Eight case studies of concurrent pathogenic mutations identified in hereditary breast and ovarian cancer gene panel

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Objectives

The availability of next-generation sequencing (NGS) and characterization of multiple genes that can increase cancer risk has caused a shift towards multi-gene panel testing for hereditary cancer. However, the occurrence of concurrent pathogenic mutations and the utility of panels in individuals who have a known mutation in the family is yet to be well evaluated. At this time, the rate of concurrent mutations has been reported in 2.9% of people who test positive (LaDuca et al. 2014). We reviewed the personal and family histories of patients found to have multiple pathogenic or likely pathogenic mutations when tested clinically for 19 genes for hereditary breast and ovarian cancer and the implications for the patient and his or her family.

Study Design and Methods

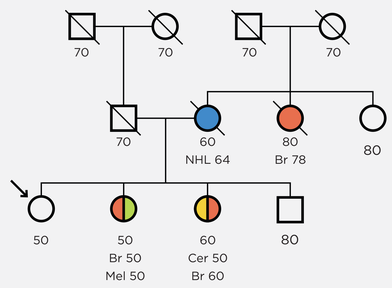
Samples were analyzed with a 19 gene panel that included next generation sequencing (NGS) of: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53*. All mutations were classified according to current American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al. 2015).

Results

Seven patients with two concurrent mutations and one with three concurrent mutations were identified in the testing of patients with a 19 gene panel for hereditary breast and ovarian cancer. Mutation combinations included: *BRCA1+CHEK2* (3), *ATM+BRCA1* (1), *ATM+CHEK2* (1), *ATM+BRCA2* (1), *BRCA1+PMS2* (1), and *BRCA1+BRIP1+CHEK2* (1). Four of the 8 (50%) patients underwent panel testing in the setting of one known family mutation. Three patients (38%) were the first person in the family to undergo genetic testing. One patient underwent previous genetic testing with a large cancer panel that identified both pathogenic mutations. Two patients (25%) had a personal history of cancer and 6 of 8 (75%) had no personal history of cancer. Seven out of 8 (88%) patients met National Comprehensive Cancer Network (NCCN) criteria for genetic testing for hereditary breast and ovarian cancer based on personal and/or family history (National Comprehensive Cancer Network. 2016).

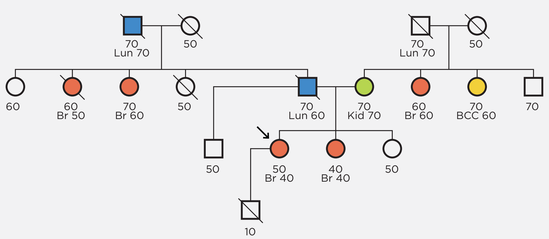
Conclusions

Identifying patients with multiple clinically actionable mutations may have important medical implications for the patients as well as for family members. These data suggest those at risk for a known family mutation may still be appropriate candidates for multi-gene panels due to the risk (2.9%) of multiple mutations. Lastly, with the cost of testing declining rapidly, the risk of missing a mutation may outweigh the arguments against testing with a broader panel both in the setting of known family mutations and in initial testing of a patient. Further research on larger data sets is needed to better elucidate the occurrence of concurrent mutations and the implications of having concurrent mutations.



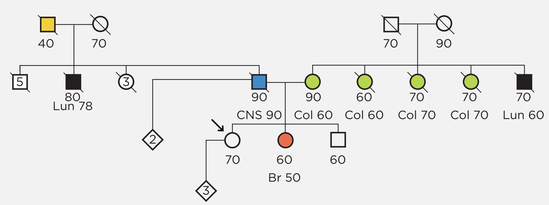
Proband 1 Pedigree

Figure 1: Proband is unaffected woman in her 50's. Her sister had previous genetic testing due to personal history of breast cancer and melanoma diagnosed in her 50's and family history of cancer. Prior testing in the sister identified a pathogenic *CHEK2* (c.470T>C) mutation. Proband's testing identified a pathogenic *BRCA1* (c.4096+1G>A) mutation as well as the *CHEK2* mutation that was identified in her sister. The presence of the *BRCA1* mutation significantly changes the management recommendations for the proband and any other family members. The *BRCA1* mutation likely explains the additional cases of breast cancer in the family. The knowledge of these mutations highlights the need for panel testing in this family.



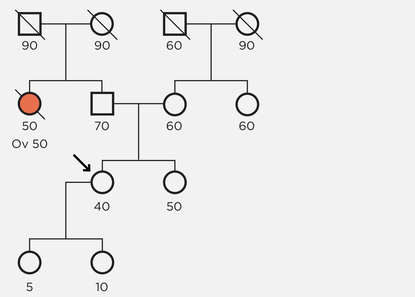
Proband 3 Pedigree

Figure 2: Proband is a woman in her 40's who was diagnosed with breast cancer in her 40's. There is strong family history of cancer on both sides of the family that is suggestive of mutations in high penetrance breast cancer genes. Interestingly, testing identified pathogenic mutations in *ATM* (c.3802delG) and *CHEK2* (c.1100delC). This case demonstrates the need for comprehensive panel testing in all families, including those that would be seemingly explained by mutations in just *BRCA1* or *BRCA2*.



Proband 6 Pedigree

Figure 3: The proband is a woman in her 60's with a family history of multiple cancers, significantly enriched for colorectal cancer. Sister who had breast cancer in her 50's was found to have a *BRCA1* (deletion of exons 20-23) mutation through prior testing. This family does not meet NCCN criteria for *BRCA1* and *BRCA2* gene testing, however the sister had previously elected to get tested. The proband's testing revealed not only the *BRCA1* mutation that her sister carries, but also a mutation in *PMS2* (deletion of exons 6-8). The *BRCA1* mutation likely contributed to the sister's diagnosis of breast cancer but the *PMS2* mutation very likely explains the strong maternal family history of colorectal cancer. It is worth noting that this family does meet NCCN criteria for Lynch syndrome testing. The identification of the *PMS2* gene mutation has clear management implications for the proband as well as her family members.



Proband 7 Pedigree

Figure 4: Proband is an unaffected woman in her 40's with Ashkenazi Jewish ancestry. The only family history of cancer is a paternal aunt with ovarian cancer in her 50's. Proband was found to have both a *BRCA1* (c.68_69delAG) and *CHEK2* (c.1283C>T) mutation. Based on ancestry alone, this patient and her family may have detected the *BRCA1* mutation. However, the *CHEK2* mutation would still have gone undiscovered. This case demonstrates how small family structures can limit the ability to accurately predict the risk for hereditary cancer predisposition.

Table: Detailed Information on Patients with Concurrent Pathogenic Mutations

Proband	Reported Ethnicity	Gene	Mutation	Affected?	Known mutation in family?	Notes
Proband 1	Caucasian; non-AJ	*BRCA1* *CHEK2*	c.4096+1G>A c.470T>C	No	Yes	Reported *CHEK2* mutation in sister.
Proband 2	Caucasian; non-AJ	*ATM* *BRCA1*	deletion of exons 17-63 c.5266dupC	No	Yes	Knew about *BRCA1* mutation on paternal side of the family.
Proband 3	Caucasian; non-AJ	*ATM* *CHEK2*	c.3802delG c.1100delC	Yes	No	No reported mutations in the family.
Proband 4	Caucasian; non-AJ	*ATM* *BRCA2*	c.5758_5759 delAA c.1813delA	No	Knew about both	Already knew about mutations in *ATM* and *BRCA2*.
Proband 5	Caucasian; non-AJ	*BRCA1* *BRIP1* *CHEK2*	c.697_698del GT c.2392C>T c.1100delC	No	Yes	Knew about *BRCA1* mutation in family.
Proband 6	African, Caucasian, Native American; non-AJ	*BRCA1* *PMS2*	deletion of exons 20-23 deletion of exons 6-8	No	Yes	Knew about *BRCA1* mutation in family.
Proband 7	Caucasian; AJ	*BRCA1* *CHEK2*	c.68_69delAG c.1283C>T	No	No	No reported mutations in the family.
Proband 8	Caucasian; AJ	*BRCA1* *CHEK2*	c.68_69delAG c.1283C>T	Yes	No	No reported mutations in the family.

References

LaDuca, Holly, A. J. Stuenkel, Jill S. Dolinsky, Steven Keiles, Stephany Tandy, Tina Pesaran, Elaine Chen, et al. 2014. "Utilization of Multigene Panels in Hereditary Cancer Predisposition Testing: Analysis of More than 2,000 Patients." *Genetics in Medicine: Official Journal of the American College of Medical Genetics* 16 (11): 830–37.

Richards, Sue, Nazneen Aziz, Sherri Bale, David Bick, Soma Das, Julie Gastier-Foster, Wayne W. Grody, et al. 2015. "Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology." *Genetics in Medicine: Official Journal of the American College of Medical Genetics* 17 (5): 405–24.

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Guidelines Version 1.2017. Available at www.nccn.org. Published September 2016.