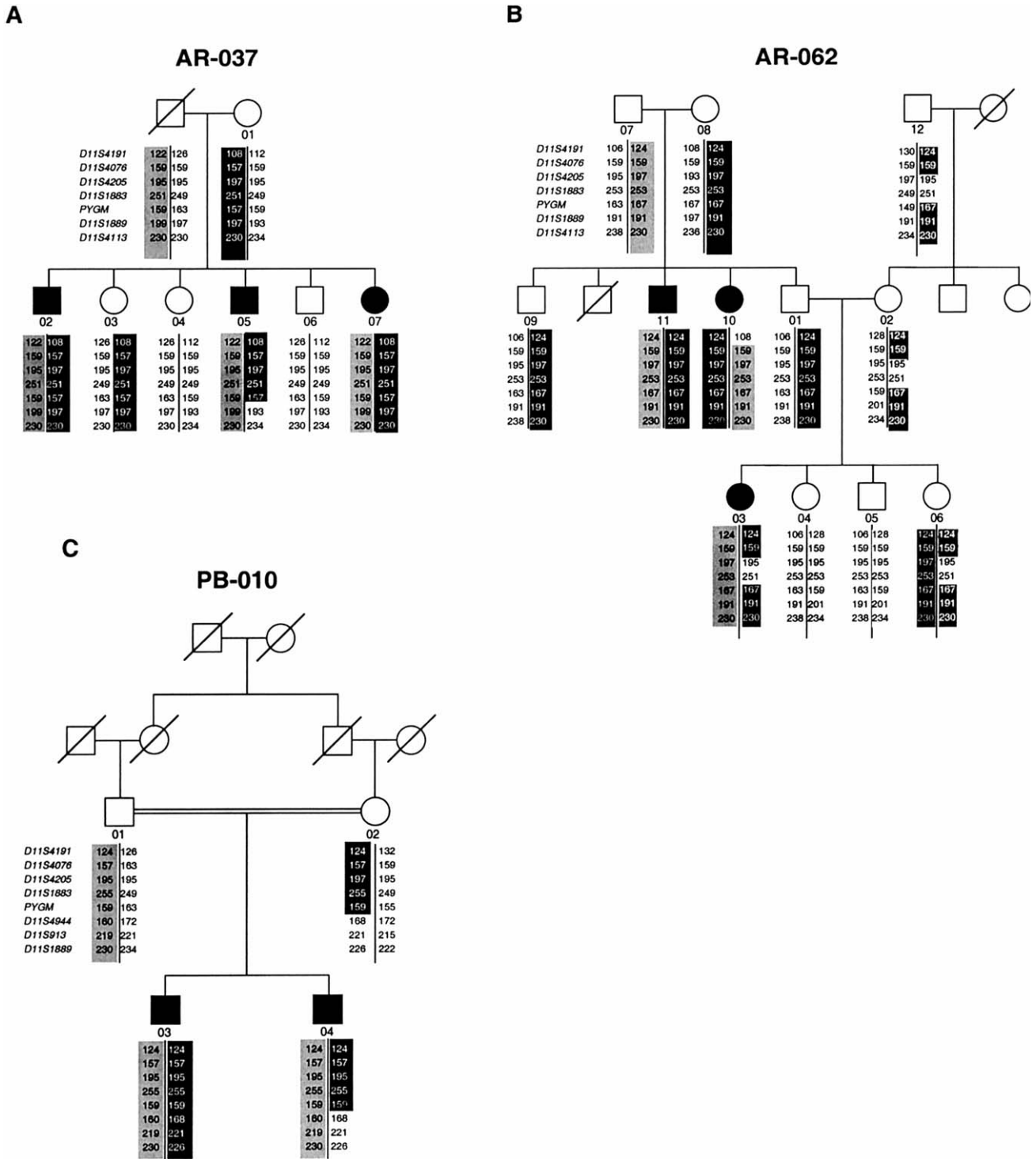

Figure 4 Illustration of the haplotypes for pedigrees AR-037(*A*), AR-062 (*B*), and PB-010 (*C*), showing the inheritance of the disease-carrying chromosome. A subset of 11q13 markers is shown, for simplicity, with the mutation-carrying chromosomes highlighted and traced through the family. These pedigrees contribute to the definition of the distal and proximal critical-region boundaries. Note that, for AR-062-12, -02, -03, and -06, the disease chromosome is interrupted between *D11S4076* and *PYGM* because of ancestral recombinations. Likewise, the ancestral recombination in PB-010 is shown.

through events that occurred in 2 of 91 of our pedigrees. We therefore envisage that, although genotyping of additional pedigrees is essential to confirm our observations, reduction of the critical region to <1.0 Mb may be limited because of the large number of families required for the analysis. Therefore, focusing on the physical analysis of the critical region may prove a more efficient means to identify the defective gene.

Acknowledgments

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

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Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for *BBS1* [MIM 209901], *BBS2* [MIM 209900], *BBS3* [MIM 600151], *BBS4* [MIM 600374] and *BBS5* [MIM 603650])
Whitehead Institute for Biomedical Research/MIT Center for Genome Research, http://www.genome.wi.mit.edu/

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