

A Population-Genetic Test of Founder Effects and Implications for Ashkenazi Jewish Diseases

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A founder effect can account for the presence of an allele at an unusually high frequency in an isolated population if the allele is selectively neutral and if all copies are identical by descent with a copy that either was carried by a founder individual or arose by mutation later. Here, a statistical test of both aspects of the founder-effect hypothesis is developed. The test is performed by a modified version of a program that implements the Slatkin-Bertorelle test of neutrality. The test is applied to several disease-associated alleles found predominantly in Ashkenazi Jews. Despite considerable uncertainty about the demographic history of Ashkenazi Jews and their ancestors, available genetic data are consistent with a founder effect resulting from a severe bottleneck in population size between A.D. 1100 and A.D. 1400 and an earlier bottleneck in A.D. 75, at the beginning of the Jewish Diaspora. The relatively high frequency of alleles causing four different lysosomal storage disorders, including Tay-Sachs disease and Gaucher disease, can be accounted for if the disease-associated alleles are recessive in their effects on reproductive fitness.

Introduction

A founder effect can result either from a true founder event (i.e., the establishment of a new population from individuals derived from a much larger population) or from an extreme reduction in population size (i.e., a bottleneck in size). In either case, alleles present in one copy immediately after the founder event or bottleneck may be found at a much higher frequency than they were previously and can reach even higher frequencies because of strong genetic drift occurring while the population is still small.

Founder effects have been used to explain the presence of high-frequency Mendelian diseases in many isolated populations (Thompson and Neel 1996; Vogel and Motulsky 1996). Even though disease-associated alleles are probably not neutral, even slightly deleterious alleles may increase in frequency because of founder effects. Both the founder effect and heterozygote advantage have been invoked to account for several disease-associated alleles in the Ashkenazi Jewish (AJ) population (Risch 2001). The hypothesis of heterozygote advantage is supported primarily by the fact that four of the diseases—Tay-Sachs disease, Gaucher disease, mucopolysaccharidosis type IV, and Niemann-Pick disease—are results of defects in sphingolipid storage (Zlotogora et al. 1988),

defects that are quite rare in most other populations. This unusual concentration of lipid-storage diseases (LSDs) suggests that selection has favored heterozygous carriers of alleles affecting lipid metabolism and storage, possibly because of resistance to tuberculosis (Motulsky 1995). Further support for heterozygote advantage comes from the discovery that more than one disease-associated allele has been found to cause LSDs in Ashkenazi Jews, the logic being that it is unlikely that more than one allele at a locus would increase in frequency only because of a founder effect (Diamond 1994; Motulsky 1995). Selection favoring heterozygous carriers would, however, select for any alleles conferring that advantage. Rotter and Diamond (1987) argue also that the wide geographic range of AJ disease-associated alleles is evidence of heterozygote advantage.

Until the 1990s, heterozygote advantage was the favored explanation for LSDs in the AJ population. More recently, however, the founder-effect hypothesis has gained acceptance, because several studies have suggested that disease-associated alleles are identical by descent and arose relatively recently (Risch et al. 1995*b*; Goldstein et al. 1999; Niell et al. 2003; Frisch et al. 2004). Risch et al. (2003) recently compiled available data and argued that founder effects rather than heterozygote advantage accounted for all LSDs in the AJ population. Risch et al. (2003) showed that there was no difference between LSDs and non-lipid-storage diseases (NLSDs) in (*a*) estimated allele ages, (*b*) numbers of disease-associated alleles, and (*c*) inferred geographic origins of alleles. They then argued that heterozygote advantage could be ruled out for two reasons. First, some NLSDs (idiopathic torsion dystonia [ITY], breast

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cancer type 1, and breast cancer type 2) are caused by dominant alleles, making heterozygote advantage unlikely. Second, similarity of the two groups can be accounted for by selection only if all disease-associated alleles benefited heterozygous carriers, which is unlikely because the NLSDs include a wide variety of disorders, including cancers, blood diseases, and neuropathies.

Risch et al. (2003) concluded further that there is evidence of three founder events: one >100 generations ago, when the Jewish population of the Middle East was founded; the second ~50 generations ago, when the Jewish populations of central Europe were founded; and the third ~12 generations ago, when the Lithuanian Jewish population was founded (under the assumption of 25 years per generation).

In this article, I introduce a statistical test of the founder-effect hypothesis by adding to a test of neutrality a test of whether an allele either was present in a single copy at the time of a hypothesized founder event or arose by mutation afterwards. The new test is applied to alleles causing Mendelian diseases in Ashkenazi Jews. Although current uncertainty about the early demographic history of the AJ population will not allow a strong conclusion to be reached, the results show that the available genetic data for AJ disease alleles are consistent with the founder-effect hypothesis if plausible assumptions are made about early AJ population sizes. This analysis cannot prove that there was no heterozygote advantage, but it does show that selection is not needed to account for current information about AJ Mendelian diseases. The test also shows, however, that alleles with frequencies >1% could not be traced to the two recent founder events discussed by Risch et al. (2003). For those alleles, the important founder event was at the beginning of the Jewish Diaspora, after the destruction of the Second Temple in A.D. 70.

Statistical Test

To test the founder-effect hypothesis, two separate tests are needed. The first is a test that determines whether there is more linkage disequilibrium (LD) with a linked marker allele than is consistent with neutrality. The neutrality test used here is equivalent to the one introduced by Slatkin and Bertorelle (2001) and is similar to the that of Thompson and Neel (1997). The test assumes that the locus of interest is effectively diallelic, with allele A being associated with the presence of a disease and the alternative allele, a, representing all other variants at this locus. The A/a locus is linked to a diallelic marker locus with alleles M and m. The information needed for the test is (a) the history of population sizes; (b) i , the number of A-bearing chromosomes in a sample of n chromosomes; (c) x , the population frequency of A; and (d) j_o , the number of A-bearing chromosomes that carry

the marker allele presumed to have been on the ancestral A-bearing chromosome. Necessarily, $j_o \leq i$, and, if $j_o = i$, there is perfect LD between the marker locus and A, meaning that Lewontin's (1964) $D' = 1$. Although the identification of the ancestral marker allele can be difficult if two or more alleles are relatively common on A-bearing chromosomes, most applications, including all in this article, are to cases in which j_o is large enough that it is clear which allele was ancestral. In general, x is estimated in very large population surveys and possibly in pooled clinical data, whereas i and j_o are obtained from smaller studies performed to either map A or understand its history.

The test of neutrality is performed by simulating the neutral coalescent with $n = i/x$ tips in a population of variable size and then examining each node to determine whether it has i descendants. If it does, then a mutation on the lineage leading to that node could give rise to an allele in i copies (see fig. 1). For each such node, called an " i -node," the program computes the probability that j nonrecombinant chromosomes are found. That probability is weighted by the length of the ancestral branch, denoted by w in figure 1, and accumulated over numerous replicates to estimate $P(j)$, the overall probability of finding j nonrecombinant chromosomes in a sample of i A-bearing chromosomes ($\sum_{j=0}^i P(j) = 1$). A one-tailed test of neutrality is obtained by finding the net probability that $j \geq j_o$, where j_o is the observed number of nonrecombinants. If

$$\Pr(j \geq j_o) = \sum_{j=j_o}^i \Pr(j) < \alpha,$$

then the data reject neutrality of A at significance level α . This tests whether A is too old to be consistent with the observed number of nonrecombinants. That is the appropriate test if the concern is with testing for positive selection on heterozygous carriers of a low-frequency allele, because heterozygote advantage, with or without lower fitnesses of homozygous individuals, tends to reduce allele age (author's unpublished numerical results). If the concern is whether A is younger than expected under neutrality, the appropriate test would be of the other tail of $P(j)$. A two-tailed test could be used as well.

To test for a founder effect at a time t_F in the past, the program computes and accumulates the numbers of lineages carrying A at t_F for each i -node. As illustrated in figure 1, the number, m , of ancestral lineages at t_F depends on t_F and t_2 , the time of the most recent common ancestor of the intra-allelic genealogy. There are three possibilities. If $t_2 \geq t_F$, then $m \geq 2$, and the program records m . If $t_2 \leq t_F \leq t_2 + w$, then, with probability $p = (t_F - t_2)/w$, A arose by mutation on the single lineage present after the population was founded,

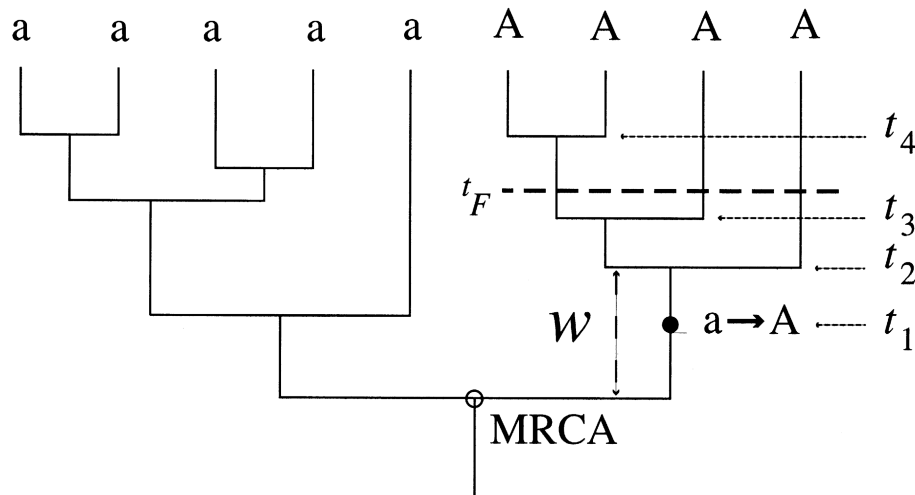


Figure 1 Illustration of an intra-allelic genealogy for the case with $i = 4$. t_1 is the age of the allele A , t_2 is the time of the most recent common ancestor (MRCA) of copies of A in the sample, and w is the length of branch on which A arose by mutation.

and, with probability $1 - p$, it arose before the population was founded and was present in one lineage at t_F . In the latter case, the program records that $m = 1$ weighted by $1 - p$. In the former case, the program records that $m = 0$ (meaning that the allele arose by mutation after the population was founded) weighted by p . If $t_2 + w \leq t_F$, the program records that $m = 0$. The outcome for each i -node analyzed is weighted both by w —because that is the time during which A could have arisen by mutation—and by $P(j_o)$. By averaging over a large number of replicates, the program estimates F_m , the probability that $m = 0 \dots i$ lineages carrying A were present at t_F .

The data are consistent with the founder effect if $m = 0$ or 1. A high probability of two or more founding lineages is inconsistent with the founder-effect hypothesis, because it implies that the allele was present at a substantial frequency at the time the population was founded. In the results, the probability that $m = 0$ or 1, $\Pr(m \leq 1) = F_0 + F_1$, is reported. If $\Pr(m \leq 1) < \alpha$, then a founder event at t_F is rejected with probability α .

In addition to estimating the number of lineages at the time of population founding, the program computes the posterior distribution of age. The posterior distribution takes account of the allele frequency, the history of population sizes, and the extent of LD with the linked marker. From the posterior distribution, averages of \bar{t}_1 and \bar{t}_2 and the associated 95% credible sets are estimated.

The program allows for arbitrary demographic histories. The current effective population size, $N_{e,0}$, as well as population sizes $N_{e,1}, \dots, N_{e,K}$ at times T_1, T_2, \dots, T_K , are specified, and the population is assumed to grow

or decline exponentially at rate $r_k = \log(N_{e,k+1}/N_{e,k})/(T_{k+1} - T_k)$ between T_k and T_{k+1} , where $T_0 = 0$. The growth rate before T_k must also be specified.

Copies of this computer program are freely available at the Slatkin Laboratory Genetics Software Web site.

Applications to AJ Diseases

History of AJ Population Sizes

To apply the founder-effect test to AJ diseases, estimates of past effective population sizes are needed. At present, Ashkenazi Jews comprise ~80% of the 13–14 million Jews in the world, with most living in the United States and Israel (Motulsky 1995). Population sizes, especially before A.D. 1500, are not known accurately, and the historical record allows only rough estimates to be made.

Ashkenazi Jews are recognized as forming distinct branch of Judaism in the 13th and 14th centuries in present-day Poland, Lithuania, Belarus, the Ukraine, and Russia (Mourant et al. 1978). The ancestors of Ashkenazi Jews descended largely from Jewish populations in present-day Germany (Weinryb 1972). Before the beginning of the Crusades in A.D. 1096, Jewish populations in Germany, France, and England had grown and thrived and are estimated to have numbered at least 100,000 individuals (Engleman 1960; Risch 2001). With the Crusades began a long period of attacks on Jews and the wholesale destruction of Jewish communities, culminating with their expulsion from present-day England, France, and Germany by A.D. ~1300. Jewish population sizes declined further in A.D. 1347 and 1348 because of the Black Death, during which mortality rates are esti-

mated to have been as high as 50%; further mortality resulted from attacks stemming from the belief that Jews were responsible for the Black Death in non-Jewish communities (Fraikor 1977).

By A.D. 1500, the AJ population size in eastern Europe is estimated to have been 10,000–20,000. There followed a period of sustained population growth at a rate of ~40% per generation until A.D. 1900, interrupted only by the Cossack massacres in 1648, which resulted in the death of ~25% of the AJ population (Weinryb 1972; Risch et al. 1995a). To account for all available information in the context of a relatively simple model, I assumed the population sizes given in table 1. The population size in A.D. 2000 is based on Motulsky's (1995) estimate. Sizes from A.D. 1500 to 1900 are from Risch (1995a). The size in A.D. 1096 is based on estimates of Engleman (1960) and Risch (2001). The size assumed at A.D. 70 (1,000,000) is a conservative estimate based on information presented by Barnavi (1992). The actual size and rate of exponential growth assumed before A.D. 70 ($r = 0.1$ per generation) are not important for considering later founder events. Alleles that arose well before A.D. 70 and that were carried by several individuals ancestral to the AJ population in A.D. 70 were probably present at relatively high frequencies in the Jewish population as a whole and would therefore likely be present in other modern Jewish populations as well. To be restricted to Ashkenazi Jews, alleles had to have been carried by a single founder chromosome or have arisen by mutation after A.D. 70.

There were at least two important bottlenecks in population size that could have led to a founder effect. The first is at the beginning of the Diaspora in A.D. 70. Although the Jewish population in present-day Israel and surrounding countries was large before A.D. 70, only small numbers made their way to the areas in western Europe in which ancestors of Ashkenazi Jews resided until the end of the 11th century. Historical records provide no information about the size of the founder group or groups. I used a range of values (150, 600, and 3,000) of N_0 , the assumed size in A.D. 70, to model founder events of different intensities. Another potential founder event occurred because of the persecutions during the Crusades and the mortality associated with the Black Death. I used a range of values of N_1 in 1348 (600, 3,000, and 6,000) as the population size after the Black Death.

The intensity of genetic drift is determined by the effective population size, not the census size. With fertility and mortality rates typical of humans, the effective size is ~1/3 the census size (Hill 1972). Ashkenazi Jews and their ancestors never comprised a randomly mating population but were instead dispersed over a wide geographic area. However, there was sufficient movement among AJ subpopulations that little genetic substructure

Table 1**Population Sizes of Ashkenazi Jews and Their Ancestors Assumed in the Simulation Program**

Year (A.D.)	r^a	N_T^b
50	78	1,000,000 ^c
70	77.2	N_0^d
1096	36.16	150,000
1348	26.08	N_1^e
1500	20	15,000 ^f
1648	14.08	200,000 ^f
1667	13.32	160,000 ^f
1765	9.4	750,000 ^f
1900	4	6,000,000 ^f
2000	0	10,500,000 ^g

^a Generations before A.D. 2000, under the assumption of 25 years per generation.

^b The effective population size was assumed to be 1/3 of these sizes.

^c Based on figure 1 of Barnavi (1992).

^d Allowed to vary; values of 150, 600, and 3,000 were used.

^e Allowed to vary; values of 600, 3,000, and 6,000 were used.

^f From Risch et al. (1995a).

^g From Motulsky (1995).

developed (Risch 2001; Risch et al. 2003). In general, population subdivision increases effective population size, but, unless dispersal is greatly restricted, the increase is minor (Nordborg and Krone 2002).

A potential complicating factor in relating census to effective population size is that fertility in AJ populations was not evenly distributed among social and economic classes (Motulsky 1979; Risch et al. 1995a, 1995b). Wealthier and better-educated families had more offspring. Risch et al. (1995a, 1995b) have argued that this social stratification led to greatly reduced effective size and created the opportunity for extreme founder effects. This argument was challenged by Zoosmann-Diskin (1995), who noted that, although differences in fertility among social classes existed in AJ populations, the vast majority of individuals were in the lower social classes, so much of the high rate of population growth had to be attributable to them. It seems difficult to account for a population growth rate of ~40% per generation with fertility excess only in wealthy and educated families.

Gaucher Disease

Type I Gaucher disease (MIM #230800) is a recessive nonlethal disorder caused by mutations at the glucocerebrosidase (GBA) locus on chromosome 1q21. The most common causative allele in the AJ population is N370S (also denoted as 1226G). Beutler et al. (1993) estimated the frequency of N370S in the AJ population to be

0.032 ± 0.004. Diaz et al. (2000) found extensive LD between N370S and several closely linked marker loci. I will present the results from the analysis of one marker locus, D1S2464, in detail and briefly summarize the results for two others. In terms of the notation here, the genetic data for D1S2624 (with allele 5 ancestral) are as follows: $i = 268$, $j_o = 163$, and p_N , the frequency of the ancestral marker on chromosomes not carrying the disease allele, is 0.205 (table 3 of Diaz et al. 2000).

The value of θ , the recombination rate, is not known precisely. Values used by Diaz et al. (2000) appear to be somewhat too large. For D1S2624, Diaz et al. (2000 [their table 4]) reported values ranging from 0.009 to 0.036, with a median of 0.015. On the basis of the July 2003 build of the human genome (available at the UCSC Human Genome Browser Web site), D1S2624 is ~1.4 Mb from GBA, and, according to the TSC SNP Linkage Map (Matisse et al. 2003; TSC SNP Linkage Map Web site), the average recombination rate in this region is ~0.5 cM/Mb, suggesting that $\theta = 0.007$ is a better estimate.

For all combinations of demographic parameter values considered, neutrality could not be rejected, but a recent founder event ($t_F = 26$, A.D. 1350) is rejected in all cases (table 2). For all combinations of N_0 and N_1 , numerous lineages carrying N370S were present at that time (fig. 2). In contrast, a founder event in A.D. 70 ($t_F = 77.2$) was possible for all combinations of N_0 and N_1 , although it was increasingly unlikely if neither N_0 nor N_1 was <3,000 (table 2). Similar results were obtained with $\theta = 0.014$.

These results also show that it is difficult to estimate the age of N370S with any confidence. Table 2 reports the expected time of the most recent common ancestor, \bar{t}_2 , and the 95% credible set, both based on the posterior distribution. The time t_2 , called the “coalescence time” by Risch et al. (2003), differs from t_1 , the time at which the allele arose by mutation (see fig. 1).

Similar results are found using two other marker loci. For D1S1600 (with allele 2 ancestral), $i = 258$, $j_o = 124$, and $p_N = 0.067$. D1S1600 is ~2.6 Mb from GBA, indicating $\theta = 0.013$. For no combination of N_0 and N_1 was neutrality rejected, and a founder event at $t_F = 77.2$ was possible under the same conditions as indicated by D1S2464. Similar results were obtained for D1S1595, considered by both Diaz et al. (2000) and Colombo (2000).

The other disease-associated mutation in AJ populations is 84GG, which has a frequency of ~0.002 (Beutler et al. 1993). By use of the marker locus D1S2464 with allele 4 ancestral, $i = 32$, $j_o = 29$, and $p_N = 0.373$ (Diaz et al. 2000). Neutrality was not rejected for any combination of N_0 and N_1 . The difference from the results for N370S is that, for $N_1 = 600$, the data are consistent with a founder event in A.D. 1348. Because 84GG is

Table 2

Results of Analyzing Data for N370S at GBA and the Linked Marker Locus D1S2464

POPULATION SIZE ^a		Pr($j \geq j_o$)	\bar{t}_2^b	Pr($m \leq 1$)	Pr($m \leq 1$)
N_0	N_1			When $t_F = 26$	When $t_F = 77.2$
150	600	.72	104 (26, 184)	0	.95
150	3,000	.73	113 (55, 188)	0	.95
150	6,000	.75	111 (61, 187)	0	.95
600	600	.66	110 (26, 186)	0	.81
600	3,000	.64	116 (64, 199)	0	.75
600	6,000	.65	118 (65, 197)	0	.74
3,000	600	.59	111 (26, 190)	0	.40
3,000	3,000	.34	143 (67, 188)	0	.10
3,000	6,000	.31	147 (74, 192)	0	.05

NOTE.—Results for each combination of N_0 and N_1 are based on weighted averages of 10,000 replicates. Genetic parameters are $x = .032$, $i = 268$, $j_o = 163$, $p_N = .205$, and $\theta = .007$.

^a N_0 is the assumed population size in A.D. 70 ($t = 77.2$), and N_1 is the assumed size in A.D. 1648 ($t = 26.08$).

^b Numbers in parentheses are the bounds of the 95% credible set based on the posterior distribution of t_2 .

found at a much lower frequency than N370S, it could have attained its current frequency under drift alone if it arose more recently.

Mucopolipidosis Type IV

Mucopolipidosis type IV (MLIV [MIM #252650]) is an LSD caused by mutations at the MCOLN1 locus on chromosome 19p13.2-13.3. The most common disease-associated mutation in Ashkenazi Jews is an A→G transition in the acceptor splice site of the third intron (IVS3-1A→G) (Bargal et al. 2000). Slaugenhaupt et al. (1999) provided haplotype data for several linked marker loci. Here, I use the marker D19S406, which is ~180 kb from MCOLN1. In this genomic region, the sex-averaged recombination rate is ~2.5 cM/Mb (Matisse et al. 2003), indicating $\theta = 0.0045$. From figure 2 of Slaugenhaupt et al. (1999), $i = 39$, $j_o = 38$, and $x = 0.0036$. Slaugenhaupt et al. (1999) did not genotype chromosomes not carrying IVS3-1A→G in the AJ population (S. Slaugenhaupt, personal communication), so I used a range of values of p_N (0.1, 0.3, and 0.5). For all combinations of parameter values, neutrality was not rejected, and a founder event at A.D. 1348 was possible.

Adenomatous Polyposis Coli (APC)

The APC locus (MIM #175100) has an allele, I1307K (a T→A transition at nucleotide position 3920), that increases the relative risk of colorectal cancer by a factor of 1.5–2 (Niell et al. 2003). This allele presents an unusual opportunity to test the founder-effect hypothesis, because it has a high frequency in the AJ population, $x = 0.06$, and it has a frequency >0.01 in Sephardi Jews.

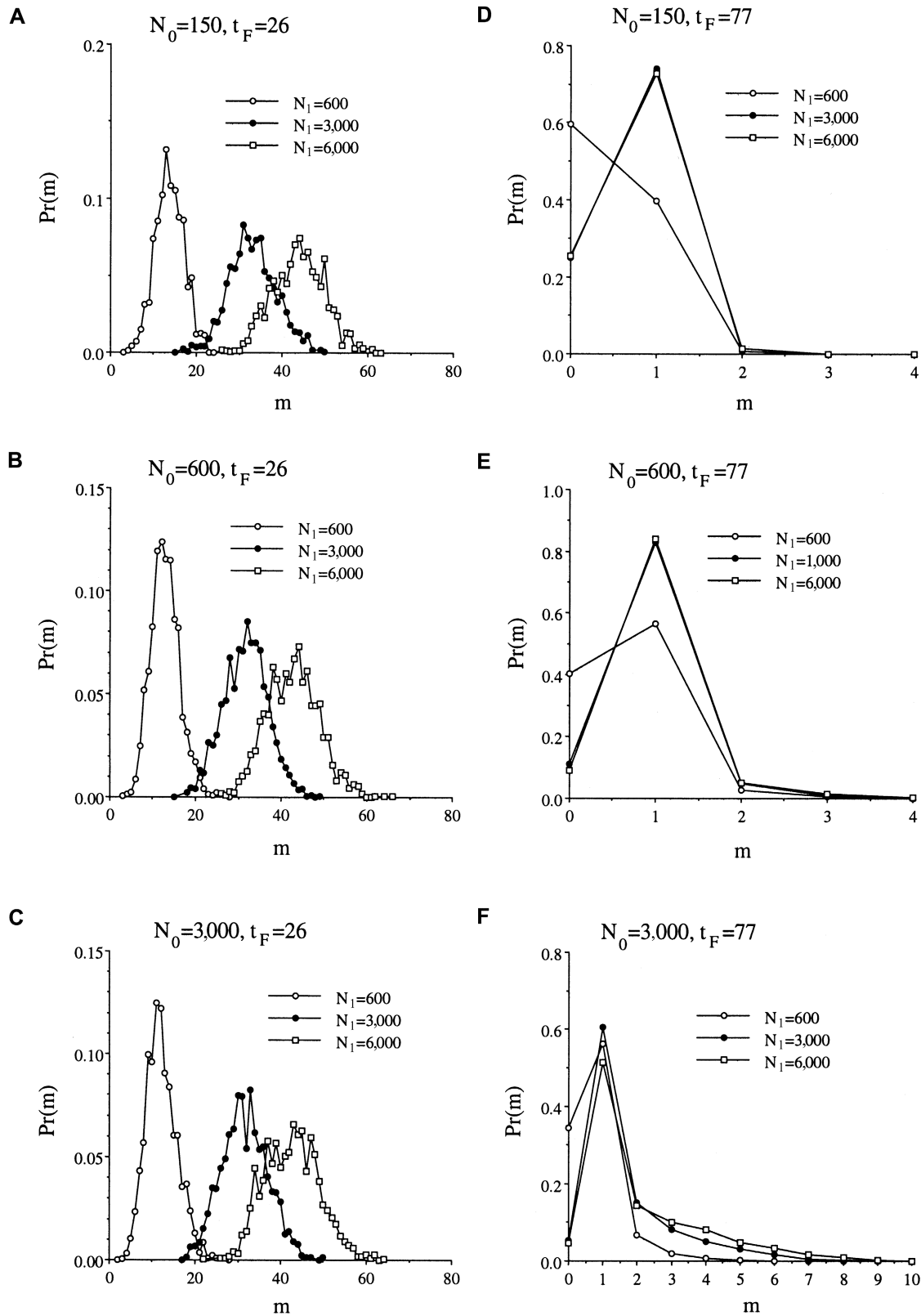


Figure 2 Estimated posterior probability distributions of the number of ancestral lineages, m , carrying N370S at GBA (which causes Gaucher disease) for the nine combinations of N_0 (the population size at A.D. 70) and N_1 (the population size at A.D. 1348) and two different hypothesized times of founder events (A.D. 75 and 1350).

Niell et al. (2003) examined several closely linked marker loci and concluded from the application of the Slatkin-Bertorelle (2001) neutrality test that their data did not reject neutrality. That conclusion is confirmed for the more elaborate demographic model used here. In this case, to be consistent with the presence of this allele in the Sephardim at a significant frequency, a founder effect in the AJ population should be unlikely.

Results from the analysis of one of the linked markers, D5S135, are shown in table 3. The genetic parameters are $i = 87$, $j_o = 83$, and $p_N = 0.343$. Two values of θ were used. The first, $\theta = 0.0046$, is based on the Kosambi map function calculation, and the second is 1/2 that value, which is slightly larger than the smallest recombination rate reported in the literature (based on table 5 of Niell et al. [2003]). Neutrality is not rejected in all cases with the smaller θ , but it was rejected in some cases with the larger θ .

Table 3 shows that a founder event in A.D. 70 is likely for the smallest assumed population size, $N_0 = 150$, but, even so, there is an ~10% chance that two or more lineages carried I1307K. For $N_0 = 150$ and 600, though, the inferred average number of lineages at A.D. 75 is small, suggesting that the allele had a low frequency before the founder event. Only if $N_0 = 3,000$ is the average higher.

These results, combined with those for N370S for Gaucher disease, weakly constrain the possible demographic histories consistent with both data sets. N370S is rare in other Jewish populations and was probably introduced to them by later admixture with Ashkenazi Jews (Risch 2001). On the basis of table 2, data for N370S are consistent with the founder-effect hypothesis for any combination of N_0 and N_1 , but a founder effect is least likely if $N_0 = 3,000$ and $N_1 = 3,000$ or 6,000. If I1307K at APC is present in Sephardi Jews because

it originated before A.D. 70 and was carried by Sephardi ancestors, then results for $N_0 = 3,000$ and $N_1 = 600$ are most consistent with these two data sets considered together. The demographic model cannot be taken literally, but these results suggest that there was a severe reduction in population size during the period between A.D. 1100 and 1400 and a less severe reduction in size after A.D. 70. A severe bottleneck in A.D. 70 or additional bottlenecks between A.D. 70 and 1348 would make a founder effect in Ashkenazi Jews more likely and, hence, would make it more difficult for I1307K at APC not to have undergone a founder effect in A.D. 70.

Other NLSDs

Several other NLSDs are caused by alleles found only in AJ individuals. Table 4 shows results of the analysis of data from five such alleles. All of these alleles are present at lower frequencies than N370S and I1307K and, hence, are easier to fit with the founder-effect hypothesis. The results in table 4 were generated using only one demographic model, $N_0 = 3,000$ and $N_1 = 600$, but results for other combinations were similar. Neutrality cannot be rejected, and the data are consistent with a founder effect. Only for the allele in highest frequency (at DYS) is a founder effect at A.D. 1348 rejected.

Allele Age and Allele Frequency

Although the results presented here support the main conclusion of Risch et al. (2003) that founder effects are sufficient to account for AJ Mendelian diseases, they do not support the more detailed conclusions concerning the times at which the founder events took place. In fact, they contradict the claim that the alleles with frequencies >1.5% (at GBA, APC, and DYS) could have reached

Table 3
Results of Analyzing Data for I1307K at APC and the Linked Marker Locus D5S135

POPULATION SIZE ^a		RESULTS WHEN $\theta = .0046$					RESULTS WHEN $\theta = .0023$				
N_0	N_1	$\Pr(j \geq j_o)$	$\Pr(m \leq 1)$ When $t_F = 26$	$\Pr(m \leq 1)$ When $t_F = 77.2$	\bar{m}	$\Pr(j \geq j_o)$	$\Pr(m \leq 1)$ When $t_F = 26$	$\Pr(m \leq 1)$ When $t_F = 77.2$	\bar{m}		
150	600	.09	0	.93	.99	.44	0	.92	1.04		
150	3,000	.03	0	.91	1.04	.28	0	.89	1.09		
150	6,000	.02	0	.92	1.04	.25	0	.89	1.09		
600	600	.08	0	.74	1.4	.41	0	.63	1.7		
600	3,000	.02	0	.61	1.9	.23	0	.49	2.4		
600	6,000	.01	0	.51	2.1	.18	0	.44	2.6		
3,000	600	.05	0	.34	3.4	.29	0	.19	4.7		
3,000	3,000	.004	0	0	9.1	.10	0	.007	10.5		
3,000	6,000	.001	0	0	10.8	.07	0	0	12.1		

NOTE.—Results for each combination of N_0 and N_1 are based on weighted averages of 10,000 replicates. Genetic parameters are $x = 0.06$, $i = 87$, $j_o = 83$, and $p_N = 0.343$.

^a N_0 is the assumed population size in A.D. 70 ($t = 77.2$), and N_1 is the assumed size in A.D. 1648 ($t = 26.08$).

those frequencies because of a founder event 40–50 generations ago. Instead, those alleles probably originated much earlier and were affected by the founder event in A.D. 70. The reason for this difference is that the method used here for estimating allele age takes explicit account of allele frequency, whereas Risch et al. (2003) and the studies cited therein use methods that estimate age only from the pattern of LD with linked markers (j_o in the notation here) and not from the allele frequency.

To determine how much information about allele age is given by j_o alone, I performed a simple forward simulation. In each replicate, a neutral allele was introduced in a single copy in a population with the history of population sizes given in table 1 (with $N_0 = 3,000$ and $N_1 = 600$). The time at which it was introduced (t_1 , the allele age) was chosen randomly from a distribution proportional to $N(t)$, because the number of targets for mutation at a locus each generation is twice the population size. The simulation generated the number of copies in each generation between $t = t_1$ generations in the past and $t = 0$ (the present) by use of a Wright-Fisher model and retained the replicate if the frequency at 0 was within a specified range. For each replicate retained, a neutral coalescent process was run backwards to generate the intra-allelic genealogy of the i copies of A in a sample. On that genealogy, a two-state Markov chain was simulated, representing the transitions from AM to Am chromosomes and the reverse, given values of θ and p_M and under the assumption that the ancestral A chromosome carried M at the marker locus. Each such replicate resulted in a value of j_o , the observed number of AM chromosomes at $t = 0$, and the value of t_2 , the time of the most recent common ancestor of the intra-allelic genealogy. Figure 3 shows the results of 1,000 replicates for parameter values chosen to mimic the N370S allele at GBA (cf. table 2 and fig. 2).

It is clear from figure 3 that a given t_2 is consistent with a wide range of values of j_o and that a given j_o is consistent with a wide range of values of t_2 . Similar

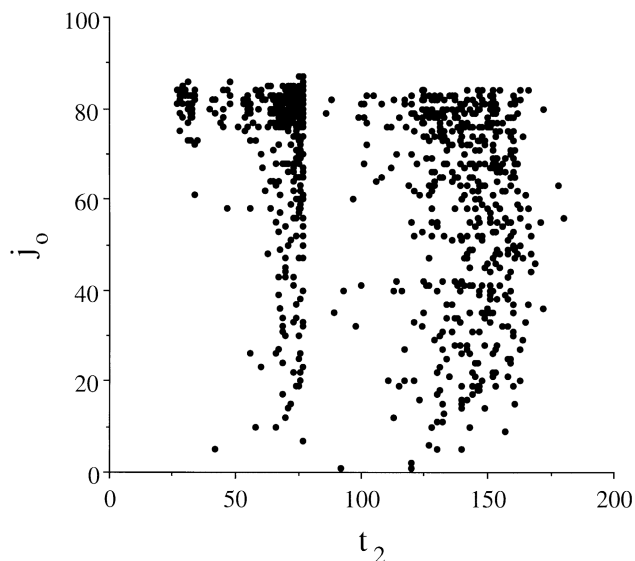


Figure 3 Scatterplot of t_2 (the coalescence time of all copies of A) and j_o (the number of nonrecombinants) generated in 1,000 replicate forward simulations of a neutral allele that was in one copy t_1 generations in the past and was found at $t = 0$ with a frequency between 0.027 and 0.037 (i.e., $x = 0.032 \pm 0.005$, which was chosen to match the frequency of N370S at GBA, 0.032). In each replicate, the allele age (t_1) was chosen randomly from a probability distribution on t in which $\Pr(t)$ is proportional to $N(t)$, where $N(t)$ is based on table 1 with $N_0 = 600$ and $N_1 = 3,000$. Parameters for A and the linked marker are the same as for N370S at GBA: $i = 268$, $j_o = 163$, $p_N = 0.205$, and $\theta = 0.007$ (cf. table 2).

results were obtained in other cases. The reason there is so much scatter is that a single recombination event early in the intra-allelic genealogy can result in multiple recombinant chromosomes, an effect similar to the well-known jackpot effect in the Luria-Delbrück model (Luria and Delbrück 1943). Under these assumptions, the correlation between j_o and t_2 is not strong enough for j_o alone to provide a reliable estimate of t_2 .

To illustrate how difficult it is for a recent founder

Table 4

Analysis of Alleles Causing NLSDs

Locus	Allele	Marker	Reference ^a	x	i	j_o	p_N	θ	$\Pr(j \geq j_o)$	$\Pr(m \leq 1)$	
										When $t_F = 26$	When $t_F = 77.2$
BRCA1	185delAG	D17S1320	Neuhausen et al. 1996	.01	15	15	.27	.005	.26	.15	.97
BLM	<i>blm</i> ^{Asb}	D15S1108	Ellis et al. 1998	.0047	52	43	.1 ^b	.00025	.98	.58	.97
DYS	2057+6T→C ^c	D9S261	Blumenfeld et al. 1999	.0158	435	403	.53	.008	.33	.02	.93
ITY1	GAG deletion ^d	ASS	Risch et al. 1995 ^b	.0005	54	47	.09	.018	.07	.98	.99
LDLR	G197del	D19S865	Durst et al. 2001	.0074	37	26	.22	.026	.21	.22	.99

NOTE.—All results are based on 10,000 replicates with $N_0 = 3,000$ and $N_1 = 600$.

^a References are to the articles from which the genetic parameters (x , i , j_o , p_N , and θ) were extracted.

^b Ancestral marker allele frequency not available. Similar results were obtained for other values of p_N .

^c Causative allele was identified and named by Anderson et al. (2001).

^d Causative allele was identified by Ozelius et al. (1997).

event to result in an allele having a relatively high frequency, I adapted Kimura's (1955) model to allow for variable population size. When this theory, which is outlined in the appendix, is used, it is possible to compute the probability that an allele that exists initially as one copy in A.D. 1348 has a frequency y at least as large as a specified frequency x . Figure 4 shows the results for two different population sizes in A.D. 1348 (200 and 1,000, corresponding to census sizes of 600 and 3,000). Even with $N_1 = 200$, there is only a very low probability (<0.02) that an allele carried by one of the 400 founder chromosomes could reach a frequency >0.015 .

Discussion and Conclusions

The founder-effect hypothesis has two components: the allele is neutral, and all copies are descended from a copy that was either carried by one of the founding individuals or arose later by mutation. The method introduced here tests both parts of this hypothesis. The tests are model-based, meaning that an explicit population-genetic model is used. Any such model is only a crude approximation of reality, but it is useful if it incorporates the most important features of the processes considered and if the conclusions are robust to violations of the underlying assumptions.

For the application to AJ Mendelian disease alleles, the genetic assumptions are that chromosomes carrying the nonancestral allele were generated by recombination of A-bearing chromosomes with non-A chromosomes and that the frequency of marker alleles on non-A chromosomes did not change. The first of these assumptions requires that recombination between A-bearing chromosomes is sufficiently infrequent that it can be ignored, which is reasonable for the low-frequency disease-associated alleles considered here. The results are not sensitive to deviations from the second assumption. Temporal variation in the background marker frequencies result in only minor changes in the results of the neutrality test (author's unpublished simulations).

The demographic assumptions for the AJ population are more problematic. Estimated population sizes after A.D. 1500 are based on historical records, but, even so, there are differences of opinion about how those records are interpreted (Risch et al. 1995a; Zoosmann-Diskin 1995). Before 1500, the historical record is meager, and only a broad outline of the history of populations ancestral to Ashkenazi Jews is known. The demographic assumptions used here allow for a bottleneck in size in A.D. 1348, after the expulsion of Jews from France and Germany and after the Black Death. The actual date of the bottleneck is not as important as the fact that the effective size decreased dramatically after the peak in size at A.D. ~1100. Varying N_1 allows investigation of bottlenecks of varying severity.

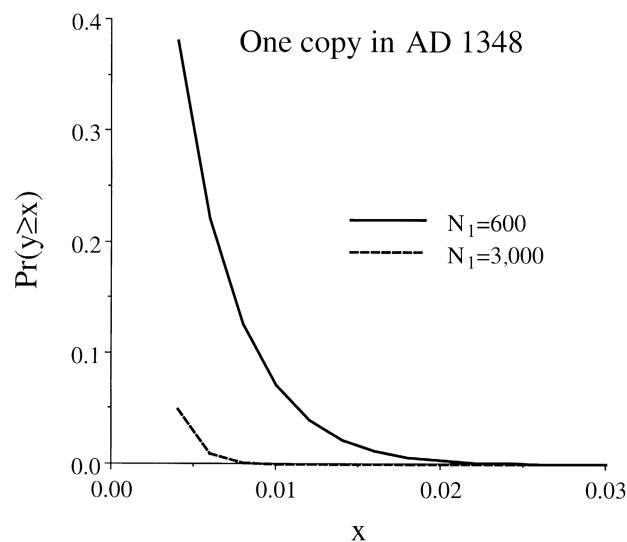


Figure 4 The probability that an allele present in one copy at $t = 0$ is still segregating and has a frequency of at least x 26.08 generations later. Calculations were made using the theory described in the appendix.

Similarly, assuming a constant exponential growth rate from a size N_0 in A.D. 70 until ~1100 is not realistic, but it embodies the idea that there was a bottleneck early in the Diaspora. If there were additional bottlenecks, as seems likely, their effects are included in N_0 , which indicates the overall potential for a founder effect between A.D. 70 and 1100. Given the absence of more-detailed historical records during this period, more-elaborate demographic assumptions are not called for.

The model assumes no population subdivision and thus ignores the fact that, until the 20th century, movement among different parts of the AJ population must have been restricted. Because the disease-associated alleles considered here are widespread in the AJ population (Risch and Tang 2003), the problem is to explain the overall allele frequency and extent of LD with linked markers, not patterns of variation among different AJ subpopulations. When considering the populationwide allele frequencies, population subdivision can be allowed for by increasing the effective population size in a coalescent model (Nordborg and Krone 2002).

Statistical Power of the Neutrality Test

Although neutrality is not rejected for the alleles considered here, the test is not expected to have much statistical power unless selection is very strong. The reason is that, roughly speaking, the prior distribution of allele age, on which the test depends, is a function primarily of $r + s$, where r is the population growth rate and s is the selective advantage of heterozygous carriers (Slatkin

2002). During the past 500 years, the AJ population has grown at a rate of ~40% per 25-year generation ($r = 0.4$). Therefore, even selection thought to be strong—say, $s = 0.1$ —will not affect the prior distribution of age by much.

I determined the power of the neutrality test by using the forward simulation described above and assuming a selective advantage to heterozygous carriers of $s = 0.1$. With parameters chosen to match I1307K at APC (see table 3), and with $N_0 = 3,000$ and $N_1 = 600$, neutrality was rejected for only 28.4% of the replicates if the allele was additive in its effect on fitness. Assuming heterozygote advantage makes little difference, because the allele frequency is so small. If homozygous individuals have a 20% lower fitness than normal homozygotes (i.e., 30% lower than heterozygotes), neutrality is rejected in 26.9% of the replicates.

The failure to reject neutrality for the alleles considered here does not provide strong evidence that they are actually neutral. But selection is not needed to account for their presence in the AJ population or the degree of LD with linked markers. A founder effect is sufficient.

Overrepresentation of LSDs

One of the strongest arguments in favor of heterozygote advantage is that alleles causing four different LSDs are found in relatively high frequency in the AJ population, despite their deleterious effects on homozygous individuals (Diamond 1994; Motulsky 1995). The analysis performed here shows that founder effects can account for the disease-associated alleles at GBA and MLIV, but it does not answer the question of why those loci and not others have alleles at relatively high frequencies in the AJ population. I suggest that alleles at the four LSD loci do not give a fitness advantage to heterozygous carriers, but they also do not reduce the fitness of carriers. Completely recessive alleles can increase in frequency when rare because of genetic drift alone. However, if those alleles are even slightly deleterious to heterozygotes, the chance of increasing in frequency in a small population is greatly diminished. In *Drosophila*, most mutations that are strongly deleterious to homozygous individuals also are slightly deleterious to heterozygotes (Crow 1979). If that is true in humans, then we would expect many apparently recessive genetic diseases to slightly decrease heterozygote fitness. Those that do not would be exceptional. If mutations at HEXA, responsible for Tay-Sachs disease, are completely recessive, that would help explain why Tay-Sachs has an elevated frequency in other isolated populations, including French Canadians, Acadians of Louisiana, and other

populations (Risch 2001).

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Appendix

In a population of effective size $N(t)$ at time t , the probability distribution of the frequency x of an allele is described approximately by the time-dependent diffusion equation

$$\frac{\partial \phi(x,t)}{\partial t} = \frac{1}{4N(t)} \frac{\partial^2}{\partial x^2} [x(1-x)\phi(x,t)] \quad (\text{A1})$$

(Kimura 1955), where $\phi(x,t)$ is the probability distribution of x at t . Time can be rescaled by defining

$$\tau(t) = \int_0^t \frac{dt'}{2N(t')} \quad (\text{A2})$$

(Griffiths and Tavaré 1994), and equation (A1) can be rewritten, in terms of τ , as

$$\frac{\partial \phi(x,\tau)}{\partial \tau} = \frac{1}{2} \frac{\partial^2}{\partial x^2} [x(1-x)\phi(x,\tau)] \quad (\text{A3})$$

Kimura (1955) derived the complete solution to equation (A3) under the assumption that the frequency at 0 is p . The solution is an infinite sum of products of hypergeometric functions that is easy to evaluate using a computer algebra program. For a given $N(t)$ and a particular time of interest—say, t^* —it is necessary only to use equation (A2) to compute the corresponding τ^* .

To find the probability that an allele initially present in one copy at $t = 0$ has a frequency $\geq x$ at τ^* , which is what is plotted in figure 4, the integral $\int_x^1 \phi(y,\tau^*) dy$ is needed. It was much more efficient computationally to integrate each term in the series analytically and then compute the sum than it was to numerically integrate the series itself. The results plotted in figure 4 also account for the fact that the allele considered is still segregating at t^* . In the model of the AJ population with $t^* = 26.04$ (A.D. 1348), $\tau^* = 0.00477$ and $p =$

0.0025 for $N_1 = 200$, and $\tau^* = 0.00175$ and $p = 0.0005$ for $N_1 = 3,000$.

Electronic-Database Information

The URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for type I Gaucher disease, MLIV, and APC)

Slatkin Laboratory Genetics Software, <http://ib.berkeley.edu/labs/slatkin/software.html>

TSC SNP Linkage Map, <http://compugen.rutgers.edu/SNPmap/>

UCSC Human Genome Browser, <http://genome.ucsc.edu/cgi-bin/hgGateway>

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