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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 patterns. 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

genetically from other white groups. Indeed, it is the French Canadians who have a comparable frequency of TSD, also with two distinct founder mutations specific to that population (but in a geographically dispersed pattern similar to the Ashkenazi Jews), but who presumably have shared little in terms of common disease exposures with the Ashkenazi Jews (De Braekeleer et al. 1992; Hechtman et al. 1992). On the other hand, another endogamous population group, the European Romani, who arrived in Europe at approximately the same time as the Ashkenazim and lived in similar locales, also show numerous founder disease mutations, but none is shared with the Ashkenazim (Kalaydjieva et al. 2001). What these groups have in common are founder effects. By contrast, Zlotogora and Bach (2003 [in this issue]) seem to be arguing that the selection factor operating on the Ashkenazim has spanned centuries and geographic locales yet stayed limited just to the Ashkenazim. As they point out, however, all arguments about specific selective factors, such as lung disease, are speculative and unconfirmed, as opposed to those involving hemoglobinopathies and malaria.

Zlotogora and Bach (2003 [in this issue]) use the observation of multiple mutations to infer selective advantage for etiologically unrelated diseases, such as metachromatic leukodystrophy (MIM 250100), Hurler syndrome (MIM 252800), hyperoxaluria (MIM 259900), and ataxia telangiectasia (MIM 208900) in Arabs and Bardet-Biedl syndrome (MIM 209900) in Bedouins. An even stronger argument might be applied to BRCA1 in the Dutch population, which, according to a recent study, has at least 12 different recurrent mutations (Peelen et al. 1997). It seems implausible that all these disease mutations have undergone selective advantage unique to one population. We do not agree that the number of mutations found in a population is a good indication of past selective forces. Rather, it is aberrantly high mutation frequencies, despite severe negative selection against homozygotes, that provide the strongest argument for carrier advantage. We believe that care needs to be applied in concluding past selection when disease mutations are specific to single founder populations. Although we cannot prove that selection has played no role in the LSDs in the Ashkenazi Jewish population, we have shown that their mutational distributions—in terms of numbers, frequencies, ages, and geography—are consistent with genetic drift alone.

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Electronic-Database Information

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for APC, ataxia telangiectasia, Bardet-Biedl syndrome, BRCA1, BRCA2, CAN, CF, CX26, F11, GD, G6PD deficiency, HI, Hurler syndrome, hyperoxaluria, metachromatic leukodystrophy, and TSD)

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Zlotogora J, Bach G (2003) The possibility of a selection process in the Ashkenazi Jewish population. Am J Hum Genet 73:438–440 (in this issue)

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