Exploring trends in mutation distribution of multi-gene panel testing based on ethnicity.

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As the uptake of genetic testing continues to increase, clinicians have questions regarding ethnic-specific mutation rates. Founder mutations explain some variability between ethnic groups, such as the Ashkenazi Jewish *BRCA1* and *BRCA2* founders. We explored differences in mutation frequencies across ethnic groups by reviewing results of 104,875 patients undergoing multi-gene panel testing (MGPT) for hereditary cancer. Ethnicity was self-reported on requisitions or attached pedigrees: Caucasian (n = 68,929), Ashkenazi Jewish (n = 6,454), African American/Black (n = 6,218), Hispanic (n = 5,867), Asian (n = 4,108), Middle Eastern (n = 598), and Native American (n = 119). Individuals with mixed, other, or unknown ethnicity were excluded (n = 12,582). Fisher's exact test was used to compare the frequencies of the detected mutations among different ethnic groups. Interesting findings in this large cohort appeared in several genes. *SDHD* mutations were significantly more frequent in Caucasians (OR 7.995, P = 1.638e-4), with p.P81L accounting for 66.7% of *SDHD* mutations. Mutations in *RAD51D* were most frequent in Asians, with c.270_271dupTA being unique to and accounting for 71.4% of *RAD51D* mutations in this population. Some genes showed ethnicity-specific trends without a major recurrent mutation. *BMPR1A* mutations were most frequent in African Americans (OR 4.267, p = 0.011) and *BRIP1* mutations were most frequent in Caucasians (OR 2.288, P = 3.170e-5). As expected, known founder mutations, such as *APC* p.I1307K and *CDKN2A* p.I49P were more frequent in the Ashkenazi Jewish and Hispanic patients (p<1.053e-6). Our results demonstrate that mutation rates vary between ethnic groups in some genes, not always due to founder effects. This suggests that some genes are worth specific consideration based on a patient's ethnicity when selecting genetic testing or interpreting the test result, such as *BMPR1A* in African Americans suspicious for hereditary colorectal cancer. Possible founder mutations were identified in genes in which data is still emerging, such as *RAD51D* c.270_271dupTA. Improved knowledge of ethnic differences in results can improve genetic counseling and risk predictions. This data underscores the need for large cohorts to draw conclusions regarding founder effects and ethnic variation, particularly for genes in which mutations are exceedingly rare, and to aid in the determination of ethnic-specific polymorphisms and newly described founder mutations.