BRCA1/2 Mutations: Not Just Ashkenazi Mutations

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With the help of modern technology, it is possible to discern cases of breast cancer caused by somatic mutations from cases of familial breast cancer caused by hereditary gene mutations. These genetically transmitted mutations are associated with an inherited predisposition to developing breast cancer; estimates show that carriers are up to 65% more likely to develop breast cancer than people who do not carry the mutation [1]. Of the known hereditary gene mutations, more than half are attributed to the *BRCA1* and *BRCA2* genes [2, 3]. *BRCA* gene mutations are found in 1 out of 40 Ashkenazi Jews, as compared to the rate of the general population which is about 1 in 400 [4, 5]. Due to the increased prevalence of these mutations in the Ashkenazi Jewish population, genetic tests often inquire whether or not patients descend from this population. However, recent studies have identified *BRCA1/2* mutations in Sephardic populations as well, so it is critical for all Jews to be screened for inherited *BRCA1/2* mutations.

About 2% of Ashkenazi Jews are carriers of *BRCA1/2* mutations, thus the Ashkenazi population is considered to be at a higher risk of developing breast cancer as compared to non-Ashkenazim, particularly Jews of Asian and African descent. More specifically, about 1% of the Ashkenazi population is considered to carry the *BRCA1* 185delAG mutation. This mutation is often mistakenly regarded as an "Ashkenazi mutation," but research suggests that the *BRCA1* 185delAG mutation is present in the Iraqi-Jewish population at comparable rates: 0.47% in Iraqi-Jews and 0.9% in Ashkenazi Jews [6]. These populations differ in the actual development of breast cancer, but this may be a consequence of alternative influences, such as environmental or genetic factors [6]. To explain the presence of the *BRCA1* 185delAG mutation in both Ashkenazi and non-Ashkenazi (specifically Iraqi) Jewish populations, scientists deduced that the mutation emerged earlier than 70 AD, prior to the onset of the Jewish Diaspora. The Ashkenazi and non-Ashkenazi populations share a similar haplotype, so it is likely that they also share a common founder. Thus, scientists summarized that the mutation may have emerged when these groups coexisted, before Jews were physically separated as a result of the destruction of the second temple [6, 7].

Furthermore, the *BRCA1* 185delAG mutation has been identified in the genomic structure of a non-Jewish, Latin American community in the San Luis Valley of Colorado. Although some members of the San Luis Valley community deny having any Jewish ancestry and lack any Jewish traditions, the common haplotype suggests that these people are in fact descendants of Jews. The presence of this particular mutation is consistent with the events pertaining to the history of the Sephardic population. In the 16th and 17th centuries, Jews living in Iberia, modern-day Spain and Portugal, faced severe discrimination. Many converted to Christianity in order to escape prosecution; these Jews became known as *Conversos*. When Spain and Portugal colonized the New World, many of these *Conversos* migrated there and even assimilated into the local population [8]. They immersed themselves in the communities of Central and South America, along with modern-day California, Arizona, New Mexico, Texas, and Colorado [3]. It is highly likely that in the process of assimilation, *Conversos* intermarried within the local population. The discovery of the *BRCA1* 185delAG mutation in the Latin American community in the San Luis Valley of Colorado provided evidence for the theory that intermarriage occurred between *Conversos* and the indigenous population and for the theory that the mutation emerged prior to the Jewish Diaspora [6, 9].

However, other more recent studies suggest that the mutation originated in the Ashkenazi population as a founder mutation and appeared in Hispanic and non-Ashkenazi communities as a result of independent migrations of Ashkenazi carriers. According to a haplotype analysis, the mutation originated 1200 years ago in the Ashkenazi population, 650 years ago in the Hispanic population, and 450 years ago in the Jewish-Iraqi population. It is inferred that the mutation originated in Ashkenazi Jews and spread to Hispanic and Sephardic populations via migration of carriers of the mutation. This contradicts previous theories that the mutation must have emerged before the Diaspora and does not have historical backing. One explanation regarding how the mutation was spread to the Iraqi-

Jewish population is that it was brought by Ashkenazi carriers involved in trade in the area [10].

Additionally, there are 5 known founder mutations in several Jewish communities. These are 185delAG, 5382insC, and 6174delT in Ashkenazi populations, 8765delAG in Yemenite populations, and p.Y978X in Iraqi, Iranian, and Afghan populations. Two potential founder mutations have been identified in Sephardic populations: p.A1708E in BRCA1 and IVS2 + IG > A in *BRCA2*. A common haplotype was detected in each of the two mutations, suggesting that they are founder mutations for the Sephardic population [11]. Although the exact rates of these mutations in the Sephardic population is unknown, this discovery provides further evidence that *BRCA* mutations are in fact found in Sephardic populations.

As technology progresses and researchers continue to uncover evidence linking inherited *BRCA* mutations to the Jewish population, it becomes increasingly important for Jews to get tested for these mutations. This includes people from both the Ashkenazi and Sephardic communities, men and women alike. The benefit of knowing whether or not one is a carrier provides a unique opportunity to explore preventive measures in the hopes of deterring onset of disease.

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