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Variants of Uncertain Significance (VUS) are More Common in Non-Caucasian Patients with Neuroendocrine Neoplasms (NENs)

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BACKGROUND

Germline pathogenic or likely pathogenic (P/LP) variants occur in approximately 10% of NEN patients with recent data suggesting a higher frequency in pancreatic NENs or paraganglioma/pheochromocytoma (PPGL). However, identification of VUS can complicate interpretation of germline results, particularly when diverse populations are under study and the optimal gene panel size for testing remains unclear.

METHODS

A single-center retrospective chart review was performed in consecutive NEN patients referred for possible germline testing at UCSF. Information was collected on demographics and tumor characteristics (site of origin, differentiation). If germline testing was performed, gene panel size and test results were recorded (P/LP, negative, or VUS).

RESULTS

435 NEN patients were referred for a discussion of germline testing at UCSF between 2004-2022. 64% of referred patients (n=277) proceeded with genetic counseling; 86% (n=239) of these patients underwent germline testing which included reporting of VUS. The test population was 53% (N=128) female; 11% (n=27) Hispanic; 73% White (n=175), 12% Asian (n=29), 3% African American (n=7), 2% American Indian/Alaska origin and Native Hawaiian (n=4), 3% Mixed race (n=8) and 7% Unknown race (n=16). Tumors included well-differentiated (WD) neuroendocrine tumors (NET) in 72% (n=173), 8.3% (n=20) poorly differentiated neuroendocrine carcinoma (NEC), 5.4% unknown differentiation (n=13), plus 13.8% PPGL (n=33). Overall, 20% (n=48) of tested patients harbored a P/LP mutation variant, 33.2% (n=79) had a negative result and report was missing in 2 cases. 46% (N=110) had at least one VUS identified, with Hispanics significantly more likely to harbor a VUS compared to non-Hispanics- 77% (n=21/27) vs 42% (n=88/207) [OR=4.73, 95% CI: 1.74-14.84, p-value<0.001].

Also, VUS detection was significantly higher in non-white population (63.4%, n=40/63) compared to 40.2% of white population (n=70/174) [OR= 2.58, 95% CI: 1.42-4.68, p-value<0.001]. VUS prevalence did not vary by tumor differentiation- 48% of NETs (n=84) and 60% of NECs (n=12) (p=0.25). Germline testing panel size increased over the study period and ranged from 1 to 155 genes panels. Median number of genes was 84, with increased detection of VUS in larger panels (p<0.001).

CONCLUSIONS

VUS detection is common in NEN patients undergoing large panel germline testing and is more frequent in non-white and Hispanic populations. This represents current disparities in clinical genetic testing and genomic research. Larger cohorts of non-white and Hispanic populations are needed to support reclassification of VUS over time. Ongoing work is focused on assessing the downstream consequences of both germline mutations and VUS in NEN patients.

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