

GENETIC HETEROGENEITY IN DISEASES: THE LONG QT SYNDROME AND CYSTIC FIBROSIS

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Abstract

A Mendelian genetic disorder which is caused by more than a single genetic factor, is defined as genetically heterogeneous. In inter-locus heterogeneity, defects at different genes are responsible for the disease, whereas in intra-locus heterogeneity, different mutant alleles of the same gene, cause the disease. This study analyzed the genetic heterogeneity in two genetic diseases in the Jewish population: cystic fibrosis (CF) and long QT syndrome (LQTS).

LQTS- A relatively rare, dominant cardiac disorder. Its main manifestations are an elongated QT interval during ECG, and a predisposition to sudden death from cardiac arrhythmias. One study of a large Utah family revealed tight linkage between the disease and the gene HRAS, located on chromosome 11. In the present study, we analyzed the linkage between HRAS and LQTS in a large Jewish family, originating from the island of Jerba in Tunis. A definite rejection of linkage between the disease and HRAS was found. This result proves intra-locus heterogeneity in the long QT syndrome. We continued searching for the gene responsible for LQTS in this family using several approaches. A cytogenetic analysis revealed no chromosomal aberrations in the family. Linkage analysis between a candidate potassium channel gene (KCNAl), and the disorder rejected linkage between LQTS and a 16 cM region spanning KCNAl, on the short arm of chromosome 12. A random search for linkage using microsatellites, rejected linkage between the disorder and a 35cM region on the long arm of chromosome 14. Due to the genetic heterogeneity, and the negative linkage results from other areas of the genome, no molecular genetic counseling is applicable at this stage, in this family. The genetic heterogeneity between the Jewish Jerba family and the Utah family is best explained as being a result of mutations at different loci, affecting cardiac electrophysiology.

CF- The most common lethal recessive disorder in the Caucasian population, affecting one in 2,500 live births. The disorder harms mainly the respiratory, digestive and reproductive systems. The abundance of CF varies between different ethnic groups. The isolation of the disease causing gene revealed a major mutation in about 70% of the CF chromosomes. Consequently, close to 400 additional, less frequent mutations were identified. In different ethnic groups, different CF mutations and relative mutation frequencies are found. This study assembled all currently known data about CF mutations in the Jewish population in Israel, analyzed the spectrum of mutations in each community, the percentage of unidentified mutations, and tried to estimate the frequency of CF in different ethnic groups in the Jewish population. The analysis revealed an enormous range of frequencies, ranging from approximately 1:2,500 in Jews originating from Europe and Libya, to under 1:30,000 among Iraqi and Iranian Jews. It was also shown that each ethnic group presented a unique mutation spectrum. These findings have an immediate implication on genetic counseling in CF, in the Jewish population, and they raise the need of performing a preliminary population screen for carriers of CF, in a few Jewish communities, in order to validate this study's findings and form a firmer genetic counseling database for these communities. The study discusses some methodological difficulties regarding the estimation of the frequency of genetic diseases in different ethnic groups in Israel. The high genetic heterogeneity between Jews of different ethnic origin, currently living in Israel, is explained by hundreds of years of life in small, geographically dispersed communities.

The high proportion of identified CF mutations in the Jewish Ashkenazi population (95%), led to a few carrier screening projects in the healthy population. The present study analyzes the results of three such screens, covering almost 4,000 chromosomes in the Jewish Ashkenazi population. This analysis results in an interesting finding: Among Ashkenazi CF patients, the most frequent mutation is W1282X (51%), and that the deltaF508 mutation is far less abundant (27%). However, in the healthy population, the frequency of these two mutations is almost equal (35:36). The difference between the relative frequencies of the two mutations is statistically significant ($p=0.025$). A striking manifestation of this difference is revealed in the analysis of patients' genotypes. There were 36 patients homozygous for W1282X, while only 7 were homozygous for deltaF508. A few possible explanations for this surprising difference are discussed in the study, including the possibility that the

difference is a result of prenatal selection that lowers the odds of homozygotes for deltaF508 to be born. The prenatal selection hypothesis has a few predictions, which are presented in the study. Such a difference between predictions based on findings in patients, and the actual findings in the healthy population, demands reexamination of the accepted procedure of inferring directly from patients' data, epidemiologic parameters concerning carriers in the healthy population. Such direct inference could mislead genetic counselors and health care policy makers.

In conclusion, the findings in this study point to the substantial genetic heterogeneity between Jewish and non Jewish populations, and between different Jewish populations. These findings are in correspondence with our knowledge of the history of the Jewish people: The Jewish communities were relatively small, and were culturally relatively isolated from the non Jewish surrounding communities, and geographically isolated from other Jewish communities. In addition, immigration and recurrent hostility from the non Jewish neighboring communities, led to genetic bottlenecks. Reproductive isolation of communities and genetic bottlenecks are major factors contributing to genetic heterogeneity, and that heterogeneity will be expressed in genetic diseases too. This vast genetic heterogeneity complicates genetic counseling in the Jewish population, and a few tools to overcome these difficulties are suggested.