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Somatic *TP53* mutations detected in germline testing: The importance of phenotypic correlation in cancer predisposition testing *J.N. Weitzel[1], K.R. Blazer[1], H. LaDuca[2], B. Nehoray[1], T. Slavin[2], T. Pesaran[1], C. Rybak[1], I. Solomon[1], M. Neil-Swiller[1], E. Chao[2]*. 1) Clinical Cancer Genetics/Population Sciences, City of Hope, Duarte, CA; 2) Amby Genetics, Aliso Viejo, CA.

Purpose: Analysis of DNA isolated from peripheral blood/saliva is typically used for diagnosis of hereditary cancer predisposition. Results from testing are accepted as representing a patient's germline, as acquired somatic mutations are rare. While somatic *TP53* mutations are detected in multiple cancer types, germline mutations are exceedingly rare and result in Li-Fraumeni Syndrome (LFS). *TP53* mutations are increasingly detected on multi-gene panels, across diverse patient scenarios, suggesting either a broader phenotype or possible detection of clonal populations with an acquired *TP53* mutation. This study evaluated whether somatic interference may be more common in genetic testing than previously anticipated.

Methods: Among patients with pathogenic *TP53* results from multi-gene panel testing, cases were selected with potentially abnormal next-generation sequencing (NGS) metrics, including decreased ratio of mutant to wild-type allele, >2 detected alleles or haplotypes, or large copy-number alterations. Clinical data was obtained from test requisition forms and compared to LFS testing criteria (classic, Chompret, or BC<age 36 years).

Results: Among 166 *TP53* positive cases, 25 were identified as higher risk for somatic interference based on abnormal NGS metrics. None of these families met Chompret or classic diagnostic LFS criteria. Four probands were diagnosed with breast cancer <36 y.o.; this is not significantly different from the testing cohort (n=21,306) as a whole (Fisher's exact test; p=0.16). To date testing additional tissues confirmed somatic origin for 4/25 cases; two were subsequently diagnosed with a hematologic disorder. Although this cohort was defined primarily based on abnormal NGS metrics, we also identified a 63 yo woman with lobular breast cancer who did not meet any LFS criteria, wherein the NGS metrics were unremarkable but subsequent testing, prompted by the clinician because of the discordant phenotype, identified a low-grade lymphoma and absence of the *TP53* mutation in DNA isolated from breast tissue. Investigation of additional cases is underway.

Conclusions: We suggest that somatic *TP53* mutations in blood/saliva may be more common than previously thought. Beyond using NGS quality control measures, clinician recognition of test results inconsistent with a LFS phenotype should create an index of suspicion, and caution is urged in the medical management of patients in whom the only criterion for LFS is a *TP53* mutation.

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