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

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BACKGROUND

- Pathogenic mutations in *CHEK2* have been implicated in some *TP53*-negative families with Li-Fraumeni Syndrome (LFS) cancer histories.
- Literature is conflicting regarding LFS phenotypes of individuals who have pathogenic *CHEK2* mutations.
- Multi-gene panel testing allows for analysis of *CHEK2* more frequently for individuals with personal and/or family histories suggestive of LFS.
- Many literature on *CHEK2* is focused on the 1100delC alteration and impact on cancer risk, with little known about non-1100delC mutations.
- The purpose of this study was to describe LFS characteristics among *CHEK2* mutation carriers and explore trends between 1100delC and non-1100delC alterations.

TABLE 1. GENES BY PANEL

	N	Pre-*BRCA1/2*	Pre-*NF1*, *RAD51D*
BreastNext – 17 genes *(ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, TP53)*	262*	36	75
OvaNext - 23 genes *(ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D,STK11, TP53)*	78	6	18
ColoNext - 14 genes *(APC, BMPR1A, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11, TP53)*	45	N/A	N/A
CancerNext - 28 genes *(APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMAD4, STK11, TP53).*	122	16	36
CancerNext-Expanded - 43 genes *(APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FH, FLCN, MX, MEN1, MET, MITF, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, STK11, TMEM127, TP53, TSC1, TSC2, VHL)*	6	N/A	N/A

*184/262 also had analysis of *STK11* prior to its removal from BreastNext in Aug 2014.

METHODS

- Clinical histories of 594 patients with pathogenic /likely pathogenic mutations in *CHEK2* who underwent multi-gene panel testing (Table 1) between 3/2012-12/2014 were queried and analyzed.
- Individuals with biallelic *CHEK2* and/or multiple pathogenic/likely pathogenic mutations were excluded from analysis.

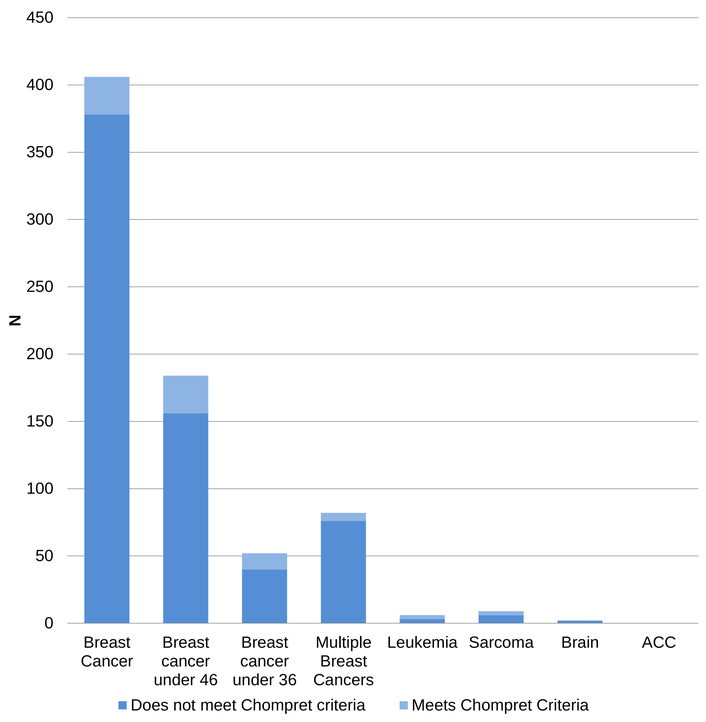
Where personal and family cancer histories were available the cohort was analyzed to:

- Determine who met *TP53* testing criteria including classic LFS, Chompret Criteria, and breast cancer <36 per NCCN guidelines (v1.2015)
- Determine who met LFS-like (LFL) criteria (Birch and/or Eeles)
- Determine the prevalence of LFS cancers including breast, sarcoma, adrenocortical carcinoma and others

RESULTS

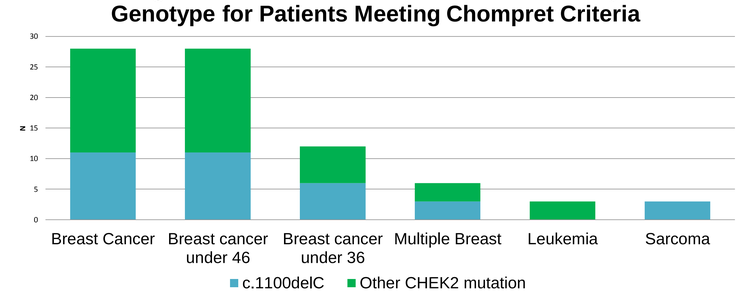
- 594/23,555 (2.5%) of patients who underwent panel testing had a *CHEK2* pathogenic/likely pathogenic mutation.
  - Patients with biallelic (n=7) or with additional mutations in other genes than *CHEK2* (n=52) were excluded.
- LFS/LFL CRITERIA:
  - 0/594 met Classic LFS criteria
  - 30/464 (6.5%) met Chompret Criteria
    - 24/30 (80%) also met Eeles
    - 1/30 (3.3%) also met Birch
  - 3/486 (0.6%) met Birch Criteria
  - 306/494 (61.9%) met Eeles criteria

FIGURE 1. PREVALENCE OF PERSONAL HISTORY OF LFS CANCERS IN *CHEK2* COHORT

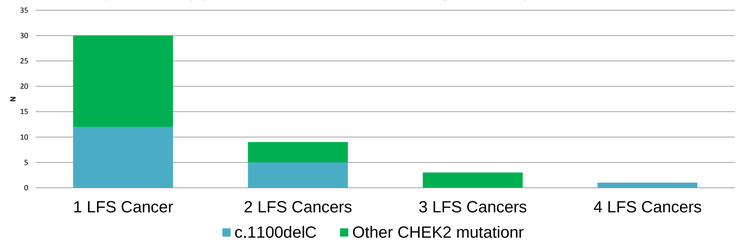


LFS IN *CHEK2* MUTATION CARRIERS

Figure 2: Personal History of LFS Cancers by Genotype for Patients Meeting Chompret Criteria



Firugre 3: Number of LFS Cancers in Family History by Genotype for Patients Meeting Chompret Criteria



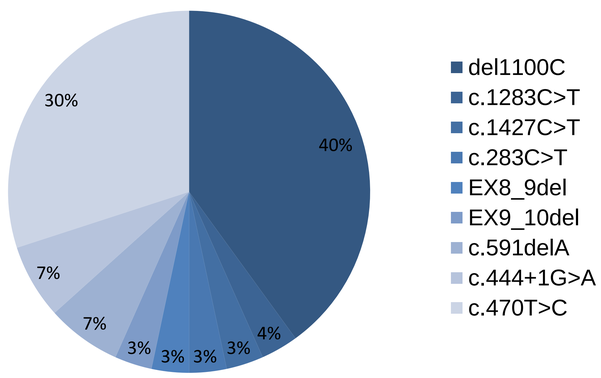
- All patients who met Chompret criteria had a personal history of cancer. Among those diagnosed with breast cancer, all were diagnosed < 46 y.
- There was no reported history of ACC.
- All patients who met Chompret criteria had a family history of cancer. Most patients had 1-2 FDR/SDRs with LFS cancers.
- 1100delC and other mutations are almost equally represented.

LFS/LFL CRITERIA

Criteria	Description
Classic[1]	Individual diagnosed age <45 y with a sarcoma **AND** FDR* diagnosed age <45 y with cancer **AND** additional FDR/SDR* in same lineage with cancer diagnosed age <45 y or sarcoma at any age
Chompret[1] *Needs one*	▪ Individual diagnosed with a tumor from LFS tumor spectrum** before 46 years of age AND at least one FDR/SDR with any of the LFS tumor spectrum cancers (other than breast cancer if the proband has breast cancer) before the age of 56 y OR with multiple primaries at any age ▪ Individual with multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum with the initial cancer occurring before age 46 years ▪ Individual with ACC* or choroid plexus carcinoma at any age of onset, regardless of family history
Birch[2]	Individual with any childhood cancer or sarcoma, brain tumor, or ACC diagnosed < 45 y **AND** a FDR/SDR with a typical LFS-related cancer (sarcoma, breast cancer, brain tumor, leukemia, or ACC) diagnosed at any age **AND** a FDR/SDR in the same lineage with any cancer diagnosed under the age of 60 y
Eeles[3]	Two different tumors that are part of extended LFS in FDR/SDR at any age (sarcoma, breast cancer, brain tumor, leukemia, adrenocortical tumor, melanoma, prostate cancer, pancreatic cancer)

**FDR: First-Degree Relative; SDR: Second-Degree Relative; ACC: Adrenocortical Carcinoma*
***LFS Tumor Spectrum per Chompret: soft tissue sarcoma, osteosarcoma, brain tumor, breast cancer, ACC, leukemia, lung bronchoalveolar cancer*

FIGURE 4. *CHEK2* MUTATION SPECTRUM FOR INDIVIDUALS WHO MET CHOMPRET



TAKE-HOME POINTS

- Hallmark LFS tumors, such as ACC and sarcoma, have a low prevalence among *CHEK2* mutation carriers identified via multi-gene panel testing.
- LFS in a *CHEK2*-positive cohort is best described by Chompret Criteria, although *CHEK2* mutation carriers are also likely to present as LFL.
- Non-1100delC mutations account for 60% of *CHEK2* carriers meeting Chompret criteria; therefore, comprehensive testing of *CHEK2* should be considered in this population when LFS is suspected.
- Comparison studies to LFS and control populations are needed to determine whether an LFS phenotype is truly associated with *CHEK2*.

REFERENCES

1. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian v1.205. www.NCCN.org
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3. Eeles RA (1995). Germline mutations in the TP53 gene. Cancer Surv 25:101-124.