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# Controversy in Human Genetics:

## Founder Effect in Tay-Sachs Disease

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In recent reports [1–3] the high incidence of Tay-Sachs disease (TSD) in Ashkenazic Jews has been ascribed to heterozygote advantage. We would like to offer an alternative explanation: founder effect.

It is known that Ashkenazic Jewish patients with TSD have ancestors stemming from certain sections of Poland, Lithuania, and Russia [1]. It is stated by Myrianthopoulos and Aronson [1] that "from our demographic studies of these areas, it appears that the Jewish communities were large enough to support synagogues and schools . . . . We can find no evidence for circumstances which theoretically might favor drift, such as migration of small groups, famine, disease, or war, affecting all or a large number of these Jewish communities simultaneously. No doubt, such circumstances existed at one time or another, within one community or another. But even under conditions of complete genetic isolation, random fluctuation of the TSD gene in some communities must have been balanced in other communities. And our demographic data show that the Jews of the United States . . . emigrated not from a few selected communities but from hundreds of cities, towns, and villages of northeastern Europe."

Migration of Jews to eastern Europe, especially Lithuania, six and seven centuries ago was in part a response to persecution during the Crusades. This migration probably took place in small bands which may have been seminomadic for many years before reestablishing permanent settlements (M. I. Herzog, personal communication, 1971; [4]). The statement that the ancestors of TSD patients stemmed from "hundreds of cities, towns, and villages" can be reconciled with the founder-effect hypothesis because the gene may have originated prior to the formation of these communities. It is suspected on linguistic grounds (M. I. Herzog, personal communication, 1971) that the Jewish communities in Poland and Lithuania stemmed from earlier isolates in the Rhineland. One isolate, in which the TSD gene might have originated, could have contributed to several communities at the later stage. A disproportionate contribution from a founder carrying the TSD gene would manifest itself only much later in history, when Jews from different Polish-Lithuanian-Russian isolates might marry in the United States and give birth to a TSD infant.

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The contention that "random fluctuation of the TSD gene in some communities must have been balanced in other communities" must be examined in light of the low frequency of the TSD gene under ordinary conditions. To balance a high frequency in a few communities would require extinction in many communities. Also, the maxim that "chance has no memory" is applicable here. One can no more expect compensation for a chance excess of frequency than one can expect a fair coin to come up heads repeatedly after 10 successive tails.

Studies of the Ellis–van Creveld syndrome in Lancaster County, Pennsylvania, Old Order Amish [5] indicate a founder effect in that situation since all parents of affected persons, distributed in 37 sibships by present count, share a common ancestral couple. Naturally, such refined genealogical tracing is not possible with respect to TSD. The advantage of the founder-effect hypothesis is that it relieves one of the necessity to postulate a selective advantage which because of changing environmental conditions could probably never be verified.

The clustering of ancestors has been noted also in Ashkenazic Jews with familial dysautonomia [6]. The areas from which the ancestors stemmed are, in general, south of the TSD areas. However, a duplication of this clustering phenomenon adds weight to the founder-effect hypothesis. Several other usually rare recessives (e.g., hereditary dystonia [7]) occur with high frequency in Ashkenazic Jews [8, 9] and can well have the same explanation. The low frequency of phenylketonuria in the same group [8, 9] may represent a negative founder effect.

Naturally under the founder-effect hypothesis it is not expected that a future increase in frequency of the TSD gene through heterozygote advantage would occur. The presently high incidence of affected infants is a transient phenomenon due to the chance encounter of recessive genes whose frequency has reached a high level partly as a consequence of diminished inbreeding. This phenomenon was discussed by Haldane in a classic paper [10].

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