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Germline pathogenic/likely pathogenic (P/LP) variants in epithelial neuroendocrine neoplasms: The case for universal germline genetic testing

Matthew Gao[1], Brittany Sears[2], Cassidy Carraway[2], Seth J. Concors[3], Po H. Ear[4], Olatunji B. Alese[4], Andrew Bellizzi[5], Chandrikha Chandrasekharan[6], Renuka Iyer[7], Jennifer A. Chan[8], Simron Singh[9], Daniel M. Halperin[4], Udhayvir S. Grewal[4]

[1]Carver College of Medicine, University of Iowa, Iowa City, IA; [2]Ambry Genetics Corporation, Aliso Viejo, CA; [3]Department of Surgical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; [4]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; [5]Department of Pathology, University of Iowa Hospitals and Clinics, Iowa City, IA; [6]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [7]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [8]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [9]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

BACKGROUND

Current National Comprehensive Cancer Network (NCCN) guidelines for germline testing in neuroendocrine neoplasms (NENs) rely on organ-specific, syndrome-driven algorithms that may not adequately capture hereditary risk. We sought to analyze prevalence of P/LP germline variants in epithelial NENs and investigate relevant associations.

METHODS

Germline genetic testing results were analyzed from 3,611 probands. Cohort 1 included 3,409 patients identified by ICD-10 code C7A (2015–2025). Cohort 2 included 201 consecutively curated patients with pathology information (2019–2021). Except 59 single-gene tests, multigene panels included a mean of 67 and 62 genes in Cohorts 1 and 2, respectively. Data was classified as P/LP, variant of uncertain significance (VUS), or negative. Comparisons of variant classification frequencies between cohorts were performed using chi-square or Fisher's exact tests. Multivariable logistic regression evaluated clinical and demographic predictors of P/ LP variant detection, with results reported as likelihood ratios (LR) and two-sided p-values (<0.05 considered significant).

RESULTS

Among all 3,611 probands, mean age was 56 years in Cohort 1 and 53 years in Cohort 2, with females comprising 63% and 71%, respectively. VUS and negative results differed between cohorts (VUS 21.9% vs 32.9%, p = 0.002; negative 67.4% vs 55.0%, p <0.001), while P/LP rates were similar (10.6% vs 12.1%, p = 1.0), permitting pooled analysis. Overall, 387 patients (10.7%) harbored P/LP variants, with 399 P/LP variants identified across 49 genes.

Sixty percent of P/LP variants were accounted for by CHEK2, MEN1, BRCA2, ATM, FH, HOXB13, PALB2, and BRCA1. Clinically actionable variants per NCCN guidelines were identified in 348 patients (9.6%). Among 479 probands with curated family history, meeting NCCN criteria for multigene testing or having a family history was not predictive of P/LP detection. Logistic regression demonstrated that male sex was a significant predictor of P/LP variants (LR = 4.538, p = 0.03), while age at diagnosis and primary site were not predictive, nor were interaction terms significant.

CONCLUSIONS

In this 10-year, multicohort study of patients at a commercial laboratory, over one in ten patients with epithelial NENs harbored a germline P/LP variant, frequently outside classic hereditary NEN syndromes and inadequately predicted by NCCN criteria, family history, age, or tumor site. These findings suggest that current germline testing frameworks may miss clinically relevant hereditary cancer risk. Broader approaches to germline testing may be needed to improve identification of hereditary cancer risk and enable personalized prevention and surveillance strategies.

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