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The Ashkenazic Jewish Bloom Syndrome Mutation *blm*^{Ash} Is Present in Non-Jewish Americans of Spanish Ancestry

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Summary

Bloom syndrome (BS) is more frequent in the Ashkenazic Jewish population than in any other. There the predominant mutation, referred to as "*blm*^{Ash}," is a 6-bp deletion and 7-bp insertion at nucleotide position 2281 in the *BLM* cDNA. Using a convenient PCR assay, we have identified *blm*^{Ash} on 58 of 60 chromosomes transmitted by Ashkenazic parents to persons with BS. In contrast, in 91 unrelated non-Ashkenazic persons with BS whom we examined, *blm*^{Ash} was identified only in 5, these coming from Spanish-speaking Christian families from the southwestern United States, Mexico, or El Salvador. These data, along with haplotype analyses, show that *blm*^{Ash} was independently established through a founder effect in Ashkenazic Jews and in immigrants to formerly Spanish colonies. This striking observation underscores the complexity of Jewish history and demonstrates the importance of migration and genetic drift in the formation of human populations.

Introduction

Bloom syndrome (BS) (MIM 210900) is a rare autosomal recessive disorder the major clinical features of which are short stature, a sun-sensitive facial erythema, and immunodeficiency (reviewed in German and Ellis 1998). BS somatic cells are hypermutable, a feature detectable at the chromosomal level as increased chromosome breakage and excessive chromatid exchange and at the biochemical and molecular levels as increased mutation at *HPRT, HLA, GPA,* and repeat-sequence loci. The consequence of this somatic hypermutability and hyperrecombinability is an enormous predisposition to cancer (German 1997). The cancers are at the sites and of the types that are both common (leukemias, lymphomas, and carcinomas) and rare (Wilms tumor, retinoblastoma, and glial neoplasms) in the general population.

In 1995, the BS gene, *BLM,* was isolated by a positional cloning strategy, and its gene product was found to have homology to the RecQ subfamily of DNA helicases (Ellis et al. 1995*a*). A reduced level of *BLM* RNA was detected in certain BS cell lines, and mutations that cause premature translation termination were found in 10 of the 13 persons with BS who initially were examined (Ellis et al. 1995*a*). These observations indicated that null mutations in *BLM* are responsible for BS, the primary biochemical defect being the absence from somatic cells of the protein BLM.

BS is more common in the Ashkenazic Jewish population than in any other so far examined (German et al. 1977), and the Ashkenazic is the only population in which a mutation in *BLM* has been other than extremely rare. Linkage-disequilibrium analysis has provided strong evidence that a founder effect is the explanation for the relatively increased frequency of BS in the Ashkenazic Jewish population (Ellis et al. 1994). Moreover, when *BLM* was isolated, the founder-effect hypothesis was supported by the fact that, of the four BS persons with Ashkenazic ancestry who were studied, each was homozygous for one and the same mutation—a 6-bp deletion and 7-bp insertion at nucleotide position 2281 in the *BLM* cDNA (BLMc.2207–2212delATCTGAinsTAGATTC)—a mutation that we refer to as "*blm*^{Ash}." This mutation is carried by 1 of every 107 Ashkenazic Jews in New York City (Li et al. 1998).

In the present study, we analyzed the *BLM* gene for *blm*^{Ash} in persons with BS, testing DNAs available through the Bloom's Syndrome Registry (German and Passarge 1989). We found, as expected, that *blm*^{Ash} was present on 58 of the 60 chromosomes examined in persons with BS who were of Ashkenazic ancestry. Re-

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markably, however, we also found *blm*^{Ash} in five non-Jewish persons with BS. Each of these lives in the Americas and has a Spanish-speaking Catholic family that has resided in the southwestern United States, Mexico, or El Salvador for many generations. Two of the five families can trace their ancestry to Spain. Molecular analysis revealed that the *blm*^{Ash} chromosomes from both Ashkenazic and non-Ashkenazic persons carry the same or related haplotypes. Together, these results, for reasons that will be given, suggest that *blm*^{Ash} is present not only in the Ashkenazic population but also in descendents of a person who several centuries ago emigrated from Spain to New Spain and who most likely was a Sephardic Jew.

Subjects, Material, and Methods

Subjects and DNA Samples

The Bloom's Syndrome Registry was the source of the biological specimens analyzed. The registry contains clinical and genetic information from 198 persons with BS, including a cohort of 169 persons comprising essentially all of the persons in whom BS was diagnosed before 1991. Only persons with bona fide clinical BS have been registered, and almost all had the diagnosis confirmed cytogenetically. The registry has obtained and preserved biological specimens from affected families as they have become available: lymphoblastoid cell lines established from blood lymphocytes, fibroblast cell lines established from skin biopsies or surgical specimens, cryopreserved or fresh blood or components of blood, and fixed and paraffin-embedded pathology specimens. Genomic DNA was prepared from all persons with BS and from those of their parents from whom a biological sample was available to the registry: 139 persons with BS, representing 125 unrelated families, and 164 parents available from 91 of these families. In certain cases, DNAs were prepared from more than one source.

The "BS/Ashkenazic" population was composed of DNA samples from 27 unrelated persons with BS (with one exception; see note to table 1), each of whose parents were Ashkenazic Jewish; DNA samples were available from 42 of their parents. An additional seven DNA samples were available from persons with BS who had a single Ashkenazic parent; DNA samples were available from 11 of their parents, and 6 of these samples were from the Ashkenazic parent. In two of these "half"-Ashkenazic families, Sephardic ancestry was recorded: In one family, the father of BS sibs 107(MyAsa) and 163(ViAsa) was a Bulgarian Jew both of whose parents were Sephardic Jewish. In the other family, the maternal grandfather of 126(BrNad) was a Sephardic Jew, and the maternal grandmother was an Egyptian Jew. As a control for the BS/Ashkenazic population, a sample designated the "non–BS/Ashkenazic" population was obtained that consisted of cryopreserved samples from 50 normal Ashkenazic Jewish men who had been participants in an unrelated epidemiological study conducted earlier at the New York Blood Center.

Table 1

***blm*^{Ash} in Persons with BS, in Families in Which One or Both Parents Are Ashkenazic Jews**

Ancestry of Parents[a]	No. of *blm*^{Ash} Alleles/No. of Chromosomes	
	Ashkenazic	Non-Ashkenazic
Ashkenazic (27)[b]	51/53	0/0
Ashkenazic-American (5)[c]	5/5	5/0
Ashkenazic-Sephardic (2)[d]	2/2	1/2
Total (34)	58/60	1/7

Note.—All affected families were unrelated, except for one in which two persons with BS had mothers who were first cousins.

[a] No. of persons with BS is indicated in parentheses.

[b] In one family, the parents are first cousins; therefore, the *blm*^{Ash} chromosomes in this family were counted only once. Two persons with BS were compound heterozygotes; one mutant allele was *blm*^{Ash}, and the other has yet to be identified (see text).

[c] In each family, one parent is Ashkenazic Jewish, and the other is American of mixed European but non-Jewish ancestry. In all of these families, *blm*^{Ash} was heterozygous in the affected person, being transmitted by the Ashkenazic parent.

[d] In each family, one parent has Ashkenazic ancestry, and the other has Sephardic ancestry (see text). In one family, *blm*^{Ash} was compound heterozygous in the affected person, being transmitted by the Ashkenazic parent. In the other family, *blm*^{Ash} was homozygous, being transmitted by both the Ashkenazic parent and the Sephardic parent.

The "BS/non-Ashkenazic" population was composed of DNAs from 91 unrelated persons with BS, neither of whose parents were Ashkenazic Jewish; DNAs were available for testing, when appropriate, from 111 of their parents. The ancestry of the parents of these persons is recorded in the registry. Of particular interest here were the seven families that came from the southwestern United States, Mexico, and El Salvador. As a control for the BS/non-Ashkenazic population, a sample designated the "non-BS/non-Ashkenazic" population was examined, which consisted of DNAs from 122 grandparents of families included in the Centre d'Etude du Polymorphism Humain (CEPH) reference panel. DNAs were prepared as described elsewhere (Ellis et al. 1995*b*).

Testing for blm^{Ash}

The *blm*^{Ash} mutation introduced a *Bst*NI restriction-enzyme site into *BLM*. Chromosomes carrying the mutation contain the *Bst*NI site, whereas other chromosomes do not (Straughen et al. 1998). PCR was performed by use of genomic DNA (50–250 ng/reaction) and oligonucleotide primers flanking the site of the *blm*^{Ash} mutation, as described elsewhere (Li et al. 1998; Straughen et al. 1998). PCR products were digested with

*Bst*NI, according to the manufacturer's instructions, and the products were separated by agarose-gel electrophoresis.

Haplotype Analysis

The polymorphic microsatellite loci *D15S996, D15S1108, D15S127, FES, D15S158,* and *IP15M9* were selected for genotyping because they are genetically linked to and physically associated with *BLM* (fig. 1) and are efficiently polymorphic. Genotypes at these six loci were determined by PCR. Information on oligonucleotide primers, expected allele sizes, distribution of allele frequencies, and conditions for PCR amplification have been described elsewhere (German et al. 1994; Dib et al. 1996; Straughen et al. 1996).

Haplotypes of Ashkenazic blm^{Ash} chromosomes and of Ashkenazic non-blm^{Ash} chromosomes were constructed on the basis of genetic information from the available parents. To construct haplotypes, we assumed that no recombination had occurred between *BLM* and the polymorphic markers in the parental meioses that immediately preceded formation of the BS zygote. This will hold true in most cases because crossing-over in the interval between *BLM* and the outside flanking markers (*D15S996* and *IP15M9*) is expected to occur at a frequency of <1%, the six polymorphic microsatellite loci under study being in a ≤1.3-cM interval (Straughen et al. 1996). The parental origin of each allele was determined unambiguously except when the parents (or parent, if only one was available) and the person with BS had the same heterozygous genotype, the situation at a single locus in five families. In two of these cases, the ambiguity was resolved without bias: in one case, a sib who inherited the maternal blm^{Ash} chromosome was examined, for comparison; in the other, a lymphoblastoid cell line from the affected person was available, the cells of which by chance had lost the maternal chromosome 15. The ambiguities in the three other cases were resolved by constructing the two possible haplotypes and selecting the one that increased the numbers of the more common haplotypes (see Results).

A Polymorphism within BLM

Detected during the initial mutational analysis of *BLM* was a nucleotide substitution, T→A at position 3699 in the *BLM* cDNA (BLMc.3625T→A), a change that causes an amino acid substitution, S→T at residue 1209. To examine the *BLM3699* polymorphism in our DNA samples, we amplified the genomic sequences flanking the site of the polymorphism, employing the primer pair E19A5′ (CCTGTATGGTACAAGTGCACAT) and E19B3′ (CGTGTCTAATTATCCGGCTTTC) to generate a fragment of 301 bp. The site of the polymorphism can be digested with the restriction enzyme *Tsp*45I: When the T base is present, digestion produces fragments of 229 bp and 72 bp; when the A base is present, digestion produces fragments of 121 bp, 108 bp, and 72 bp (the 72-bp fragment being present in both digestions).

Results

blm^{Ash} *in BS/Ashkenazic Families*

The blm^{Ash} mutation was detected by PCR analysis of genomic DNA. Of the 27 unrelated BS/Ashkenazic persons examined, 25 were homozygous for blm^{Ash}, and 2 were compound heterozygotes (table 1). Of the 47 available parents of the BS/Ashkenazic persons, 45 transmitted the blm^{Ash} allele to the person with BS, and 2 transmitted yet-to-be-defined mutant alleles present in the 2 aforementioned compound heterozygotes. Of the seven persons with BS who had only a single Ashkenazic parent, all were compound heterozygotes for blm^{Ash}. Of the six available Ashkenazic parents of the "half"-BS/Ashkenazic persons, all transmitted the blm^{Ash} allele. Al-

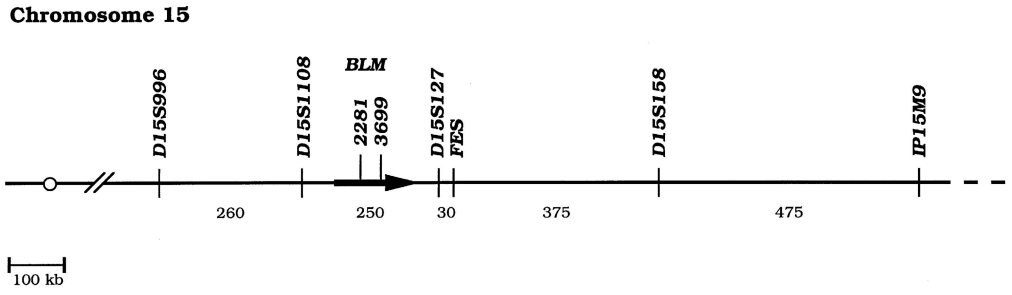

Figure 1 Order and physical location of the seven polymorphic markers and one mutation examined (see Straughen et al. 1996). The orientation of the genomic segment relative to the centromere (*circle*) was determined by analysis of recombinant chromosomes that were detected in BS families (German et al. 1994; Ellis et al. 1995*b*). The physical distances (in kb) between loci is shown under the line that represents the genomic sequences.

together, the *blm*^{Ash} allele was found on 58 of the 60 BS/Ashkenazic chromosomes examined (table 1).

blm^{Ash} *in Non-Ashkenazic Persons*

The *blm*^{Ash} mutation was conspicuously absent from the several western European populations that historically have long been in contact with the Ashkenazic population (table 2). Not a single *blm*^{Ash} chromosome was detected in 31 non-Jewish North American persons with BS who were of mixed European ancestry, 8 Germans, 8 Italians, 6 persons of Dutch and Belgian ancestry, and 1 Englishman. In striking contrast, and completely unexpected, *blm*^{Ash} was detected in five unrelated persons whose families came from New Mexico (one family), southern Colorado (one family), Mexico (one family), and El Salvador (two families) (see table 2). In three families, the person with BS was a *blm*^{Ash} homozygote. Parental consanguinity can explain the homozygosity in the Colorado family but was not recorded in the other two. *blm*^{Ash} was found in two of the three El Salvadoran families studied. In one of these families, the person with BS was a *blm*^{Ash} homozygote; in this family the parents denied consanguinity. In the other family, the person with BS was a *blm*^{Ash} compound heterozygote; the mother, who was El Salvadoran, transmitted the *blm*^{Ash} allele, whereas the Ecuadoran father transmitted a different *BLM* mutation to the affected child.

None of these five families in which *blm*^{Ash} was segregating were aware of Ashkenazic ancestry; instead, they reported their families to be Christian as far back as was known, and two of the families reported specifically that their ancestors were from Spain. Spanish has been spoken for generations in each of the five families. These observations suggest that the *blm*^{Ash} mutation in these families came to the Americas from Spain. If the *blm*^{Ash} mutation came from Spain, then it is highly probable that, given the presence of *blm*^{Ash} in the Ashkenazic population, the mutation in the Spanish American non-Jewish families in fact derives from the Sephardic population. None of these families reported Sephardic ancestry, except for one that had lived in Jalisco for many generations and in which the tradition has been passed down that the patient's maternal grandmother had "a Sephardi ancestor." Consistent with a Sephardic origin of *blm*^{Ash} segregating in Spanish Americans, 107(MyAsa), a person with BS who was living in New York City, inherited a *blm*^{Ash} mutation from her Bulgarian father, a Sephardic Jew (table 1). Thus, of the two Sephardic chromosomes mutated at *BLM* that we have been able to analyze, one carries *blm*^{Ash}.

Haplotype Analysis of blm^{Ash} *Chromosomes*

The molecular nature of the *blm*^{Ash} mutation suggests that it arose only once. However, in order to learn whether the *blm*^{Ash} chromosomes in the Ashkenazic and non-Ashkenazic populations were indeed from a common ancestor, haplotype analysis was performed. In our earlier study (Ellis et al. 1994), we described a linkage disequilibrium between *BLM, D15S127,* and *FES* in Ashkenazic Jews with BS. In the present study, we have determined, in persons with BS who carry *blm*^{Ash} and in those of their parents who were available, the genotypes of six polymorphic microsatellite loci flanking *BLM,* including *FES* and *D15S127* (see Straughen et al. 1996), and also the genotype of one diallelic locus within *BLM,* the *BLM3699* polymorphism described above. On the basis of this information, haplotypes were constructed from 51 Ashkenazic *blm*^{Ash} chromosomes (fig. 2). Con-

Table 2

***blm*^{Ash} Chromosomes in 91 Unrelated Persons with BS Who Were Born into Non-Ashkenazic Families**

Ancestry (No. of Persons)	No. of Chromosomes	
	Non-Ashkenazic[a]	*blm*^{Ash}
American, European ancestry (31)	56	0
German (8)	15	0
Italian (8)	11	0
Japanese (8)	13	0
Dutch and Belgian (6)	12	0
American, African ancestry (4)	6	0
Brazilian (4)	8	0
American, Spanish ancestry (4)[b]	3	4
Turkish (4)	6	0
El Salvadoran (3)[c]	3	3
French Canadian (2)	3	0
Argentinean (1)	2	0
Australian, European ancestry (1)	2	0
Ecuadoran (1)	2	0
English (1)	1	0
Indian, Bombay region (1)	2	0
Lebanese (1)	1	0
Persian Jewish (1)	1	0
Portuguese (1)	2	0
Spanish (1)	1	0

[a] Calculated as follows: in the families in which parental consanguinity was known, only one chromosome mutated at *BLM* was counted; to this was added the number of mutated chromosomes from the families lacking known parental consanguinity.

[b] Parents of the persons with BS were born in Mexico (6), southern Colorado (2), Utah (1), and New Mexico (1). In one of the two Mexican families and in the one Colorado family, *blm*^{Ash} was homozygous in the person with BS. Parental consanguinity was recorded in the Colorado family but not in the Mexican family. In the New Mexican family, the person with BS was a *blm*^{Ash} compound heterozygote. In the second Mexican family, *blm*^{Ash} was not present. As in footnote "a," the *blm*^{Ash} chromosome in the consanguineous family is counted as a single chromosome

[c] In one family, *blm*^{Ash} was homozygous in the person with BS; in another family, it was compound heterozygous; in a third, it was absent. In one family listed as being El Salvadoran, the mother, who carried *blm*^{Ash}, was from El Salvador, and the father, who carried a different mutation at *BLM,* was from Ecuador. Consanguinity was not recorded in any of these three families.

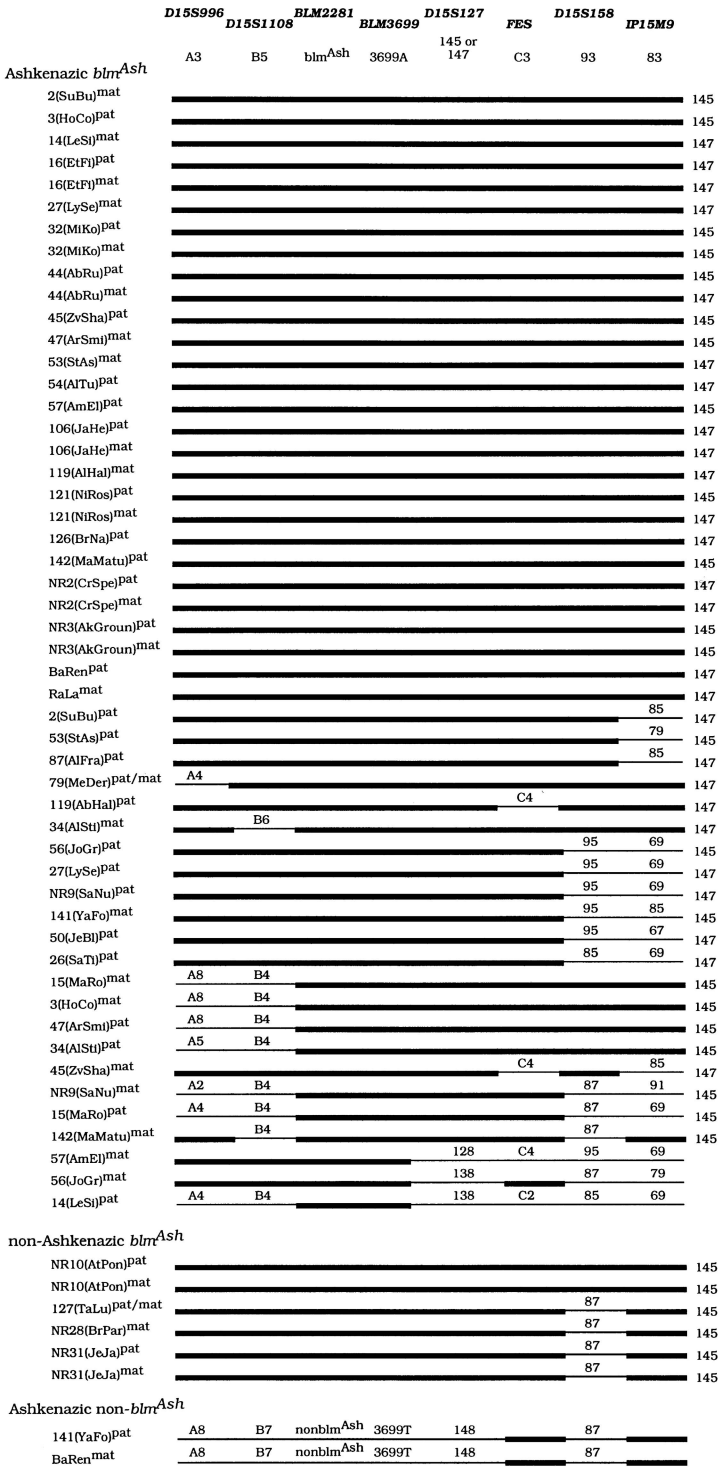

Figure 2 Haplotypes of 51 Ashkenazic *blm*^{Ash} chromosomes, 6 non-Ashkenazic *blm*^{Ash} chromosomes, and 2 Ashkenazic non-*blm*^{Ash} chromosomes (determined as described in the text). The identification at the left of each chromosome is taken from the Bloom's Syndrome Registry's designation of the person with BS; the parental origin of each chromosome is indicated: pat = paternal, mat = maternal. Reference to all except the most recently accessioned persons can be found in one of the reports from the registry, which have been made serially since 1977 (see German and Passarge 1989). The genetic history of each registered person whose chromosomes are represented here as Ashkenazic indicates that each of his or her chromosomes was transmitted from a parent who was an Ashkenazic Jew. The genetic history of persons whose chromosomes are represented here as non-Ashkenazic indicates that each chromosome was transmitted in this case by a Spanish-speaking Christian person whose families have dwelt for many generations in the southwestern United States, Mexico, or El Salvador. The eight loci (*boldface*) are arrayed in the order that they assume in the human genome (fig. 1). The alleles present on the founder's haplotype, named across the top, are indicated by the thicker portion of each line; alleles not present on the founder's haplotype are indicated by the thinner portions of each line, and there the allele present on each is indicated. To the right of each haplotype is indicated the *D15S127* allele (145 bp or 147 bp) that is present on that chromosome.

sistent with the linkage disequilibrium described earlier, a single allele predominates at each locus, thus forming a predominant haplotype, with one exception (see below). Twenty-seven of the 51 chromosomes carry this haplotype—the founder's haplotype—which very likely represents the chromosome on which the *blm*^{Ash} mutation arose.

The exception just mentioned is at polymorphic locus *D15S127*. There, two alleles are present at roughly equal frequencies (fig. 2). On the Ashkenazic *blm*^{Ash} chromosomes, the 147-bp allele is present on 25 chromosomes, and the 145-bp allele is present on 23 chromosomes; 3 chromosomes carry neither of these two alleles. Of the chromosomes carrying the founder's haplotype, the 147-bp allele is present on 15, and the 145-bp allele is present on 12. The founder carried a chromosome that had one of these two alleles at *D15S127;* the other allele probably arose from this allele by a mutational event that added or subtracted a single dinucleotide in the CA-repeat array constituting the polymorphic segment at *D15S127*. The haplotype data suggest that the mutational event is relatively frequent, such that, over time, neither allele predominates. Thus, for the haplotype analysis presented here, we have combined the chromosomes to represent the founder's haplotype.

As stated above, 28 of the 51 Ashkenazic *blm*^{Ash} chromosomes carry the founder's haplotype. On the remaining 23 chromosomes, there are 18 different haplotypes; however, 22 of these 23 chromosomes carry some portion of the founder's haplotype at a minimum of three contiguous loci (fig. 2). The one remaining chromosome, the one transmitted by the father of 14(LeSi), carries only a single allele represented in the founder's haplotype; but, important to the present argument, it is the one in the *BLM* gene itself (see below). These 18 different haplotypes are derived from the founder's haplotype either by recombinational events between the *BLM* gene and the loci flanking it, by mutational events at the marker loci themselves, or by both.

Haplotypes could be constructed from six of the seven non-Ashkenazic *blm*^{Ash} chromosomes identified in the Spanish Americans with BS, and a striking pattern emerged (fig. 2). First, only two haplotypes were found—namely, the founder's haplotype and a haplotype that carries an 87-bp allele at *D15S158,* instead of the founder's 93-bp allele. Second, at *D15S127,* only the 145-bp allele is present, in contrast to the Ashkenazic *blm*^{Ash} chromosomes that exhibit both the 145-bp and 147-bp alleles. The data indicate that *blm*^{Ash} is present in the Spanish American families through a founder effect.

Analysis of the BLM3699 Polymorphism

One allele of the founder's haplotype is present on all the *blm*^{Ash} chromosomes examined (table 3). The polymorphism is a T→A nucleotide substitution at bp 3699 of the *BLM* cDNA. Although the A base is present on all *blm*^{Ash} chromosomes, we have not found it on any other chromosome tested. The one person in the non-BS/Ashkenazic population who carried the A base proved also to be a carrier of *blm*^{Ash}*!*

Table 3

***BLM3699* Polymorphism in Unrelated Ashkenazic and Non-Ashkenazic Persons**

Population (No. of Persons)	No. of Chromosomes Carrying	
	A Base	T Base
BS/Ashkenazic (27)[a]	51	2
BS/Ashkenazic-American (5)[b]	5	5
BS/Ashkenazic-Sephardic (2)[c]	3	1
BS/non-Ashkenazic (87)[d]	7	144
Non-BS/Ashkenazic (50)[e]	1	99
Non-BS/non-Ashkenazic (117)	0	234

[a] See footnote "b" to table 1.

[b] See footnote "c" to table 1. The A base was always inherited from the Ashkenazic parents.

[c] See footnote "d" to table 1. Four persons were not typed at *BLM3699*. The A base was inherited from each of the Ashkenazic parents and by one of the Sephardic parents, the Bulgarian Jew referred to in the text.

[d] See footnote "a" to table 2. The A base was present only in persons who carried *blm*^{Ash}. In the Colorado person with BS whose parents were cousins, the chromosome carrying the A base was counted only once.

[e] The one non-BS/Ashkenazic person sampled who carries the A base is also a carrier of *blm*^{Ash}.

*The BS/Ashkenazic Non-*blm^{Ash} *Chromosomes*

As mentioned above, two BS/Ashkenazic chromosomes were identified in which *blm*^{Ash} is not the *BLM* mutation. These two chromosomes also fail to carry more than two alleles of the founder's haplotype, and, specifically, they do not carry the *BLM3699* A base (see fig. 2) Thus, these two chromosomes did not come from the *blm*^{Ash} founder. However, because the two chromosomes have an identical haplotype, we conclude that they too are derived from a founder individual and thereby carry the same mutation at *BLM*.

Discussion

The data presented here demonstrate conclusively that the *blm*^{Ash} mutation in the BS/Ashkenazic population is derived from a founder individual. Therefore, chromosomes carrying the *blm*^{Ash} mutation have increased in frequency in the Ashkenazic population by random genetic drift. Linkage disequilibrium between *BLM, FES,* and *D15S127,* detected in Ashkenzic Jews with BS, had earlier suggested the same conclusion (Ellis et al. 1994). Moreover, when *BLM* was cloned, the *blm*^{Ash} mutation

was found in all of the four Ashkenazic persons with BS who were examined (Ellis et al. 1995*a*). The alternative view—that a heterozygote advantage caused an increase in the gene frequency of *blm*^{Ash} in the Ashkenazic population—seems unlikely, for two reasons: (1) The frequency of heterozygotes in the Ashkenazic population is only 1/107 (Li et al. 1998), and (2) a single mutation—namely, *blm*^{Ash}—predominates in the Ashkenazic population, rather than several common mutations, which is the situation for Tay-Sachs and Gaucher diseases (Eng et al. 1997; Kronn et al. 1998).

In the present study, we have tested directly for the *blm*^{Ash} mutation in all persons with BS from whom DNA samples were available, and we have found, not surprisingly, that 58 of the 60 BS/Ashkenazic chromosomes examined carried *blm*^{Ash}. Two Ashkenazic Jews with BS were identified who carry a mutation different from *blm*^{Ash}. The non*blm*^{Ash} mutation could have either entered the Ashkenazic population from another population by admixture or arisen as a new mutation in *BLM* in the Ashkenazic population.

It was surprising, however, to find *blm*^{Ash} segregating in present-day Christian families of Spanish decent who for generations have dwelt in the southwestern United States, Mexico, or El Salvador. These Spanish American *blm*^{Ash} chromosomes have haplotypes that also are present on the Ashkenazic *blm*^{Ash} chromosomes, indicating that they are derived from a common ancestor. However, only two different haplotypes were found on the six Spanish American *blm*^{Ash} chromosomes, and both of these contained just the 145-bp allele at *D15S127*. These data suggest that *blm*^{Ash} is present in certain Spanish American families through a founder effect that occurred more recently than, and in a place different from the origin of, the founder effect responsible for the relatively high frequency of *blm*^{Ash} in the Ashkenazic population.

The data on the *BLM3699* polymorphism, a diallelic DNA variant, are particularly strong evidence for a single origin of the *blm*^{Ash} mutation, and they support the hypothesis that the *blm*^{Ash} chromosomes discovered in both the Ashkenazic population and the non-Ashkenazic Spanish American population ultimately trace to a common ancestor. They also raise the possibility that, even today, a population exists in which the A base is segregating, but on a chromosome that is not mutant at *BLM*. Such a population could be the one in which the *blm*^{Ash} mutation arose.

How can *blm*^{Ash} in American non-Jewish persons be explained? One improbable explanation is that a recent ancestor in each of these five Spanish-speaking American families is an Ashkenazic Jew who carried *blm*^{Ash}. Very few Ashkenazic Jews settled in the southwestern United States, Mexico, or El Salvador prior to the 1880s, and most present-day descendants of such Ashkenazic Jews would be expected to consider themselves Ashkenazic (Rochlin and Rochlin 1986; Barnavi 1992). Two of the five families were able to provide reliable information concerning their recent generations, and there was no mention of Ashkenazic ancestry. For these reasons, we do not favor the idea of a recent Ashkenazic ancestor for the five families.

Could Spanish American *blm*^{Ash} have come from an Ashkenazic Jew who immigrated either to Spain or to the Spanish colonies during a preceding century? Answering this question depends on knowing when and where the *blm*^{Ash} founder effect occurred in the Ashkenazic Jewish population. This population began in medieval Europe during the Carolingian period; it grew in number, from ~5,000 at the end of the first millennium, to 20,000, at the end of the 11th century; and it was forced to move, in piecemeal fashion, from England, northern France, and the Rhineland during the 13th and 14th centuries. Many moved to eastern Europe during that period, thereby establishing Polish Jewry in the areas that presently are Poland, Lithuania, Belarus, and Ukraine. The *blm*^{Ash} mutation is increased in frequency in Jewish persons who trace their ancestry to these eastern European regions (German et al. 1977; Li et al. 1998); however, the event that led to the relatively increased frequency of *blm*^{Ash} in the Ashkenazim cannot be dated with certainty to either their eastward migration or the millennial formation of the Ashkenazic population in western Europe. It is therefore difficult to know whether *blm*^{Ash} came to the Americas via eastern Europe, whether Ashkenazic admixture with the Sephardic population prior to the establishment of Polish Jewry could have brought *blm*^{Ash} from northern Europe to Spain, or whether, in the absence of gene flow from the Ashkenazic population, the *blm*^{Ash} mutation was present in the Sephardic population in Spain.

All of these explanations are possible. After the Expulsion Decree made by Ferdinand and Isabella in 1492, many Sephardic Jews migrated to parts of the New World that were held by Spain. Eventually, however, the Inquisition became active in repressing Judaism there, as it had in Spain (Gerber 1992). Thus, it is conceivable that a 16th- or 17th-century Sephardic immigrant to the New World who had converted to Christianity and who carried *blm*^{Ash} could have been the ancestor of Spanish American Christians carrying *blm*^{Ash} chromosomes today. A similar explanation could be given for the founder effect that has been detected in persons of Spanish ancestry who have Laron syndrome and who are now living in Ecuador, all of whom carry the E180 splice mutation (Berg et al. 1994). The E180 splice mutation was also found in an Israeli Jew with Moroccan ancestry, suggesting a Sephardic ancestor to both Ecuadoran and Moroccan persons who carry the E180 splice mutation. In the example from BS, the Sephardic Jew who brought *blm*^{Ash} to the New World could have inherited *blm*^{Ash}

from an Ashkenazic Jew in his ancestry, but, alternatively, he could have inherited *blm*^{Ash} from a Jewish person who was ancestral to both the Ashkenazic and Sephardic populations.

Our finding of *blm*^{Ash} in the father of 107(MyAsa), a Bulgarian Sephardic Jew, also could be accounted for by either of two explanations given above; that is, it could be due to either Ashkenazic-Sephardic admixture during the years of the Ottoman Empire or to the massive immigration of Sephardic Jews to Turkey during the 16th century.

In summary, screening for *blm*^{Ash} in families ascertained through BS has uncovered a fascinating historical-genetic mystery. The *blm*^{Ash} mutation, common among persons of Ashkenazic ancestry, has been found to be segregating in Spanish-speaking Christian BS families who for many generations have dwelt in the southwestern United States, Mexico, or El Salvador, at least some of whom can trace their ancestry to Spain. *blm*^{Ash} was not detected in any other non-Jewish population. Many different historical events could explain this unexpected observation. What can be said with certainty is that the *blm*^{Ash} mutation is present in these two different populations as a result of two independent founder effects. The results underscore both the complexity of historical events that surround the formation of different human populations and the effects of that complexity on present-day genetic studies. They also emphasize the central role of migration and founder effect in the genetics of human populations.

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