BRCA1:185delAG found in the San Luis Valley probably originated in a Jewish founder

I Makriyianni, N Hamel, S Ward, W D Foulkes, S Graw

Key points

- The BRCA1:185delAG mutation is a frequent founder mutation in the Ashkenazi Jewish population. This mutation was also observed in breast cancer patients from the San Luis Valley (SLV) of Colorado and New Mexico.
- Seven nearby markers known to be conserved on the 185delAG Jewish haplotype were tested to determine whether the SLV mutation shares an origin with the Jewish mutation, or whether it arose independently.
- All 185delAG mutation carriers were found to share the conserved allele at each of the seven loci tested.
- These results suggest that individuals in the SLV who carry the 185delAG mutation share a common ancestor with Jews who also carry this mutation.

Table 1 shows the genotypes of the subjects for each marker in reference to the conserved Jewish haplotype. We found that all 185delAG mutation carriers share a conserved allele at each of the seven loci tested. Moreover, subject 7, a non-carrier, does not have the conserved alleles at any of the loci. These results are consistent with the hypothesis that individuals in the SLV who carry the 185delAG mutation share a common ancestor with Jews who also carry this mutation. This finding suggests that individuals in this population have at least one ancestor of Jewish origin.

COMMENT

The BRCA1:185delAG mutation has previously been observed on different haplotypes in both Jewish and non-Jewish mutation carriers, which implies that the mutation arose more than once. However, the existence of only one haplotype in the Ashkenazi Jews indicates a single origin within this population. Two previous studies also found that non-Jewish populations of Hispanic origin segregate the 185delAG mutation with the Ashkenazi Jewish haplotype. One study was on a Spanish gypsy population and another on a Chilean family with no known Jewish ancestry. Most recently, Weitzel et al found that BRCA1:185delAG is the most frequent deleterious BRCA1 mutation in women of Hispanic origin living in Los Angeles. All patients with the BRCA1:185delAG mutation from this area also show conservation of the common Ashkenazi haplotype at markers centromeric to and throughout the BRCA1 gene.

The linked haplotype is commonly referred to as the “Ashkenazi Jewish haplotype” because it was originally identified and has been extensively studied in Ashkenazi Jews. However, this does not mean that the haplotype is unique to this population. Indeed, other non-Ashkenazi...
Jewish populations also carry the 185delAG mutation. One possible interpretation of this finding is that the mutation could have arisen at an ancient time before the dispersion of Jews. However, Neuhausen et al determined that the mutation occurred around 1235 CE (90% confidence interval ranging from 396 to 1536 CE) based on the 500 kb conserved region that they found centromeric to the mutation. Although one of our previous studies narrowed down the conserved region to 200 kb, suggesting that the mutation is actually older, its origin is still likely more recent than the last dispersion of the Jews in the Diaspora, estimated to be around 70 CE. A second possibility that the mutation could have arisen after the divergence of the Jews and the “Ashkenazi” 185delAG alleles is a result of isolated population admixture. Ah Mew et al speculated that the Chilenan family in their study most probably has Sephardic ancestry because the family established in Chile before the most recent Ashkenazi Jewish immigration to the Americas (late 1800s to early 1900s). Sephardic Jews lived in Spain and Portugal until the Spanish Inquisition in the late 1400s; then they migrated to several regions around the world, including the Americas.

Mullineaux et al speculate that the present day Hispanic population of the SLV descended from a core group of Spanish settlers in 1598. We believe that a Sephardic Jewish member of the group introduced the mutation to the valley, although we cannot exclude the possibility that the founder of this mutation in the valley was Ashkenazi Jewish. For example, in 1648 the Westphalia agreement was signed between the Netherlands, Spain, and other European nations, ending 80 years of war. This resulted in increased movement between Europeans, and a Jewish settler of the valley could conceivably have come from anywhere in Europe, and thus could have been Ashkenazi. Nevertheless historical dates and the presence of the mutation in other Hispanic populations are evidence to support the view that the founder of the mutation in such populations was Sephardic. In summary, it is our belief that the Jewish ancestor(s) of the SLV were also Sephardic in origin, as the De Ofate expedition arrived in 1598, close to the time of the Spanish inquisition and considerably earlier than the recent Ashkenazi immigration to the Americas.

“Ashkenazi” founder mutations have also been observed in non-Ashkenazi Jewish populations in other syndromes. Examples of these are the mutations causing Bloom syndrome and Creutzfeldt–Jakob disease. Bloom syndrome is a rare autosomal recessive disorder that causes short stature, skin pigmentation anomalies, and immunodeficiency. A study of Bloom patients of non-Ashkenazi origin in America revealed an “Ashkenazi” mutation, present in 100% of patients from a Jewish population in Tunisia, in 47% of Libyan Jewish patients, and in 100%, 33%, and 43% of patients from non-Jewish populations of Spain, Italy, and Chile, respectively.

The results of this and previous studies on non-Jewish populations support the presence of well known Ashkenazi Jewish founder mutations in non-Jewish individuals. Specifically, these studies illustrate the presence of Jewish ancestry in patients with a personal or familial history of breast cancer who identify themselves as having Spanish origins. Future studies are necessary to evaluate the frequency of this mutation in the San Luis Valley population.
REFERENCES


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