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SHORT REPORT

Lower frequency of Gaucher disease carriers among Tay-Sachs disease carriers

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The heterozygote frequency of Gaucher disease (GD) and Tay-Sachs disease (TSD) is distinctly high among Ashkenazi Jews (1:29 for TSD and 1:16 for GD). Two main theories have been suggested to explain this high occurrence: a founder effect with subsequent genetic drift, and a selective advantage of heterozygotes. We compared the frequency of the GD most common mutation (1226A□G) among carriers of the common TSD mutation (+1277 TATC) with the frequency of this mutation in the general Ashkenazi population. The frequency of GD carriers among 308 TSD heterozygotes was 1:28 which is about half the expected (*P* = 0.03). These results indicate that carriers of both diseases do not possess additional evolutionary advantage over single mutation carriers. A reasonable interpretation of these findings is that one or both mutations have arisen relatively recently in different regions of Europe and have not yet reached genetic equilibrium.

Tay-Sachs disease (TSD) and Gaucher disease (GD) are glycolipid storage diseases caused by the impaired activity of the lysosomal enzymes hexosaminidase A (EC 3.2.1.52) and glucocerebrosidase (EC 3.2.1.45), respectively.[1,2] The incidence of both diseases is relatively high among the Jewish Ashkenazi population, reaching a frequency of about 1:29 for TSD carriers and 1:16 for GD carriers.[1,2]

Two major hypotheses were proposed to account for this high frequency. One hypothesis suggests that genetic drift associated with a remarkable expansion of this population in Europe during the 16th to 19th centuries is the cause of the elevated carrier frequency.[3] The other theory proposes that heterozygotes possess a selective advantage over non-carriers.[2] The advantage of carriers of lysosomal storage diseases has been attributed to the subclinical accumulation of the corresponding glycolipids in the lysosomes.[4–6] If heterozygotes for each disease have indeed an evolutionary advantage, carriers of mutations for both diseases might be endowed with an additional advantage and their relative frequency in the population should increase. To test this hypothesis we studied the frequencies of the two predominant mutations of TSD and GD: the insertion mutation (+1277TATC) which accounts for about 83% of mutant TSD alleles, and the 1226□G (1226G) mutation accounting for more than 70% of GD alleles[1,2,7,8] We compared the frequency of the GD 1226G carriers among Ashkenazi heterozygotes of the TSD +1277TATC with that found in the general Ashkenazi population. Carriers of TSD were identified through the nation-wide TSD screening and prevention programme. All participants completed a questionnaire

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Table 1 Frequency of GD heterozygotes[a] among TSD carriers[b]

Ashkenazi Jews	*Total*	*GD carriers*	*Ratio*
General population	1503	108	1:14
TSD heterozygotes	330	13	1:25.5

[a]Carriers of the 1226G mutation.
[b]Carriers of the +1277TATC mutation.

regarding ethnic extraction of their parents and grandparents.

About 11500 individuals with all four grandparents originating in Eastern or Central Europe were included. DNA samples of individuals who were diagnosed enzymatically as carriers[9] were examined for the presence of the +1277TATC insertion mutation, by heteroduplex formation;[10] 308 DNA samples carrying the TSD mutation were further analysed (anonymously) for the existence of the GD allele, 1226G, identified by the creation of the XhoI restriction site.[11] The frequency of the 1226G GD mutation among the general Ashkenazi population was estimated by testing 1304 samples obtained through the routine screening service. The data presented in Table 1 show that the occurrence of GD carriers, bearing the 1226G mutation in the Ashkenazi Jewish population screened by us (0.07), was similar to the recently published values[1]. However, among TSD heterozygotes, who carry the (+1277TATC), we found a significantly ($\chi^2 = 4.62$, $P = 0.03$) lower frequency of the GD carriers (0.039). Thus, the occurrence of individuals who carry both mutations is significantly lower than expected from the combined frequencies of these two mutations in the Ashkenazi population.

These results suggest that carriers of both diseases do not possess an evolutionary advantage over carriers of the single mutation. On the other hand, they do not rule out the possibility that heterozygosity to each disease confers such an advantage. The remarkable deficiency of double hetrozygotes may apparently indicate a disadvantage. However, this interpretation is not very likely since it would imply 50% lethality of double heterozygotes in the last generation, whereas there is no evidence suggesting that such individuals have any impairment of their health.

The most straightforward interpretation of our findings is that one or both mutations have arisen in the Ashkenazi population relatively recently in different regions of Europe and have not yet reached genetic equilibrium.

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