



NEWS

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Comprehensive testing for all known inherited breast cancer gene mutations explains occurrence of the cancer in women with normal *BRCA* genes

Since 1994, many thousands of women with breast cancer from families severely affected with the disease have been tested for inherited mutations in *BRCA1* and *BRCA2*. The vast majority of those patients were told that their gene sequences were normal.

With the development of modern genomics sequencing tools, the discovery of additional genes implicated in breast cancer and the change in the legal status of genetic testing for *BRCA1* and *BRCA2*, it is now possible to determine how often families in these circumstances actually do carry cancer-predisposing mutations in *BRCA1*, *BRCA2*, or another gene implicated in breast cancer, despite the results of their previous genetic tests.

This was the challenge addressed by Mary-Claire King, Ph.D., American Cancer Society Professor of Medicine and Genome Sciences, and Tomas Walsh, Ph.D., Associate Research Professor of Medical Genetics, both at the University of Washington, Seattle. They conducted complete genomic sequencing of all genes implicated in breast cancer on DNA samples from breast cancer patients who had normal *BRCA1* and *BRCA2* commercial test results. The commercial testing occurred because the patients had a severe family history of breast cancer, defined as a family with three or more relatives affected by breast or ovarian cancer.

The results were presented today by Dr. Walsh at the American Society of Human Genetics 2013 meeting in Boston.

The researchers found that over 25 percent of index patients with normal results from commercial testing of *BRCA1* and *BRCA2*, but with families severely affected by breast cancer, could be resolved by sequencing all genes known to be involved in breast cancer.

Sequencing was carried out using BROCA, an openly available, targeted capture and genomic sequencing approach that was developed and validated by Drs. Walsh and King in 2010. BROCA detects all single base substitutions, insertions and deletions and copy number variants in all 24 genes implicated in breast cancer.

The researchers used BROCA to test 2,285 members of 743 families with at least three relatives with breast or ovarian cancer. Each of those families included at least one woman with breast cancer who had

(more)

received normal results from complete commercial genetic testing for *BRCA1* and *BRCA2*. The commercial tests were based on both Sanger sequencing and supplementary testing for large genomic rearrangements in both genes.

Of the 743 families, 26% (191) were resolved by BROCA. The 191 resolved families were found to harbor 149 different inherited, damaging mutations in 18 distinct genes.

Of the 191 resolved families, 35% (66) carried inherited, damaging mutations in *BRCA1* or *BRCA2* that were not detected by commercial sequencing. The scientists explained that the *BRCA* mutations were not detected by commercial testing for one of two reasons. In some families, the patient who was tested had normal sequences of *BRCA1* and *BRCA2*, but her relatives with breast cancer carried a mutation in one of those genes. In other families, both the patient who was tested and her relatives carried a *BRCA1* or *BRCA2* mutation of a type not reported by commercial testing.

In the remaining families resolved by BROCA, 65% (125) carried inherited, damaging mutations in genes other than *BRCA1* or *BRCA2* that also have been associated with breast cancer. The researchers found that 18 different genes harbored cancer-predisposing mutations in those 125 families, but each affected person carried a mutation in only one gene.

Carriers of mutations in some of the genes were at significantly increased risk of ovarian cancer for women and increased risk of breast cancer in men as well as in women.

Comprehensive testing is rapidly becoming more widespread. “It is important to determine more precisely the risks associated with damaging mutations in each of these genes so as to incorporate them most effectively into clinical care,” Dr. Walsh said.

These assessments are best undertaken by sharing data across all centers that carry out genetic testing for breast and ovarian cancer risk, said Dr. King.

Title of the ASHG abstract: “[More than 25% of breast cancer families with wild-type results from commercial genetic testing of *BRCA1* and *BRCA2* are resolved by BROCA sequencing of all known breast cancer genes.](#)”

About ASHG

The American Society of Human Genetics is the primary professional membership organization for nearly 8,000 human genetics specialists worldwide. The ASHG Annual Meeting is the world's largest gathering of human genetics professionals and a forum for renowned experts in the field. For more information about ASHG, visit: <http://www.ashg.org>.