Analysis of Ashkenazi Jewish genomes reveals diversity, history

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Through genomic analysis, researchers at Emory University School of Medicine have shown that the Ashkenazi Jewish population is genetically more diverse than people of European descent, despite previous assumptions that Ashkenazi Jews have been an isolated population. In addition, analyses of disease-related genes of higher prevalence in the Ashkenazi Jewish population indicate that only a minority of traits show signs of positive selection, suggesting that most have arisen through random genetic drift.

The results are published online this week in the early edition of the Proceedings of the National Academy of Sciences.

Investigators in the laboratory of Stephen Warren, PhD, chairman of human genetics at Emory University School of Medicine, used DNA microarray technology to read variant sites across the entire genomes of 471 Ashkenazi Jews. The work comes from a collaboration between Warren and Ann Pulver, ScD, associate professor of psychiatry and behavioral sciences at Johns Hopkins University School of Medicine, who recruited the participants for a study of schizophrenia genetics.

Researchers looked for close to one million single nucleotide polymorphisms (SNPs): common alternative spellings in the genome, analogous to American and British spellings of words such as organize/organise. One measure of genetic diversity in a population is heterozygosity, or how many of the SNPs inherited from the mother and father are different; a more inbred population has less heterozygosity.

"We were surprised to find evidence that Ashkenazi Jews have higher heterozygosity than Europeans, contradicting the widely-held presumption that they have been a largely isolated group," says first author Steven Bray, PhD, a postdoctoral fellow in Warren's laboratory.

The researchers went on to measure linkage disequilibrium, a measure of how "chunky" a population's genomes are. If two individuals from separated groups have children, their descendants' genomes are shuffled by recombination. Successive generations continue the shuffling process, so that the linkage between traits located near each other in the genome is gradually lost over time.

High linkage disequilibrium can come either from an isolated population (for example, an island whose residents are all descendents of shipwreck survivors) or the relatively recent mixture of separate populations. Bray and his colleagues did find evidence of elevated linkage disequilibrium in the Ashkenazi Jewish population, but were able to show that this matches signs of interbreeding or "admixture" between Middle Eastern and European populations.

The researchers were able to estimate that between 35 and 55 percent of the modern Ashkenazi genome comes from European descent.

"Our study represents the largest cohort of Ashkenazi Jews examined to date with such a high density of genetic markers, and our estimate of admixture is considerably higher than previous estimates that used the Y chromosome to calculate European admixture at between five and 23 percent," Bray says.

He adds that his group's analysis agrees with a recently published study from New York University and Albert Einstein College of Medicine, and supports estimates of a high level of European admixture, accounting for up to half of the genetic make-up of contemporary

Ashkenazi.

The genomic analysis also provided information about selection pressures on mutations prevalent in the Ashkenazi Jewish population, such as those leading to conditions like Tay-Sachs disease or mutations in cancer susceptibility genes like BRCA1.

This line of research seeks the answer to the question: why doesn't a harmful mutation simply disappear from the population? A classic example of positive selection is sickle-cell anemia. Two copies of the mutation are required for the disease to occur, but when an individual has one copy of the mutation, it provides resistance against malaria. Some scientists have proposed that disease-related mutations have persisted in the Ashkenazi Jewish population because of a similar hidden positive effect.

"Only six of the 21 disease genes that we examined showed evidence of selection," Bray says. "This supports the argument that most of the Ashkenazi-prevalent diseases are not generally being selected for, but instead are likely a result of a genetic bottleneck effect, followed by random drift."

Besides examining the genes responsible for previously identified diseases, Bray and colleagues went on to look for other regions of the Ashkenazi Jewish genome that display signs of selection, in comparison to European genomes. The two strongest differences between the Ashkenazi and European populations were on chromosome 2 and 12. A region including the lactase gene, which confers lactose tolerance, on chromosome 2 showed signs of strong selection in Europeans but not the Ashkenazi.

"A variant of the lactase gene swept through Europe at around the same time as the domestication of cattle several thousand years ago," Bray

says. "This result suggests the selection preceded the European establishment of the Ashkenazi Jewish population, which is consistent with the historical record."

In addition, a region on chromosome 12 showed selection in the Ashkenazi Jewish population but not Europeans. This area encompasses 18 genes but the investigators noticed that one of these, ALDH2, is important in alcohol metabolism, and genetic variation in ALDH2 has previously been shown to affect alcohol consumption, Bray says.

"This is consistent with historical and modern reports of lower alcoholism rates in Jews, although social and religious practices are also thought to play a role," he says. "However, a more detailed analysis of variants in the ALDH2 gene would be necessary to show a mechanistic link."

More information: References:
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