Hereditary cancer gene panel identifies 54 concurrent pathogenic mutation carriers

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Introduction

While there has been a recent shift towards multi-gene panel testing for hereditary cancer risk, the occurrence of concurrent pathogenic mutations and the utility of panels in individuals who have a known family mutation (KFM) is yet to be well understood. We reviewed the personal and family histories of people found to have multiple concurrent pathogenic or likely pathogenic mutations identified by a 30-gene hereditary cancer panel.

Methods

Samples were analyzed with a NGS-based 30 gene panel that included: *APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GREM1, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*. Mutations were classified according to current American College of Medical Genetics and Genomics (ACMG) guidelines[1].

Additional Results

- Three probands had prior knowledge of at least one of the mutations in themselves.
- Twenty-seven individuals (50%) were the first person in their family to undergo genetic testing.
- Nineteen individuals (35%) reported a personal history of cancer.

Conclusions

- Identifying individuals with multiple clinically actionable mutations may have important medical implications for probands and family members.
- These data suggest individuals with a KFM may still benefit from a multi-gene panel test due to the possibility of multiple mutations.
- Lastly, with the cost of testing declining rapidly, the risk of missing a mutation outweighs the arguments against testing with a broader panel. Further research on larger data sets is needed to determine the rate and implications of having concurrent mutations.

Results

Mutation Spectrum

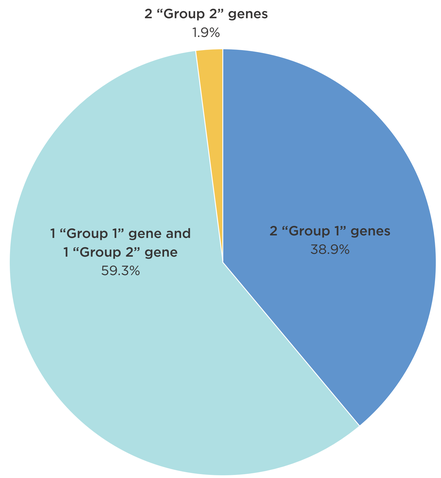
We identified 54 probands with concurrent mutations: 51 probands with two concurrent mutations, two probands with three concurrent mutations, and one proband with a homozygous mutation who was found to have another mutation in a second gene.

The genes and/or specific alleles in which these concurrent mutations were found is listed in Table 1. Mutations known to be lower penetrance are categorized as "Group 2" and all other mutations are categorized as "Group 1". As shown in Figure 1, only one proband had both concurrent mutations in Group 2. Thirty-two (32) had one in Group 1 and one in Group 2. Importantly, 21 probands had two mutations in Group 1.

Table 1

Group	Gene	# of mutations	% of cohort
1	*BRCA1*	13	11.8%
	CHEK2	13	11.8%
	BRCA2	12	10.9%
	MITF	7	6.4%
	NBN	7	6.4%
	ATM	5	4.5%
	MLH1	3	2.7%
	MSH2	3	2.7%
	MSH6	3	2.7%
	BARD1	2	1.8%
	BRIP1	2	1.8%
	PALB2	2	1.8%
	RAD51C	1	0.9%
	RAD51D	1	0.9%
	TP53	1	0.9%
2	*APC* I1307K	13	11.8%
	MUTYH het	12	10.9%
	CHEK2 I157T	10	9.1%

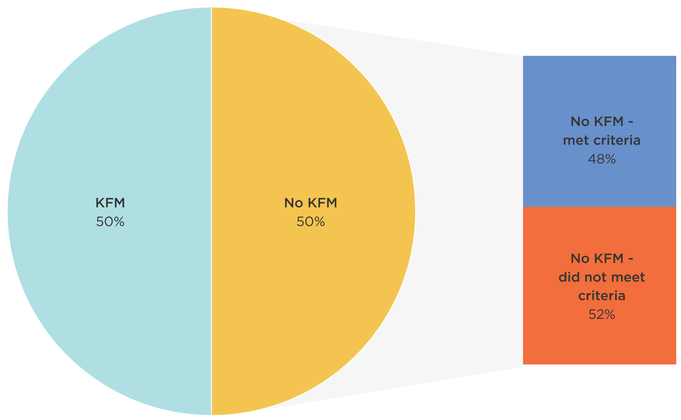
Figure 1



Known Family Mutations

Half of the cohort (27 individuals) had a previously known family mutation (KFM), as shown in Figure 2. Of those that did not have a KFM, over half would not have been eligible for genetic testing. Testing eligibility was determined for at least one gene on the panel based on personal/family history using applicable NCCN guidelines or Medicare, as appropriate depending on age.

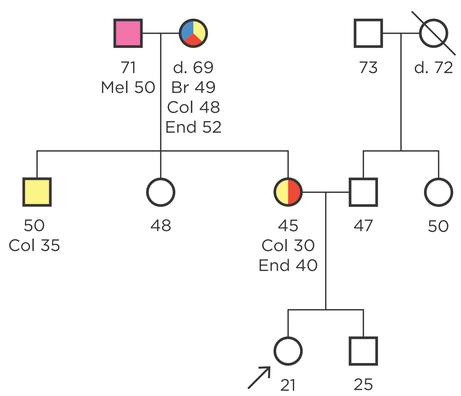
Figure 2



Case Studies

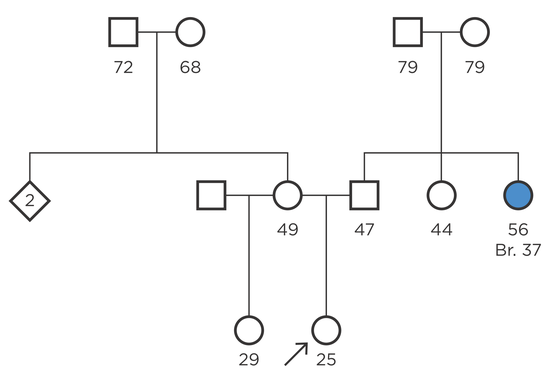
Case Study 1: Third mutation identified in a family with 2 previously identified mutations

In this family there were two mutations previously identified: *ATM* (c.3G>A) and *MLH1* (c.2135G>A). They were found in the mother of two brothers who received genetic testing using Color. One brother was found to carry both of the known family mutations, as well as a third mutation found in *MITF* (c.925G>A). The other brother carried that *MITF* mutation as well as the *MLH1* mutation, and was confirmed to be a true negative for the mutation in *ATM*. Single- or limited-gene testing for the known family mutations may have missed some of the mutations in these 2 and 3 concurrent mutation carriers.



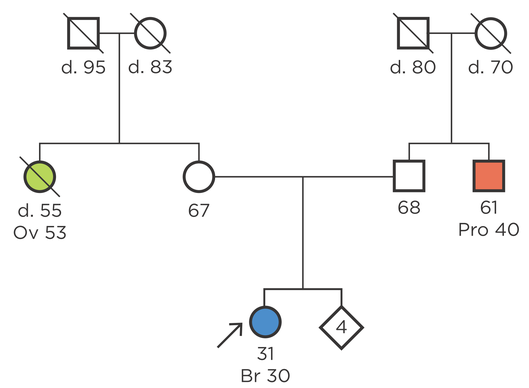
Case Study 2: Second mutation identified with implications for half sibling

This family had a previously known mutation in *BRCA1*, identified in the proband's paternal aunt. In addition to the known family mutation (*BRCA1* c.5346G>A), a second mutation was identified (*CHEK2* c.793-2A>G). While the lineage of this *CHEK2* mutation has not yet been determined, this finding could have important testing implications for the proband's half sister, who might not have otherwise considered testing.



Case Study 3: South American client

This proband is from South America, where genetic testing is much more limited and infrequent than in the United States. There were no known mutations in this family, but two mutations were identified in the proband: *BRCA1* c.2014A>T and *CHEK2* c.846+1G>C. Genetic testing of early diagnosed breast cancer patients in South America is often restricted to *BRCA1/2*, which would have missed this additional *CHEK2* mutation.



References

[1] Richards, S. et al. 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. Genet. Med. 17, 405–424 (2015).