Double jeopardy? A closer look at cancer histories of individuals with multiple germline pathogenic variants

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Background: Germline multigene panel testing has led to the increased detection of multiple co-occurring pathogenic variants (PV) in the same individual. As this occurrence is still relatively rare, reports of these individuals have been limited. Therefore, we sought to describe the clinical features of individuals with multiple PV identified at a single high-volume diagnostic laboratory.

Methods: We performed a retrospective review of demographics and clinical data for individuals with >1 pathogenic or likely pathogenic variant (PV) who underwent hereditary cancer panel testing (5-67 genes) between May 2012 and April 2017. In recessive genes (i.e. *MUTYH*), PV were only included when biallelic. PVs with reduced penetrance (*APC* p.I1307K; *CHEK2* p.I157T, p.S428F, p.T476M) were excluded. In individuals with the most common combinations of genes, personal cancer history and age at cancer diagnosis was evaluated.

Results: A total of 555 individuals were identified with multiple PVs. Most individuals were female (85.1%), had a personal history of cancer (73.3%) and 26.3% had two or more primary cancers. *CHEK2* was most often seen in co-occurrence with a PV in a different gene (137 observations), followed by *ATM* (120 observations), *BRCA2* (110 observations), and *BRCA1* (88 observations). Among cases in which clinical information was provided (n=545), the five most frequent co-occurring combinations were in *ATM/CHEK2* (25), *ATM/BRCA2* (23), *BRCA1/CHEK2* (19), *CHEK2/CHEK2* (16), and *BRCA2/CHEK2* (14). Individuals with co-occurring PVs in *CHEK2/CHEK2* had the youngest age at first cancer diagnosis (mean = 41.5y; median = 42y), the highest rate of breast cancer diagnoses and other cancer diagnoses (100.0% and 70.6% of individuals, respectively), and the highest proportion of individuals with >1 primary cancer (52.9%).

Conclusions:

Our results indicate that individuals with two PVs in *CHEK2* have an average age of cancer onset that is similar to individuals with either a *BRCA1* or *BRCA2* concurrent PV. Additionally, individuals with two PVs in *CHEK2* were more likely to have multiple primary cancers as compared to others in the cohort with concurrent PVs including those with either a *BRCA1* or *BRCA2* concurrent PV (Table). Continued studies, including comparisons to individuals with one PV, will provide valuable insight to aid in counseling and management of individuals with multiple germline PV.

PV Gene Combination	Total individuals	n Female (%) *n Male (%)*	Mean age 1st cancer diagnosis (median)	n breast cancer (%)	n other cancer (%)	n >1 primary cancer (%)
ATM/CHEK2	25	23 (92.0%) *2 (8.0%)*	42.5 (44)	20 (80.0%)	7 (28.0%)	5 (20.0%)
ATM/BRCA2	23	18 (78.3%) *5 (21.7%)*	47.9 (49)	13 (56.5%)	7 (30.4%)	4 (17.4%)
BRCA1/CHEK2	19	17 (89.5%) *2 (10.5%)*	42.1 (43)	10 (52.6%)	7 (36.8%)	4 (21.1%)
CHEK2/CHEK2	17	17 (100.0%) *0 (0.0%)*	41.5 (42)	17 (100.0%)	12 (70.6%)	9 (52.9%)
BRCA2/CHEK2	14	14 (100.0%) *0 (0.0%)*	43.1 (45)	9 (64.3%)	2 (14.3%)	2 (14.3%)