Title:
Characteristics of Li-Fraumeni Syndrome in a CHEK2 multi-gene panel cohort

Authors

Leslie Bucheit, MS, CGC
Ambry Genetics
lbucheit@ambrygen.com

Carla Mason, MS, CGC
Ambry Genetics
cmason@ambrygen.com

Holly LaDuca, MS, CGC
Ambry Genetics
hladuca@ambrygen.com

Rachel McFarland, BS
Ambry Genetics
rmcfarland@ambrygen.com

Shuwei Li, PhD
Ambry Genetics
sli@ambrygen.com

Elizabeth Chao, MD, FACMG
Ambry Genetics
University of Irvine
echao@ambrygen.com

Pathogenic mutations in *CHEK2* have been implicated in some *TP53*-negative patients with Li-Fraumeni Syndrome (LFS) cancer histories. Literature is conflicting regarding LFS phenotype of *CHEK2*+ patients. With the use of multi-gene panel testing, *CHEK2* is investigated in this population more frequently. The purpose of this study was to describe LFS characteristics amongst *CHEK2* mutation carriers (*CHEK2+)*. Clinical histories of 494 patients who underwent panel testing between 3/2012-12/2014 and harbored pathogenic/likely pathogenic *CHEK2* mutations were queried. Where personal and family cancer history (hx) were available, the cohort was analyzed for *TP53* testing criteria met including classic LFS, Chompret, and breast cancer <36 criteria per National Comprehensive Cancer Network guidelines (v1.2015). The cohort was analyzed to determine who met LFS-like (LFL) criteria (Birch or Eeles). The prevalence of LFS cancers including breast (BR), sarcoma (SAR), adrenocortical carcinoma (ACC) and others was also reviewed. *CHEK2* mutations were identified in 594/23555 patients (2.5%). Patients with biallelic mutations in *CHEK2 (*n=7*)*, or with additional mutations in genes other than *CHEK2* (n=52) were excluded from analysis. No *CHEK2*+ patients met criteria for classic LFS; 30/464(6.5%) met Chompret; 3/468(0.6%) met Birch; and 306/494(61.9%) met Eeles. *CHEK2*+ patients who met Chompret criteria (*CHEK2*+ LFS) included 12 1100delC mutation carriers and 18 non-1100delC mutations. No *CHEK2*+ LFS patients reported personal/family hx of ACC. No SAR was reported in non-1100delC carriers. Four patients had multiple LFS cancers: 2/18(11%) non-1100delC and 2/12(16%) 1100delC carriers. 6/12(50%) *CHEK2*+ LFS patients with 1100delC mutations reported BR diagnosed < 36 compared to 6/18 (33.3%)

non-1100delC carriers. 6/12(50%) CHEK2+ LFS patients with 1100delC mutations reported family hx of more than one LFS cancer compared to 7/18 (38%) for non-1100delC carriers. This study confirms the presence of LFS/LFL phenotypes in a subset of *CHEK2*+ patients with both 1100delC and non-1100delC mutations.