Majority of *PTEN* mutations identified on multi-gene panel tests are in non-classic patients: Expanding clinical phenotype or incomplete clinical history?

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PTEN hamartoma tumor syndrome (PHTS), including Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), and *PTEN*-related Proteus syndrome (PS), is a phenotypically diverse but well-described clinical condition. Pathogenic *PTEN* mutations are detected in most patients meeting clinical criteria for CS and BRRS (up to 85% and 65%, respectively). However, individuals harboring *PTEN* mutations without meeting criteria for PHTS have been reported. In this study, we sought to characterize the clinical phenotypes of individuals who were found to harbor a pathogenic *PTEN* mutation through hereditary cancer multi-gene panel testing.

A retrospective analysis of 14,897 hereditary cancer multi-gene panels including comprehensive analysis of *PTEN* reported at our laboratory from March 2012 to March 2014 identified 23 cases with pathogenic *PTEN* mutations (0.15%). Multi-gene tests included: high risk breast cancer panel (6 genes), moderate/high risk breast cancer panel (18 genes), colon cancer panel (14 genes), ovarian cancer panel (23 genes), and general cancer panel (28 genes). Clinical histories were reviewed for these cases, with emphasis on whether a clinical diagnosis of CS, BRRS, or other PHTS condition was suspected.

Six of the 23 *PTEN*-positive cases (26.1%) met National Comprehensive Cancer Network (NCCN) CS/PHTS testing criteria. Most of the *PTEN*-positive cases in our study population (n=17, 73.9%) did not meet diagnostic or testing criteria for CS. Of these 17 cases who did not meet criteria, histories were confirmed in 15 by additional consultation with the ordering clinician. Seven individuals reportedly met one major and one minor criterion, five met one major criterion only, one met two minor criteria only, and two individuals met no CS criteria.

Ordering clinician bias toward cancer history may result in incomplete clinical data and explain why most positive patients did not appear to meet CS criteria. It is also possible that a broader PHTS phenotype is being revealed through multi-gene panel testing, which is often ordered for individuals whose clinical features are atypical or of lower penetrance. Follow-up analyses of PHTS features in *PTEN*-positive individuals identified through panel testing, who have a broader spectrum of referral indications, will provide additional insight regarding the lack of CS in a panel-based PHTS-positive cohorts.