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Electronic-Database Information

URL for data in this article is as follows:

Hereditary Hearing Loss home page, http://dnalab-www.uia.ac.be/dnalab/hhh (for loci and markers)

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Prevalence of Bloom Syndrome Heterozygotes among Ashkenazi Jews

To the Editor:

Bloom syndrome (MIM 210900) is a condition of intrauterine and postnatal growth failure, facial erythema, immunodeficiency, and early malignancies (German 1995). Death from malignancy typically occurs in the second or third decade (German 1997). At the cellular level, mutations in both alleles of the Bloom syndrome gene (*BLM*) lead to chromosomal breakage, an excess number of somatic mutations, and an observed increase in the frequency of sister chromatid exchange in cultured cells (German et al. 1996). Among 28 of 29 Ashkenazi Jewish individuals, a single, noncomplementing mutation has been observed (Ellis et al. 1995). This was shown to be a deletion of 6 bp, followed by insertion of 7 bp, leading to a frameshift with premature termination of the encoded gene product (Ellis et al. 1995). The finding of linkage disequilibrium of this mutation with neighboring DNA markers demonstrated that this unusual mutation had a single genetic origin in the Ashkenazi Jewish population ~400–500 years ago (Ellis et al. 1994). A 1977 survey of Israeli patients with Bloom syndrome suggested that 1 in 110 Ashkenazi Jews was a heterozygote for a mutated *BLM* gene (German et al. 1977).

A number of autosomal recessive conditions are known to occur with increased frequency among Ashkenazi Jews, including Tay-Sachs disease, cystic fibrosis, Gaucher disease, Canavan disease, Fanconi anemia complementation group C, Niemann-Pick disease, familial dysautonomia, and Bloom syndrome (Motulsky 1995). Early success of Tay-Sachs carrier-screening programs has led to increased interest in screening for other prevalent disorders, and as the genetic basis for these conditions is identified, the new information is used to develop carrier-screening tests (Eng et al. 1997; Kronn et al. 1998). The recent identification of the gene for Bloom syndrome provided an opportunity to determine the frequency of heterozygotes in the Ashkenazi Jewish pop-

ulation and thus the practicality of offering heterozygote testing for this condition (Ellis et al. 1995).

The present study was undertaken to determine the frequency of the *BLM* 6bp del/7bp ins mutation (BLM^{Ash}) in a group of Ashkenazi Jews, unselected for personal or family history of Bloom syndrome. Patient samples were collected as part of a carrier-screening program for Tay-Sachs, Gaucher, and Canavan diseases and cystic fibrosis. Eastern European Jewish ancestry was confirmed by the subjects prior to enrollment in the testing program. They also filled out a questionnaire checking for a family history of genetic diseases, including Bloom syndrome, and none of the patients included in this study indicated any family history of Bloom syndrome. As required by New York State law, patients provided written informed consent for the tests that they requested. In addition, they provided written consent indicating their willingness to participate in a research program to determine the frequency of other disease-susceptibility genes, for which the identity of their DNA samples would be kept anonymous. This protocol was approved by the institutional board of research associates at New York University Medical Center.

To design primers that would enable the amplification of the region of interest from genomic DNA, we amplified the upstream intron for subsequent automated DNA sequencing by using the Gene Walker Kit (Clontech). A sense primer in the intron between exons 9 and 10 (5′-CCACCACGCCCTGCCTGAGTTATGCTTA-3′) and an antisense primer in exon 10 (5′-TCTGGAGTGACATATAGAAGTTTTATGATTGGGTCTTTTT-3′) were designed, to amplify a 305-bp fragment encompassing the mutation site. The identity of the amplified fragment was confirmed by DNA sequencing (Genbank cDNA sequence accession number U39817), and the sequence of the BLM^{Ash} mutation was similarly confirmed by use of the control cell lines GM03403 and GM09960 (National Institute of General Medical Science [NIGMS] Human Genetic Mutant Cell Repository).

Genomic DNA was extracted by standard techniques. The region flanking the BLM^{Ash} mutation was amplified by PCR by means of a hot-start procedure performed with a Hybaid Omnigene themocycler with the following cycle conditions: 1 min at 94°C, 1 min at 55°C, and 1 min at 72°C for 35 cycles, with an additional extension at 72°C for 10 minutes. Mutations were then screened by Southern blot analysis of the amplified fragment and chemiluminescent detection (ECL Kit, Amersham) of the mutant and wild-type alleles with the following allele-specific oligonucleotide probes: mutant probe: 5′-ACATTAGATTCCAGGT-3′, wild-type probe: 5′-TACATATCTGACAGGT-3′.

The mutation was observed in 5 of 1,155 individuals, yielding a frequency of 1/231 (95% CI 1/123–1/1848). The confidence interval suggests that the previously estimated frequency for heterozygotes in the Israeli Ashkenazi Jewish population may have been slightly high and is consistent with an absence of heterozygote advantage for carriers of one copy of the mutant allele (German et al. 1996). The frequency of heterozygotes for other autosomal recessive conditions within our panel, including Tay-Sachs (1/28); cystic fibrosis (1/25); Gaucher disease (1/15); the *BRCA2* mutant allele, 6174delT (1/106); Canavan disease (1/41); and Fanconi anemia complementation group C (1/116; authors' unpublished data), have been validated in other studies, suggesting that the test panel is representative of the Ashkenazi Jewish population (Abeliovich et al. 1992, 1996; Beutler et al. 1993; Kaback et al. 1993; Verlander et al. 1995; Eng et al. 1997; Kronn et al. 1998). Just as for these other mutant alleles, we believe that genetic drift is a sufficient explanation to account for the frequency of the BLM^{Ash} mutation in this population group.

Tay-Sachs disease carrier testing is the paradigm for genetic screening in the Ashkenazi Jewish population. It has been widely accepted, with nearly 1 million people tested worldwide as of 1992 (Kaback et al. 1993). In recent years, people participating in carrier-screening programs have elected to undergo screening for cystic fibrosis and Gaucher disease as well as for Tay-Sachs disease (Eng et al. 1997; Kronn et al. 1998). Recent availability of testing for Canavan disease, a severe neurodegenerative disorder, has led to inclusion of this condition in heterozygote screening programs (Kronn et al. 1995). In these screening programs, patient interest in specific tests has paralleled disease morbidity more closely than carrier frequency, with screening for the most prevalent disease (Gaucher disease: 1/15) chosen the least frequently (Eng et al. 1997; Kronn et al. 1998). Consistent with its high morbidity and the ability of mutational analysis to identify a high proportion of carriers in the Ashkenazi population (97%), the American College of Obstetricians and Gynecologists (1998) recommended carrier screening be offered, ideally, prior to conception to all Ashkenazi couples on a voluntary basis with proper informed consent, despite its lower carrier frequency (1/41). Mutational analysis for Bloom syndrome meets many of the previously defined criteria of Tay-Sachs disease heterozygote-detection programs (Kaback et al. 1977) and could be used for screening in this population, despite the fact that the carrier frequency is one-fifth that of Canavan disease. The availability of multiplex genetic screening could contain costs and thus lead to inclusion of Bloom syndrome in heterozygote screening programs for Ashkenazi Jews.

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

Genbank, http://www.ncbi.nlm.nih.gov/Web/Genbank (for Bloom syndrome cDNA sequence)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for Bloom syndrome [MIM 210900])

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Optimal Ascertainment Strategies to Detect Linkage to Common Disease Alleles

To the Editor:

The genetic dissection of complex diseases is of great current interest. The complexity of the task has led to serious discussion regarding competing strategies for data collection and analysis. In a previous issue of the *Journal,* Badner et al. (1998) contended that extended densely affected pedigrees (multiplex pedigrees with many affected individuals) are of little benefit for detection of linkage to complex traits such as bipolar disorder (a common psychiatric disorder of complex etiology). They state that such pedigrees are no more powerful than nuclear families when the susceptibility allele is common, and there may be loss of power in the collection of pedigrees with many affected individuals. Hence, they voice concern over pedigrees collected by others for linkage analysis of bipolar disorder (Egeland et al. 1987; Baron et al. 1994). However, there is merit to a broader perspective on this important problem.