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The Possibility of a Selection Process in the Ashkenazi Jewish Population

To the Editor:

In a recent article, Risch et al. (2003) analyzed the frequencies of the various inherited disorders that are found in relatively high frequency among Ashkenazi Jews. By comparing three parameters—namely, the numbers of allelic mutations, allele frequency distribution, and estimated coalescence dates of mutations—Risch et al. (2003) demonstrated a similar pattern of these parameters between lysosomal storage disorders (LSDs) and 14 prevalent nonlysosomal disorders (NLSDs) that are prevalent among Ashkenazi Jews. Their conclusion, therefore, was that the LSDs are not unique in this population and the relatively high prevalence of LSDs stems from a genetic drift, rather than a selection process in favor of the LSDs in this population, as suggested elsewhere (Zlotogora et al. 1988). However, although we agree on the importance of the genetic drift to explain the high frequency of mutation in the Ashkenazi Jewish population, we still think that selective advantage for carriers of LSDs was apparently another important factor.

Among >10,000 established gene loci (MIM Statistics, March 2003), >20 are responsible for disorders found with an increased prevalence among Ashkenazi Jews. As expected in a random process, there is no known relationship between most of the genes responsible for these disorders. The exceptions are the four prevalent LSDs among Ashkenazim—namely, Tay-Sachs disease (TSD [MIM 272800]), Gaucher disease (GD1 [MIM 230800]), Niemann-Pick disease (NPD [MIM 257200]), and mucopolidosis type IV (MLIV [MIM 252650])—in which the mutations are in genes that encode for enzymes from a common biochemical pathway. In all cases, the main storage substances are sphingolipids: GM2 ganglioside in TSD, glucosylceramide in GD, sphingomyelin in NPD, and various gangliosides in MLIV. A further indication of a nonrandom process is the number of mutations responsible for each disorder. As expected for random events, in almost all the NLSDs, one mutation is prevalent, and, if more than one mutation is found, its frequency is significantly <10% of the first mutation. This

is true for almost all the NLSDs, except cystic fibrosis (CF [MIM 219700]), where a selection process has been suggested, and factor 11 deficiency (PTA [MIM 264900]). On the other hand, in all four LSDs among Ashkenazim, the second allele is >10% prevalent, when compared with the frequency of the major mutation. For instance, in NPD, three mutations are found in equal frequencies, and, in MLIV, there are two common mutations with a ratio of ~2:1. In TSD, the ratio of the three common mutations is 73:18:3.5. In GD, the ratio between the two common mutations is 77:13 (Zlotogora et al. 2000). Furthermore, it should be noted that the data for allelic frequencies in the Risch et al. (2003) paper was partially based on the frequencies obtained by the Dor Yeshorim screening program, which uses mutation analysis. That program is aimed at the detection of heterozygotes for some eight prevalent severe disorders among Ashkenazim and is designed for a specific section of that population, the ultraorthodox community. We have shown elsewhere (Bach et al. 2001) that the frequency of TSD and allelic distribution of the three common mutations, in a sample of 32,000 individuals in the Dor Yeshorim program, is significantly different from the distribution found in the Ashkenazi population at large. We have seen a similar trend with other disorders as well, including familial dysautonomy (FD [MIM 223900]), MLIV, and others (G. Bach, unpublished data). Indeed, this community represents a relatively close section in which most individuals originated from specific locations in Europe. Thus, the data for allelic distribution in the Ashkenazi population, as reported in the article (Risch et al. 2003), does not fully represent the true picture.

Risch et al. (2003) demonstrated a diverse geographic distribution of allelic mutations in some of the Ashkenazim with LSDs; certain mutations originated in Central Europe, whereas others originated in Eastern Europe. We suggest that this does not contradict a selection process, but that it may point to a secondary genetic drift. A well-known selection process by malaria in favor of heterozygotes has been demonstrated for sickle cell anemia (HBB [MIM 603903]) and is suspected for other blood disorders, such as thalassemia (HBB [MIM 141900]). If we focus on β thalassemia as an example, many mutations have been described in the populations that were exposed to malaria for centuries. Comparing the allelic distribution among Jews who originated from

a relatively small geographic region, the mutations were significantly different in the Iranian, Turkish, and Iraqi parts of the Kurdistan Mountains (Rund et al. 1991). Nowadays, the high prevalence of thalassemia among the Kurdish Jews in Israel is due to several mutations, as a result of two processes: selection and genetic drift. Determining the forces that led to the present observations in the Ashkenazi Jews is complicated, and there is no clear data for the nature of the selection process in favor of the carriers of LSDs, if that process occurred. It was suggested that certain lung disorders (i.e., pneumonia and tuberculosis) conferred a heterozygous advantage for these disorders (Myriantopoulos and Melnick 1977). If this is indeed the basis for the selection phenomenon or, in fact, any other similar environmental factor, the occurrence of different geographic origins of the various allelic mutations or different coalescence dates does not contradict a selection process but, rather, strengthens it. Regarding Ashkenazi Jews, although we have no clear evidence for the selection force, we can safely assume that the environmental factor lasted for centuries and that there is no reason to doubt that this selection force was effective in Central Europe as well as in the eastern part. Medical care for the Jewish people was not basically different in these regions. Thus, we would expect to find diverse distributions of allelic mutations for a selection process. Although the four LSDs are recessive, it can be postulated that, under extreme conditions, such as lung disorders, heterozygotes might undergo even a slight lysosomal storage of these substances, which might confer beneficial resistance to these conditions.

To try to understand the past, one can look at the present and foresee the future. This can be done for genetic diseases found nowadays in populations whose living conditions are similar to those of the Ashkenazi Jews in Europe. One example is the Arab population living in the Middle East, in which the preference is for consanguineous marriages, as was the case for the Ashkenazi Jews. For the Jews who lived in Europe, like the Arabs living nowadays in Israel, further reasons to marry within the community were religious and geopolitical. In these populations, many genetic diseases are found with a high prevalence, and, although most are due to a single random mutation, others present a different distribution.

For instance, among Arabs in Galilee, several diseases are found with an increased prevalence. On a molecular basis, in most cases, a single founder mutation explains the relatively high frequency for each disease. However, for other diseases—such as metachromatic leukodystrophy (MLD [MIM 250100]), Hurler syndrome (MPS1 [MIM 252800]), hyperoxaluria (HP1 [MIM 259900]), or ataxia telangiectasia (AT [MIM 208900])—many different mutations were found (Zlotogora 2002). In each

case, all the patients were homozygous for a single mutation that was frequent, in general, in one village only.

Another example is the high frequency of Mendelian disorders among the Bedouins of the Negev, owing to, in most cases, random founder mutations (Sheffield et al. 1998). However, Bardet-Biedl syndrome (BBS [MIM 209900]) is present among the Bedouins of the Negev in a very high prevalence, owing to mutations in three different genes. These observations, of either several mutations in the same gene or mutations in different genes responsible for the high prevalence of some genetic diseases in relatively small populations, cannot be explained as a random phenomenon. The possibility of a selective phenomenon must be raised, even though it has not yet been characterized. It may be expected that, in the future, with the expansion and mixing of the population, some of these mutations will be lost, whereas others will remain. Some mutations that are the result of genetic drift will be relatively prevalent in the general Arab population.

One may wonder why the selection phenomenon was restricted primarily to the Ashkenazim and not to the non-Jewish people around them. Two, equally plausible, assumptions might explain this phenomenon. (a) The Jews in Europe, particularly in earlier periods (i.e., the 10th–17th centuries) lived for the most part in an extremely poor socioeconomic status with poor medical management. Thus, a selection force by heterozygous advantage might have been more effective for that population. (b) The genetic background of Jews was shown to be unique and different from that of other European people. It can be postulated that this particular genetic structure might have conferred a higher sensitivity or susceptibility to certain lung disorders, when compared with other people in the same region.

We, therefore, conclude that the LSDs among Ashkenazim represent a unique group indicating a nonrandom phenomenon that might be explained by a selection process. This does not contradict a genetic drift, as was indicated by Risch et al. (2003)

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Electronic-Database Information

URLs for data presented herein are as follows:

MIM Statistics (March 2003), <http://www.ncbi.nlm.nih.gov/Omim/Stats/mimstats.html>

Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for TSD, GD1, NPD, MLIV, CF, PTA, FD, sickle cell anemia, thalassemia, MLD, MPS1, HP1, AT, and Bardet-Biedl syndrome)

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Selection in the Ashkenazi Jewish Population Unlikely—Reply to Zlotogora and Bach

To the Editor:

Zlotogora and Bach (2003 [in this issue]) raise a number of issues that argue for distinctiveness of the lysosomal storage diseases (LSDs) versus the nonlysosomal storage diseases (NLSDs). They note that the four LSDs involve a similar biochemical pathway. However, our list of NLSDs also includes three tumor-suppressor genes—breast cancer type 1 (BRCA1 [MIM 113705]), breast cancer type 2 (BRCA2 [MIM 600185]), and adenomatous polyposis of the colon (APC [MIM 175100])—and a similar argument could be applied to these. Other populations experiencing founder effects also show such pat-

terns. For example, the European Romani population demonstrates founder effects for three different sensory neuropathy syndromes (Kalaydjieva et al. 2001). An alternative explanation to heterozygote advantage is detection bias—namely, the recognition of one or two LSDs in the Ashkenazi Jewish population focused greater attention on the identification of others. For example, it is likely that additional cancer mutations will also be identified in the Ashkenazi Jewish population.

Zlotogora and Bach (2003 [in this issue]) suggest that the number of mutations differs between the LSDs and NLSDs, with the LSDs having a higher frequency of secondary mutations. However, our table 1 (Risch et al. 2003) shows this not to be the case. The maximum frequencies for secondary mutations for LSDs are .003, for Tay-Sachs disease (TSD [MIM 272800]) (mutation 1421), and .002, for Gaucher disease (GD [MIM 230800]) (mutation 84GG). Secondary mutations with frequencies as high or higher also exist for factor 11 deficiency (F11 [MIM 264900]), connexin 26 (CX26 [MIM 121011]), Canavan disease (CAN [MIM 271900]), and cystic fibrosis (CF [MIM 219700]). In addition, breast cancer type 1 (BRCA1 [MIM 113705]) and hyperinsulinism (HI [MIM 256450]) also have secondary mutations in this frequency range. There is no difference in number and frequency distribution for the second-most-frequent mutations between the LSDs and NLSDs. The data in table 1 that we used for this analysis were derived entirely from the literature and not from Dor Yeshorim and thus should be representative of the Ashkenazi Jewish population generally. The Dor Yeshorim database was used only for the geographic analyses presented in tables 4 and 5 (Risch et al. 2003). In fact, we showed that it is because the Dor Yeshorim population derives a greater proportion of ancestry from Central Europe, versus Eastern Europe, that its frequency ratio for TSD mutation 1277 versus mutation 1421 differs from other Ashkenazi Jewish samples.

The β thalassemia (MIM 141900) example described by Zlotogora and Bach (2003 [in this issue]) provides a useful point of discussion. For β thalassemia, a recessive lethal disease, various mutations have been found at excessively high frequency (much higher than any reported in Ashkenazi Jews, as given in our table 1 [Risch et al. 2003]) and in various populations that had been historically exposed to malaria. The same applies to glucose-6-phosphate dehydrogenase (G6PD) deficiency (MIM 305900). This is the opposite of the pattern observed for the LSDs in the Ashkenazim. These diseases are not increased in frequency in any group living historically in neighboring locales with shared environmental exposures, even over centuries. Despite potential economic differences, it seems unlikely that prevalent diseases would not also have an impact on non-Jews; also, except for founder mutations, the Ashkenazi population is not that different