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A Founder Effect in the Newfoundland Population Reduces the Bardet-Biedl Syndrome I (*BBS1*) Interval to 1 cM

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Summary

Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive disorder; major phenotypic findings include dysmorphic extremities, retinal dystrophy, obesity, male hypogenitalism, and renal anomalies. In the majority of northern European families with BBS, the syndrome is linked to a 26-cM region on chromosome 11q13. However, the finding, so far, of five distinct BBS loci (*BBS1,* 1q; *BBS2,* 16q; *BBS3,* 3p; *BBS4,* 15q; *BBS5,* 2q) has hampered the positional cloning of these genes. We use linkage disequilibrium (LD) mapping in an isolated founder population in Newfoundland to significantly reduce the *BBS1* critical region. Extensive haplotyping in several unrelated BBS families of English descent revealed that the affected members were homozygous for overlapping portions of a rare, disease-associated ancestral haplotype on chromosome 11q13. The LD data suggest that the *BBS1* gene lies in a 1-Mb, sequence-ready region on chromosome 11q13, which should enable its identification.

Introduction

Bardet-Biedl syndrome (BBS; MIM 209900) is a rare, autosomal recessive disorder in which the combination of dysmorphic extremities, retinal dystrophy, obesity, male hypogenitalism, and renal anomalies may be associated, to varying degrees, with mental retardation and/or diabetes mellitus (Green et al. 1989; O'Dea et al. 1996). Of the five genetic subtypes, *BBS1* appears to be the most common locus in affected individuals of northern European descent: as many as 50% of pedigrees show linkage to *BBS1* (Beales et al. 1997; Bruford et al. 1997; Woods et al. 1999). *BBS1* was initially mapped to chromosome 11q13 by combining the positive LOD scores achieved in 17 of 31 North American kindreds as a result of a genome scan (Leppert et al. 1994). The other BBS loci, *BBS2* (16q; Kwitek-Black et al. 1993), *BBS3* (3p; Sheffield et al. 1994), *BBS4* (15q; Carmi et al. 1995) and *BBS5* (2q; Young et al. 1999), were located by homozygosity mapping in extended inbred kindreds. In the original study by Leppert et al. (1994), the putative *BBS1* gene was tightly linked to two loci on chromosome 11q13: the gene for human muscle glycogen phosphorylase (*PYGM*) and the anonymous DNA marker *D11S913* (AFM164zf12), and was localized to a 26-cM interval between *D11S1298* and *INT2* (*FGF3*). A more precise genetic and physical location of *BBS1* is required if the *BBS1* gene is to be positionally cloned.

Refined mapping of disease genes has recently been accomplished by linkage disequilibrium (LD) mapping in founder populations (reviewed by Jorde 1995 and by Xiong and Guo 1997). When a disease mutation is first introduced into a population, it resides on a single disease haplotype (DH) of linked markers. As a result of meiotic recombination, the length of this DH decreases as a function of genetic distance so that, with successive generations, only the original marker alleles in the vicinity of the disease locus cosegregate on disease chromosomes. Although fine mapping of disease genes was established initially in old populations like the Finnish (Hastbacka et al. 1992), recent success in fine mapping has been accomplished in relatively young populations (Labuda et al. 1996; Groenewald et al. 1998). The island population of Newfoundland, considered a genetic isolate because of the nature of its founding and subsequent isolation, is enriched for BBS, with 10 times the incidence in other white populations of northern European ancestry (Green et al. 1989; O'Dea et al. 1996). A single founder effect has been reported in two recent studies of families from the island with either hereditary nonpolyposis colorectal cancer (HNPCC) or multiple endocrine neoplasia type 1 (MEN1) (Olufemi et al. 1998;

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Froggatt et al. 1999). In the present study we show that, in five unrelated families from Newfoundland, the family members affected with BBS are homozygous for an ancestral DH, and we use recent and historical recombinations to the ancestral DH to map the *BBS1* gene within a 1-Mb region on chromosome 11q13.

Subjects and Methods

Subjects

In a recent population survey, 17 BBS families of English ancestry were haplotyped at the *BBS1*, *BBS2, BBS3,* and *BBS4* loci. Of these families, three (B8, B10, and B19) were assigned to *BBS1* and three (B7, B12, and B15) could not be excluded from this locus because they yielded positive LOD scores and haplotypes consistent with linkage to *BBS1* (Woods et al. 1999; table 1). Of these six families, parental consanguinity was documented in family B8 and suspected in families B10, B12, B15, and B19 on the basis of progenitors with the same surname originating from the same community. Extensive genotyping with markers mapping to the *BBS1* critical region was performed in the six families, representing 8 BBS patients and 44 first- and second-degree relatives. Informed consent had been obtained previously, and the clinical presentations of the adult patients have been described elsewhere (Green et al. 1989; O'Dea et al. 1996).

Genotyping

DNA was extracted from the lymphocytes of venous blood by a simple salting-out procedure (Miller et al. 1988). Fifty to 100 ng of template DNA in standard 10-μL reactions containing 1.5 pmol of primer, 200 μm dNTPs, 0.125 units of Tf1 DNA polymerase, and a trace amount of γ[^{32}P] end-labeled forward primer was amplified by temperature cycling in a Perkin Elmer 9600 thermocycler. Products were run on 6%–8% polyacrylamide sequencing gels with formamide (Litt et al. 1993) and were subjected to autoradiography. The markers *D11S1298, D11S956, D11S480, D11S4205, D11S1883, D11S4945, PYGM, D11S4946, D11S4940, D11S4938, D11S449, D11S4941, D11S913,* and *FGF3* were typed in key family members. Family B7 was excluded from the study, because several samples failed to amplify.

Family Studies

Haplotypes were constructed, for each family, to give the minimum number of recombinations. DHs were identified from alleles that were transmitted from both unaffected parents to affected offspring. Pairwise linkage analyses between BBS and six markers spanning the *BBS1* critical region were performed under an autosomal recessive model with a penetrance of 0.95 and a disease-allele frequency of .004. The disease-allele frequency for BBS was calculated from the Newfoundland population estimate of 1/17,500 (Green et al. 1989), adjusted to reflect an estimated 50% contribution of the *BBS1* locus to the overall population frequency. All markers were assumed to have nine alleles of equal frequency in the population. LOD scores were calculated by the MLINK subroutine program of FASTLINK (V3.0P) (Lathrop and Lalouel 1984; Cottingham et al. 1993; Schäffer et al. 1994).

Population Studies

The marker-allele frequencies in disease and normal (nontransmitted) chromosomes of the 10 obligate BBS carriers (parents) were compared. Normal alleles from each parent were used as population controls, to avoid the possibility of inadvertently including *BBS1* disease alleles from random carriers in the population. Allelic association was tested by means of Fisher's exact test, with one-sided probability. The DHs were compared between families in the search for (i) common *BBS1* haplotypes that would indicate that the parents of two or more families were distantly related and (ii) a common ancestral DH.

Table 1

DHs on Chromosome 11q13 Segregating in Six BBS Families

	B7		B8		B10		B12		B15		B19	
Marker	p	m	p	m	p	m	p	m	p	m	p	m
D11S1298	7	3	10	10	7	10	7	9	11	11	…	…
D11S956	6	8	8	8	10	8	7	5	7	7	11	11
D11S480	9	5	6	6	9	6	5	9	5	5	9	9
D11S1883	10	10	10	10	10	10	10	8	10	10	7	7
D11S913	6	7	7	7	6	7	6	5	6	6	6	6
FGF3	7	12	5	5	7	5	9	9	9	9	…	…

NOTE.—Haplotypes are arranged with the paternal haplotype (p) on the left and the maternal haplotype (m) on the right. For markers *D11S913* and *FGF3,* the phase of the paternal haplotype in B12 is assumed.

Results

Preliminary Evidence of a Founder Effect among Families with BBS1

Five of the six families in this study live along the south and southwest coasts of Newfoundland (fig. 1). Although a common ancestor was not identified in ancestral lineages, genetic evidence suggests that the families are interrelated. The affected individuals in family B10 are apparently heterozygous for a copy of the DH identified in family B8 and a portion of the DH transmitted by the father of family B7 (table 1). It was noted that these three families originate from closely-linked communities on the southwest coast of the island (fig. 1). The data also suggest that the father of a south coast family (B12) shares a recent common ancestor with both parents of family B15, the only family not residing on the south coast of the island. Therefore, on the basis of shared DHs and geographical location, preliminary evidence suggested the presence of a founder effect among *BBS1* cases in the Newfoundland population.

Evidence of Linkage to BBS1

In a previous study, three families (B8, B10, and B19) were assigned to *BBS1* (Woods et al. 1999, table 1). Family B10 consists of a large sibship in which two affected individuals share a unique genotype on chromosome 11q13, compared with their nine unaffected sibs (fig. 2). A maximum LOD score of 1.662 at recombination fraction (θ) 0 was obtained with fully informative markers that mapped telomeric to *D11S1883*. Family B10 was previously excluded from linkage with *BBS2, BBS3, BBS4* (Woods et al. 1999), and *BBS5* (M. O. Woods, unpublished data) on the basis of established exclusion criteria. For a locus to be excluded, one or both of the following conditions had to be met: (i) an affected individual(s) inherited the same genotype as one or more unaffected sibs, and (ii) two or more affected individuals inherited different genotypes. Family B8 is a consanguineous family in which a single affected offspring was homozygous by descent (HBD) for the entire *BBS1* locus (fig. 2). A maximum LOD score of 1.405 ($\theta = 0$) was obtained with fully informative markers (e.g., *D11S1883*). Homozygosity (in the affected member only) was not observed at other BBS loci: *BBS2* and *BBS3* loci were excluded. Family B19 consists of a large sibship with one affected individual. The affected offspring was homozygous (presumably HBD) for all markers typed within the *BBS1* interval, whereas seven unaffected sibs were either heterozygous or homozygous for a normal haplotype. Homozygosity was not observed at other BBS loci, and the *BBS3* locus could be excluded (Woods et al. 1999).

In three families (B7, B12, and B15), BBS could not be excluded from, or confidently assigned to, the *BBS1* locus (Woods et al. 1999). Family B15 consists of a large sibship with one affected and eight unaffected sibs available for genotyping. Homozygosity in the affected individual was observed only at the *BBS1* locus, and the *BBS3* locus could be excluded. Family B7 has two affected individuals who share a unique genotype on chromosome 11q13, compared with their four unaffected sibs (fig. 2). A maximum LOD score of 1.074 ($\theta = 0$) was obtained with fully informative markers, and BBS in this family was excluded from linkage to *BBS3, BBS4,* and *BBS5* (M. O. Woods, unpublished data). Family B12 is relatively uninformative for linkage but was excluded from *BBS3* because the only affected individual (PID 14) inherited the same genotype as his unaffected sister. He is homozygous for the *BBS1* marker *D11S913,* but the phase of the paternal chromosomes cannot be determined for the *D11S913-FGF3* interval because of an apparent recombination in one of the offspring.

The pairwise LOD scores calculated for the six families at six markers covering the 26-cM *BBS1* critical region were summed. Four of six markers examined reached statistical significance when the families were considered together (LOD score >3; table 2). The finding of common DHs among *BBS1*-assigned families (B8 and B10), between *BBS1*-assigned and unassigned families (B7 and B10), and among unassigned families with evidence of linkage to *BBS1* (B12 and B15) (table 1) corroborates the linkage and haplotype data that these are,

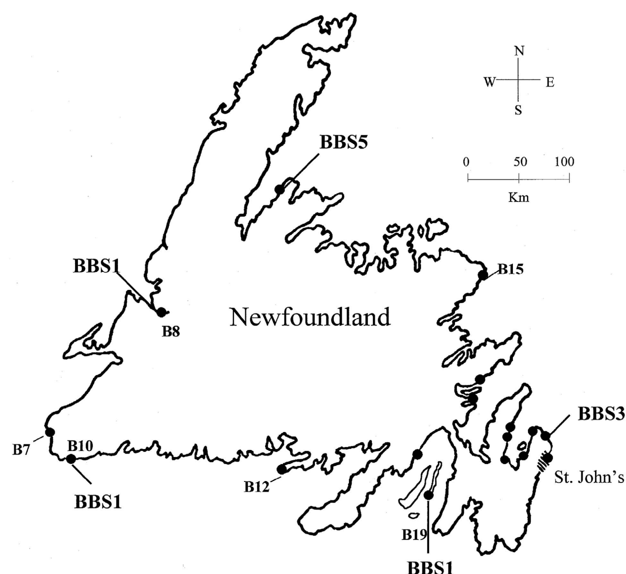

Figure 1 Geographical distribution of 17 Newfoundland families with BBS (blackened circles), indicating linkage with *BBS1, BBS3,* or *BBS5* as determined in previous studies (Woods et al. 1999; Young et al. 1999). The families genotyped in the present study are indicated by family number.

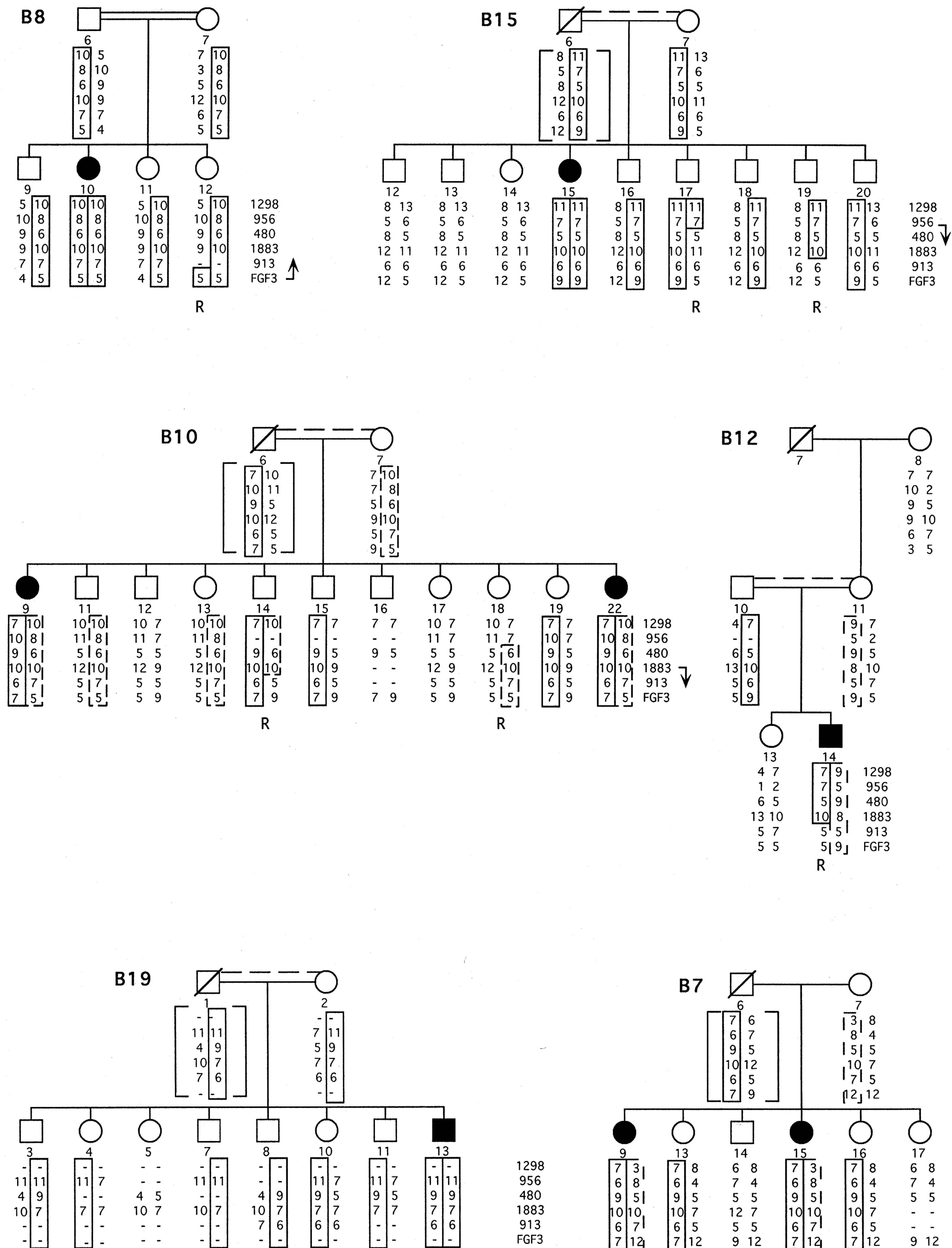

Figure 2 Three families with linkage to *BBS1* (B8, B10 and B19) and three unassigned families (B7, B12, and B15) haplotyped for six polymorphic markers spanning the 26-cM *BBS1* interval on chromosome 11q13. Only core pedigrees are presented. Blackened symbols indicate individuals with diagnoses of BBS. Boxed haplotypes (solid and dashed lines) indicate DHs. Double marriage lines depict consanguineous unions, either documented (solid line) or suspected (dashed line). "R" indicates that the DH is recombinant.

Table 2

Sum of the Pairwise LOD Scores at Chromosome 11q13, in Six Families with BBS

	LOD Score at θ=						
Marker	.000	.010	.050	.100	.200	.300	.400
D11S1298	2.227	2.263	2.169	1.856	1.124	.052	.142
D11S956	3.419	3.439	3.275	2.867	1.910	.972	.279
D11S480	2.809	2.819	2.623	2.202	1.288	.559	.137
D11S1883	3.657	3.663	3.430	2.952	1.868	.894	.241
D11S913	3.019	2.923	2.546	2.093	1.264	.587	.151
FGF3	3.777	3.662	3.203	2.644	1.599	.739	.190

in fact, all *BBS1* families. Because the exact relationships among the pedigrees are unknown, the summary LOD scores given in table 2 are presumed to be underestimated. Obligate recombinations involving the DHs were detected in several families and used to refine the *BBS1* interval. In family B10, an unaffected individual, PID 14, inherited a nonrecombinant DH from his father and a recombinant DH from his mother. The presence of two DHs for the centromeric portion of the *BBS1* critical region (*D11S1298* to *D11S1883*) in an unaffected individual suggests that marker *D11S1883* is the new centromeric boundary for *BBS1* (fig. 2). Similarly, a recombinant paternal haplotype inherited by an unaffected sib in family B8 (PID 12) suggests that *BBS1* is located centromeric to *FGF3*. Intrafamilial recombinations on DHs reduce the *BBS1* interval from a 26-cM region to a 15-cM interval between *D11S1883* and *FGF3* (fig. 3).

LD and Detection of a Founder Haplotype

Extensive genotyping at the *BBS1* locus focused on markers within the new *BBS1* interval (fig. 3). The distribution of alleles at 14 polymorphic loci in disease and normal chromosomes is shown in table 3. Significant LD between specific marker alleles on DHs was observed across the families. Strong associations were observed between alleles at five consecutive marker loci: *D11S4205, D11S1883, D11S4945, PYGM,* and *D11S4946*. Comparison of allele frequencies between disease and normal chromosomes showed that three of these associations were statistically significant. Allele 10 at marker *D11S1883* was present on 70% (7/10) of DHs but only 20% (2/10) of normal chromosomes ($P < .05$). Similarly, allele 8 at the *PYGM* locus was present on 100% of the DHs and 50% of normal chromosomes ($P < .05$), and allele 5 at marker *D11S4946* was present on 100% of the disease chromosomes and 30% of normal chromosomes ($P < .01$). Although allele 4 at marker *D11S4205* and allele 9 at marker D11S4945 were present on 90% and 100% of disease chromosomes, respectively, these associations were not significant, because both alleles are common in the general population; they are present on 70% of the normal chromosomes (table 3).

A single ancestral DH was readily identified in the vicinity of marker loci with strong allelic associations. All disease chromosomes segregating in *BBS1* families contained the -9-8-5- subhaplotype at *D11S4945, PYGM,* and *D11S4946,* respectively. The affected members in families B10 and B12 that initially appeared to be heterozygous at the *BBS1* locus (table 1) are, in fact, HBD for a region centered around the *PYGM* locus (table 3). As well, the DHs that appeared unique on the basis of six polymorphic markers (e.g., family B19, table 1) are indistinguishable from all other DHs identified in the population. In contrast, the -9-8-5- subhaplotype was found only on a single normal haplotype (family B8). This suggest that, although rare, the -9-8-5- subhaplotype is not exclusive to *BBS1*-carrying chromosomes in the Newfoundland population. The longer - 4-10-9-8-5- haplotype (encompassing the -9-8-5- subhaplotype and the centromeric markers *D11S4205* and *D11S1883*) was identified on 60% of the DHs but none of the normal chromosomes. This longer haplotype may represent a larger portion of the ancestral DH. In this case, DHs discordant for allele 10 at *D11S1883* (families B12 and B19) may have resulted from either

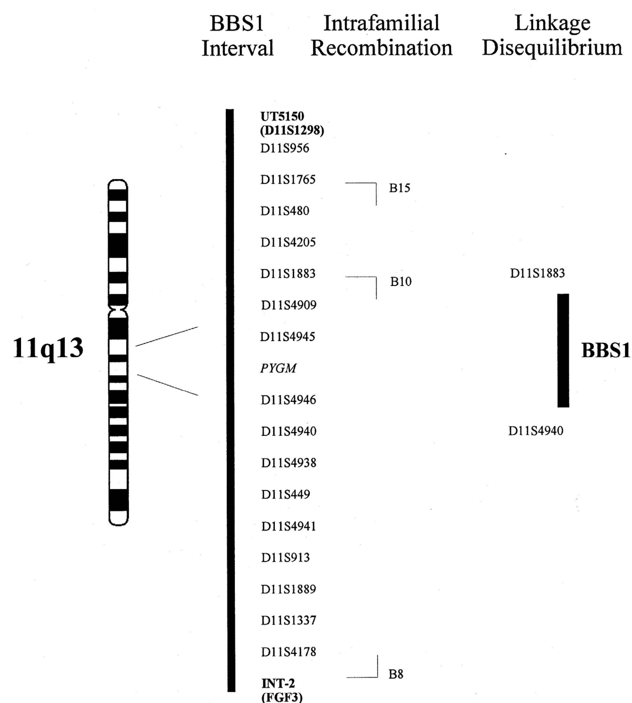

Figure 3 Refinement of the *BBS1* interval by recombinational and LD mapping in Newfoundland families. The markers and their relative positions were selected from the map of the *MEN1* region on 11q13 (Manickam et al. 1997; Sixth International SCW 11 Workshop 1998).

Table 3

LD at the *BBS1* Locus on Chromosome 11q13 among Five Newfoundland Kindreds

	DH for Kindred										Normal Haplotype for Kindred									
	B8		B10		B12		B15		B19		B8		B10		B12		B15		B19	
Locus	p	m	p	m	p	m	p	m	p	m	p	m	p	m	p	m	p	m	p	m
1298	10	10	7	10	7	9	11	11	…	…	5	7	10	7	4	7	8	13	…	…
956	8	8	10	8	7	5	7	7	11	11	10	3	11	7	1	2	5	6	11	7
480	6	6	9	6	5	9	5	5	9	9	9	5	5	5	6	5	8	5	4	5
4205	4	4	3	4	4	4	4	4	4	4	3	4	4	5	4	4	3	4	4	4
1883	10	10	10	10	10	8[a]	10	10	7	7	9	12	12	9	13	10	12	11	10	7
4945	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	4	10	10	9	9
PYGM	8	8	8	8	8	8	8	8	8	8	8	8	6[a]	8	2	4	4	8	8	4
4946	5	5	5	5	5	5	5	5	5	5	4	5	5	4	4	1	1	5	3	3
4940	5	5	7	5	7	5	7	7	3	3	5	5	5	5	5	3	5	7	7	5
4938	5	5	3	5	5	3	5	5	5	5	9	3	5	3	5	9	5	5	…	9
449	7	7	3	7	3	6	5	5	3	3	5	3	4	3	4	2	5	5	3	4
4941	9	9	11	9	2	2	4	4	4	4	8	3	6	11	2	4	4	6	4	4
913	7	7	6	7	6	5	6	6	6	6	7	6	5	5	5	7	6	6	7	6
FGF3	5	5	7	5	9	9	9	9	…	…	4	5	5	9	5	5	12	5	…	…

Note.—Haplotypes are arranged with paternal haplotype (p) on the left and the maternal haplotype (m) on the right. Specific alleles associated with disease chromosomes are boxed.

[a] Allele is not associated with disease chromosome.

(i) historical recombinations to the ancestral DH between *D11S1883* and *D11S4945* that were not informative at *D11S4205*, a notably uninformative marker in the population, or (ii) de novo mutations at the more polymorphic *D11S1883* locus. In any case, the evidence suggests that the -9-8-5- subhaplotype represents either the remnants of a founder *BBS1* chromosome imported from England or the background haplotype that sustained a *BBS1* mutation de novo in the germline of a single English settler.

Location of BBS1

LD mapping supports a position for the *BBS1* gene within a 1-cM region between markers *D11S1883* and *D11S4940*, surrounding the *PYGM* locus. The *D11S1883* boundary is also supported on the basis of intrafamilial recombination (fig. 3). This 1-cM genetic interval represents a physical distance of ∼1 Mb (Manickam et al. 1997) within a region of the genome that is gene rich and, fortuitously, sequence ready as a result of physical mapping efforts to clone the Best vitelliform macular dystrophy (*VMD-2*) and multiple endocrine neoplasia (*MEN1*) genes that map to this region (Cooper et al. 1997; Guru et al. 1997; Manickam et al. 1997).

Discussion

The island of Newfoundland is a sparsely populated region of Canada in which 50% of the population of 560,000 reside in small coastal communities. The colonization of the island occurred primarily by a natural increase from northern European settlers of predominantly English and Irish extraction who arrived before 1835. Most founders originated from the West Country of England and from southeast Ireland (Mannion 1977). Mating segregation between Irish Catholics and English Protestants, low immigration, and geographical isolation of communities have resulted in genetic isolation of the population. In a review of the historical development of genetic isolation in three Newfoundland outports, Bear et al. (1988) observed that only 1%–8% of breeding parents were immigrants to the area and 60% of births had been to parents originating from the same small community.

The scattered distribution of families with BBS and the recent identification of at least three distinct genetic BBS subtypes in Newfoundland (Woods et al. 1999) is not consistent with the expectation of a single cluster of families with a recessive disease in a young founder population. However, we noted that five of the six families with evidence of linkage to *BBS1* reside on the south and southwest coasts of the island, a region that was settled predominantly by the spread of settlers by sea in an east-to-west direction (Mannion 1977). The genotyping data also suggest that these families have complex relationships with each other in that large regions (up to 26 cM) on disease-associated haplotypes were shared among kindreds. In the absence of mutation analysis, the identification of a single founder effect would require that all patients were homozygous for specific alleles at

marker loci tightly linked to the *BBS1* gene. We have shown that all *BBS1* patients identified in the Newfoundland population are homozygous for a relatively rare haplotype spanning a 1-cM region centered around the *PYGM* gene on chromosome 11q13. The relatively high incidence of BBS and the scattered distribution of affected families in the Newfoundland population are attributable to a combination of locus heterogeneity and at least one founder effect.

The power of LD mapping is well illustrated from this study: a total of six affected individuals in five families were used to fine map the *BBS1* gene to within 1 Mb by this method. Even families not informative for linkage (e.g., B12) provided valuable information on historical recombinations. In contrast, two recent studies reporting on a total of 47 families with BBS failed to identify informative recombinations at the *BBS1* locus (Beales et al. 1997; Bruford et al. 1997). The localization of *BBS1* within a 1-Mb interval between *D11S1883* and *D11S4940* is small enough to promote the positional cloning of the *BBS1* gene. The Newfoundland population may also be useful for the analysis of other genetic diseases, especially those that have a relatively high incidence in the population: nonsyndromic deafness, various forms of retinal dystrophy, neuronal ceroid lipofuscinosis, and neural tube defects (J. Green, unpublished data).

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Electronic-Database Information

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

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for BBS [MIM 209900])

Sixth International SCW 11 Workshop (Nice, France, 1998), http://www.genetics.wustl.edu/gerhard/SCW11/SCW11.html

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