San Antonio Breast Cancer Symposium - December 8-12, 2015

Characterization of Li-Fraumeni Syndrome Using a 25-Gene Hereditary Cancer Panel

Abstract #851614

Thereasa Rich, MS, CGC; Marianne Lotito, MS, CGC; John Kidd, MS; Jennifer Saam, MS, CGC, PhD; Johnathan Lancaster, MD, PhD

Myriad Genetic Laboratories, Inc., Salt Lake City, UT

BACKGROUND

- Li Fraumini syndrome (LFS) is a hereditary cancer syndrome caused by germline mutations in the *TP53* gene.
- LFS is associated with adrenocortical carcinoma, leukemia, and brain cancer, as well as a wide range of other malignancies, including breast cancer, colorectal cancer, melanoma, and sarcoma. These malignancies are often diagnosed at an early age.
- The widespread adoption of multi-gene/syndrome panels for assessment of inherited cancer risk has led to the identification of individuals with pathogenic variants (PVs) in *TP53* who would not previously have been tested for LFS.
- Establishing the significance of PVs in *TP53* detected with clinical testing may be complex. Next Generation Sequencing (NGS) technology is able to more reliably and precisely detect variants present with allele frequencies other than the expected 50%. This appears to be especially common for *TP53* and may be indicative of somatic mosaicism rather than LFS in some patients.

AIMS

- This analysis evaluated the clinical characteristics of individuals identified as having a *TP53* PV through clinical testing with a 25-gene hereditary cancer panel.
- Clinical characteristics of individuals with likely germline PVs were summarized and compared to the overall testing cohort and individuals suspected of somatic mosaicism for *TP53* PVs.

METHODS

- Patients with a PV in *TP53* were identified from 135,609 consecutive cases tested with a 25-gene hereditary cancer NGS panel.
- PVs were defined as all mutations that received a laboratory classification of Deleterious or Suspected Deleterious.
- Patient clinical data were obtained by healthcare provider report on test requisition forms.
- Each *TP53* mutation carrier was evaluated to determine whether the National Comprehensive Cancer Network (NCCN) guidelines were met for *TP53* testing.
- For this analysis, *TP53* PVs observed with NGS read frequencies that were highly imbalanced were defined as likely somatic.

RESULTS

- 82/128 individuals found to have a PV in *TP53* carried a likely germline mutation, based on allele frequency (Table 1).
  - The mean age at first cancer diagnosis was 40.0 years of age.
  - 89.0% (73/82) had a personal history of cancer.
- 30.5% (25/82) of individuals with a likely germline *TP53* PV had more than one cancer diagnosis (Table 2).
  - This is substantially higher than the general testing population (10.6%).

Table 1. Demographics

		TP53 PV Carriers	Remaining Testing Cohort
Age at Testing	N	82	135,332
	Mean (SD)	45.9 (16.14)	48.6 (13.52)
	Min, Max	19, 83	8, 101
Age at First Cancer Diagnosis	N	72	62,202
	Mean (SD)	40.0 (15.25)	49.1 (12.74)
	Min, Max	11, 79	0, 96
Gender	Male	5 (6.1%)	4,243 (3.1%)
	Female	77 (93.9%)	131,238 (96.9%)
Cancer Status	Affected	73 (89.0%)	63,638 (47.0%)
	Unaffected	9 (11.0%)	71,843 (53.0%)

Table 2. Number of Cancer Diagnoses

Number of Cancers	*TP53* PV Carriers (N = 82)	Remaining Testing Cohort (N = 135,481)
0 (No Cancer)	9 (11.0%)	71,843 (53.0%)
1	48 (58.5%)	49,299 (36.4%)
2	15 (18.3%)	11,505 (8.5%)
3	4 (4.9%)	2,258 (1.7%)
4	4 (4.9%)	460 (0.3%)
5	2 (2.4%)	92 (0.1%)
6	0	18 (<0.1%)
7	0	3 (<0.1%)
8	0	3 (<0.1%)

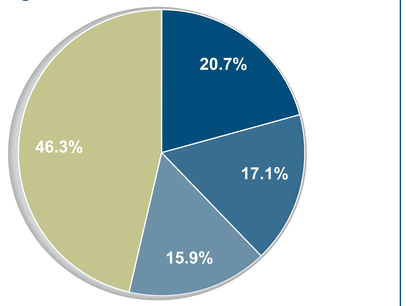
- Table 3 summarizes the personal cancer history among individuals with a likely germline *TP53* PV and the overall testing population.
  - The most common cancer diagnosis was breast (67.1%), which was greatly enriched relative to the remaining testing cohort (32.1%).
  - Other hallmark LFS cancers (brain, sarcoma, melanoma) are also enriched in *TP53 PV* carriers.
  - 43.6% (24/55) of women with a personal history of breast cancer were diagnosed ≤35 years of age, compared to 8.4% in the remaining testing cohort.
- Of the 25 individuals with more than one primary cancer diagnosis, 20 (80%) had a second primary at a site for which increased surveillance is recommended in LFS.
  - 16 of these individuals would not have met NCCN criteria for *TP53* testing at their first cancer diagnosis.

Table 3. Personal Cancer History*

Cancer Type	*TP53* PV Carriers (N = 82)	Remaining Testing Cohort (N = 135,481)
No Cancer	9 (11.0%)	71,843 (53.0%)
Breast	55 (67.1%)	43,472 (32.1%)
Women Diagnosed ≤ 35	24 (43.6%)	3,632 (8.4%)
Brain	1 (1.2%)	23 (<0.1%)
Sarcoma	3 (3.7%)	204 (0.2%)
Melanoma	3 (3.7%)	1,755 (1.3%)
Colon	7 (8.5%)	4,919 (3.6%)
Colon (polyps)	3 (3.7%)	4,284 (3.2%)
Endometrial	0	3,230 (2.4%)
Gastric	1 (1.2%)	186 (0.1%)
Ovarian	9 (11.0%)	8,323 (6.1%)
Pancreas	1 (1.2%)	423 (0.3%)
Prostate	2 (2.4%)	232 (0.2%)
Other	13 (15.9%)	7583 (5.6%)
Other (polyps)	0	63 (<0.1%)

*Includes multiple cancers in a single individual

Figure 1. Proportion of Individuals with *TP53* PVs who Met Testing Criteria



- Overall, 54% of individuals with a likely germline PV in *TP53* presented with some clinical concern for LFS.
- 31 likely germline *TP53* carriers met NCCN criteria for *TP53* testing (Figure 1).
  - 17 individuals met NCCN testing criteria based only on having early onset breast cancer.
  - 14 individuals had family histories consistent with LFS and met Chompret criteria.
- 13 individuals did not meet criteria themselves but had a first- or second-degree relative who did.

Table 4. Clinical Characteristics of Individuals Identified as Carrying a Likely Somatic PV in *TP53* (n=46)

Age at Testing*	Mean (SD)	59.2 (14.90)
Age at First Cancer Diagnosis**	Mean (SD)	49.3 (13.91)
Gender	Male	3 (6.5%)
	Female	43 (93.5%)
Cancer Status	Affected	44 (95.7%)
	Unaffected	2 (4.3%)
Diagnosed with Breast Cancer	N	28
	Women Diagnosed ≤ 35	6 (21.4%)
Met Testing Guidelines*	N	5 (11.1%)

*45/46 individuals were evaluable **44/46 individuals were evaluable

- 46/128 (35.9%) individuals with a *TP53* PV displayed allelic imbalance, consistent with somatic mosaicism, rather than an inherited germline mutation.
- 5/46 (10.9%) individuals with likely somatic PVs in *TP53* met NCCN testing criteria, all of whom met based on a personal diagnosis of early onset breast cancer.
- Table 4 shows that there are some distinct differences between individuals with a likely somatic PV in *TP53*, relative to likely germline carriers.
  - Older mean age at diagnosis (49.3 vs 40.0).
  - Higher proportion of affected individuals (95.7% vs 89.0%).
  - Lower incidence of breast cancer before age 35 in women (21.4% vs 43.6%).

CONCLUSIONS

- This analysis demonstrates that a high proportion of likely germline *TP53* PV carriers would not have been identified as at risk for LFS based on NCCN guidelines.
- Individuals with likely germline *TP53* PVs in this cohort have a much higher risk for multiple primary cancers and early onset breast cancer relative to the remaining testing cohort. This highlights the value of a multi-gene/syndrome panel for the identification of individuals who can benefit from targeted surveillance and other cancer risk reduction interventions.
- Approximately one-third of the *TP53* PVs detected displayed allelic imbalance and the clinical presentation of these individuals were distinct from the likely germline carriers. This is consistent with other recent reports, supporting the need for caution in the interpretation of *TP53* PVs detected in individuals with results suggestive of mosaicism or absent of any clinical history consistent with LFS.
- Every PV in *TP53* should be evaluated cautiously in light of the patient's clinical history and follow-up testing may be appropriate.

Presented at SABCS - December 11, 2015