Multi-gene hereditary cancer panel testing identifies mutations unexpected based on family pedigree: 4 case reports

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Introduction

Current hereditary cancer testing guidelines employ criteria based on personal and family history of cancer to determine eligibility for genetic testing. New data, such as the cases presented here, suggest broader testing may be appropriate given limitations in family history information. The decreasing cost of multi-gene panel tests may facilitate such a broader testing approach. Here were report 4 case studies of probands who underwent multi-gene panel testing and were found to have a mutation that would not have been predicted from their family history alone.

Methods

Participants received genetic testing from Color Genomics (Burlingame, California) either via a 19-gene panel for hereditary breast and ovarian cancer risk (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53*) or a 30-gene panel for hereditary cancer risk (*APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CDKN2A, CHEK2, EPCAM, GREM1, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*). The service includes both clinical genetic testing in a CLIA and CAP accredited laboratory and genetic counseling. Testing for all participants was ordered by a healthcare provider.

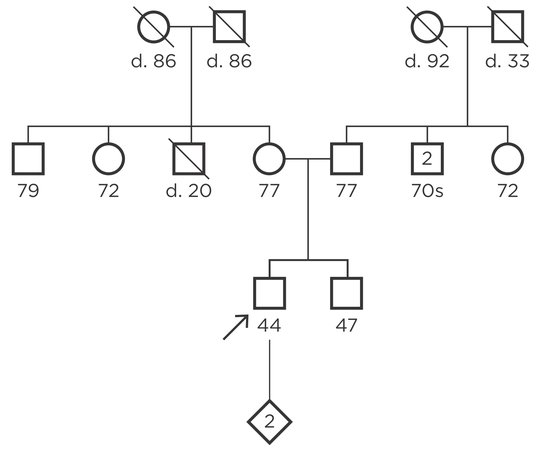
Discussion

- These four cases highlight the clinical utility of broader panel testing to identify mutations that would not be predicted based on family history alone.
- Case 1 exemplifies that current NCCN guidelines can lead to clinically actionable mutations being missed.
- Case 2 shows an example of the limitations of disease-specific panel testing. Even in a family with history of a certain cancer, other clinically actionable mutations may exist that would not be picked up by a narrower panel.
- Case 3 and 4 show that even in families with a known mutation, single-site or single gene testing would have missed clinically actionable mutations. The identification of additional mutations in families with one known family mutation has both clinical implications for the proband and testing implications for their family members. Family members who had previously undergone single site or single gene testing may have been erroneously told they were true negatives.
- Further research is warranted to identify the frequency of mutations in individuals who do not meet current guidelines to inform future testing strategies.

Case Studies

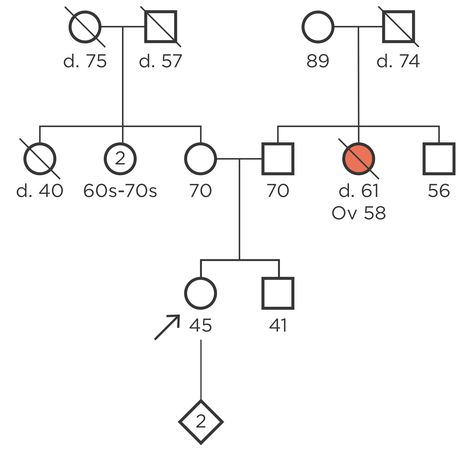
Case 1

An Asian proband, who has a relatively large family with no history of hereditary cancers, was found to have a pathogenic variant in *BRCA2* (c.9117G>A). This proband had 9 first and second degree relatives and 4 third degree relatives with no history of cancer, and therefore would have been ineligible for genetic testing under current NCCN guidelines.



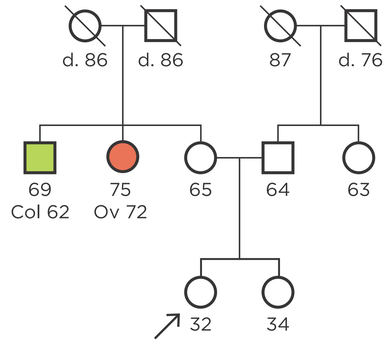
Case 2

A Caucasian proband had a family member with a history of ovarian cancer. No mutations associated with ovarian cancer were found in the proband, but a mutation associated with other hereditary cancers, *ATM* (c.6100C>T), was identified. Limited panel testing for ovarian cancer related genes would have missed this mutation.



Case 3

Here, panel testing revealed an unexpected result in a family where there was a known family mutation (KFM) in *BRCA1*. The KFM was found to be present in the proband's mother, maternal aunt, and maternal uncle. The KFM was confirmed to be absent in the Caucasian proband, but a different mutation was found in *RAD51C* (c.224dupA). Single site testing for just the KFM would have missed this mutation.



Case 4

In this case, a KFM in *BRCA1* had been identified in the proband's sister. Therefore, the proband would likely have only qualified for single site testing. However, using a multi-gene panel, the proband was found to carry the *BRCA1* (c.697_698delGT) KFM as well as mutations in two additional genes (*BRIP1* c.2392C>T and *CHEK2* c.1100delC). These results could have a large impact for family members who may have been told they were true negative for the KFM even though they had one or both of the BRIP1 and *CHEK2* mutations. In this case, single site testing, or a *BRCA1/2* gene testing strategy where reflex to a full panel is only performed if negative, would have missed clinically actionable mutations.