Hereditary Risks of Male Breast Cancer in a Multi-Gene Panel Testing Cohort

Elizabeth Chao[1,5], Mary Pritlzaff[1,†], Pia Summerour[1,†], Rachel McFarland[1], Shuwei Li[1], Patrick Reineke[1], Jill Dolinsky[1], David E. Goldgar[2], Hermela Shimelis[3], Fergus J. Couch[3,4], and Holly LaDuca[1]

While the population-based risk for breast cancer in males remains relatively low (1:1000), inherited predisposition can significantly raise this to as high as 10%, in men who carry a mutation in the *BRCA2* gene. Lifetime breast cancer risks of 1-2% have also been reported in men who carry a mutation in *BRCA1.* These risks, as well as elevated risks of prostate, pancreatic, and melanoma cancers, are important to discuss in families diagnosed with Hereditary Breast and Ovarian Cancer Syndrome, which is often viewed as being clinically relevant only to the women in an affected family. However, beyond the BRCA*1/2* genes, limited data is available on hereditary predisposition to male breast cancer.

We analyzed clinical histories and molecular results from multi-gene panel testing for hereditary cancer predisposition in a cohort of 715 men affected by breast cancer. A total of 708 male breast cancer patients were eligible for inclusion in the final analysis. Molecular testing included analysis of 5 to 59 genes for DNA coding sequence and copy number variants by next-generation sequencing and microarray. Genetic variants identified were classified according to a 5-tier system using previously validated algorithms[1,2]. Only those variants classified as pathogenic or likely pathogenic were included in the analyses as positive for a mutation. Overall, a mutation was detected in 18% of these men. Four subjects carried a mutation in two different breast cancer predisposition genes. *BRCA2* and *CHEK2* were the most frequently mutated genes. The risk of breast cancer was significantly elevated compared to public controls in individuals with a mutation in *BRCA2* (odds ratio (OR)=13.9; p=1.92x10-16), *CHEK2* (OR=3.8; p=6.24x10-24) and PALB2 (OR=6.6, p=0.01). Average age was similar amongst men with (63.5±2.7 years) and without (62.3±1.2 years) mutations, as were clinical and family histories of additional cancers.

The high overall diagnostic yield suggests the utility of testing all male breast cancer patient regardless of age or family history by multigene panel testing, and provides data to support risk-based counseling and medical recommendations for screening and/or prevention in male mutation carriers.

1. LaDuca et al. Genet Med. 2014 Nov;16(11):830-7
2. Richards et al. Genet Med. 2015 May;17(5):405-24