Mutations in *STK11* identified exclusively in individuals with clinical histories suggestive of Peutz-Jeghers syndrome

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Abstract:

Pathogenic mutations in STK11 are detected in an estimated 80% of individuals clinically diagnosed with Peutz Jeghers syndrome (PJS). PJS is characterized by gastrointestinal PJS type hamartomatous polyposis, mucocutaneous pigmentation, and cancer predisposition including breast cancer, which can occur at early ages in PJS with up to a 57% breast cancer risk by age 70. Due to the risk of early onset breast cancer, it has been proposed that family members could develop breast cancer prior to polyposis symptomatology. Thus, STK11 has been included on a number of commercially available and academic research hereditary breast cancer (HBC) multigene panel tests. In this study, we sought to identify individuals with a STK11 mutation detected on HBC multigene panels offered by Ambry Genetics from March 2012 through May 2014. We hypothesized that some individuals with HBC in the absence of other PJS features will harbor a STK11 pathogenic mutation. 12,928 individuals underwent panel testing with BRCAplus (BRCA1, BRCA2, CDH1, PTEN, STK11, TP53) or BreastNext (BRCAplus genes and ATM, BARD1, BRIP1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, RAD50, RAD51C, RAD51D). Clinical data submitted via test requisition form and subsequently verified by the clinician was assessed for individuals with a STK11 mutation. Clinical data from an additional 73 individuals with mutations in STK11 identified through single gene testing or another multigene panel was also assessed. Several probands had histories consistent with HBC, however those probands met clinical criteria for PJS. Remaining individuals with a STK11 pathogenic mutation had a clinical diagnosis of PJS or features consistent with PJS, including one individual identified through a HBC panel. The remaining 12,927 individuals referred for HBC multigene panel testing did not harbor a STK11 pathogenic mutation. While variants of unknown significance (VUS) are not common in STK11, having been identified in approximately 0.44% of the HBC multigene cohort, there are significantly more VUS than mutations identified in STK11 on HBC panels ($p<0.001$). This analysis does not support our hypothesis, but rather suggests that inclusion of STK11 may not be appropriate on multigene HBC panels, introducing more uncertain results without improving diagnostic yield. STK11 testing should be reserved for broad spectrum hereditary cancer panels, polyposis panels or single gene analysis in individuals with a history suggestive of PJS.