Genetic Insights into Hereditary Cancer Risk in the Global Population

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Introduction

Current hereditary cancer risk data is mostly based on genetic testing performed in Caucasian and Ashkenazi Jewish populations. As a result, the distribution of mutated genes and their associated cancer risk in other ethnicities is not well understood. Asian, Hispanic, and African populations are significantly under-represented in studies and databases of hereditary cancer mutations, despite the clear value this information can provide to populations around the globe[1]. Interestingly, in some countries, more than 1 in 4 breast cancer patients were reported to have a *BRCA* mutation[2], indicating that the proportion of hereditary breast cancers in other populations is even higher than previously reported for high risk Caucasian (12.1%)[3] and Ashkenazi Jewish cohorts (10.3%)[4]. However the utility of multi-gene panels for hereditary cancer risk have not been reported[5]. This study aims to provide insights into hereditary cancer risk across 17 countries across multiple continents for breast cancer as well as ovarian, colorectal, melanoma, pancreatic, prostate, uterine and stomach cancers.

Methods

We describe the demographics and genetic results of 7952 international hereditary cancer high risk individuals from 17 countries (Argentina, Australia, Belgium, Brazil, Canada, Colombia, Spain, Finland, United Kingdom, Greece, Hong Kong, Ireland, Israel, Japan, Mexico, Peru, Uruguay) who received the physician ordered 30-gene or 19-gene Color hereditary cancer test to assess their risk for hereditary cancer.

The 30-gene panel assesses the following genes associated with hereditary breast, ovarian, colorectal, melanoma, pancreatic, prostate, uterine and stomach cancers: *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,* and *TP53*. The 19-gene panel assesses the following genes associated with hereditary breast and ovarian cancer: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11,* and *TP53*. Ethnicity assignments and health history were based on self-reported information. The relatedness of individuals was not assessed in this study.

Conclusions

- Here, we present the results of testing high-risk individuals from 17 countries with a 30-gene panel for hereditary cancer risk and a 19-gene panel for breast and ovarian cancer risk. The overall pathogenic mutation rate was 15.6%.
- Pathogenic variants were identified in 26 different genes on the panel, with proportions varying widely by country, highlighting the utility of broader panel testing in global populations.
- Nearly half of this high-risk cohort reported a personal history of breast cancer. The *BRCA1* and *BRCA2* mutation carrier rate for breast cancer patients in this cohort was 9.9%, which is similar to previously reported rates in Caucasian and Ashkenazi Jewish populations.

References

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Results

Figure 1. Cohort by country and ethnicity

Number of individuals from each country, stratified by reported ethnicity. Overall positive rate in the cohort was 15.6%, and the percent positive by ethnicity was 16.7% for Caucasian, 20.6% for Hispanic, 16.3% for Ashkenazi Jewish, 11.2% for Asian, 13.2% for other ethnicities (including African, Native American, and Multiple Ethnicity), and 13.7% for unknown ethnicities.

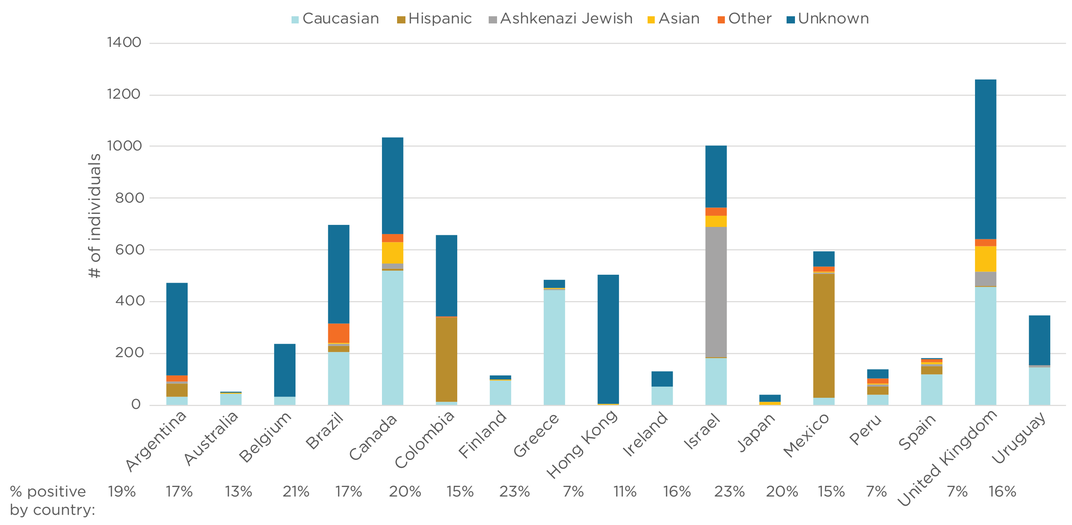

Figure 2. Pathogenic variants identified by gene

Genes in which pathogenic or likely pathogenic variants were identified. The *BRCA1* and *BRCA2* positive rate in the cohort was 5.9%. Importantly, a majority (62.7%) of the pathogenic variants were identified in genes other than *BRCA1* or *BRCA2*. Nine (9) individuals were found to carry two different *MUTYH* pathogenic variants.

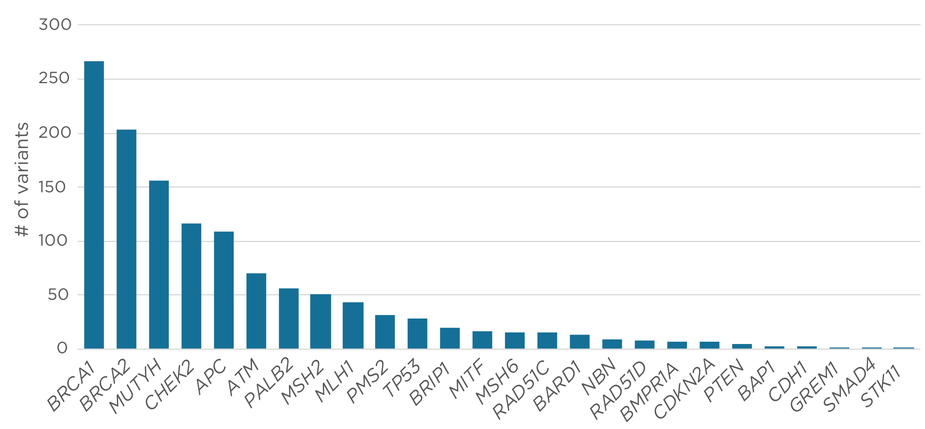

Figure 3. Mutation spectrum by country

Genes in which pathogenic or likely pathogenic mutations were identified, stratified by country.