Personal and Family Cancer History in Li-Fraumeni Syndrome Diagnosed on Multi-gene Testing

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Introduction:

- Next Generation Sequencing (NGS) has created the ability for cost effective evaluation of more than one cancer predisposition syndrome simultaneously
- The emergence of NGS testing has led to unexpected results in families that do not meet previously established clinical criteria for various cancer predisposition syndromes
- The gold standard for a clinical diagnosis of LFS includes Classic LFS and Chompret criteria

Methods:

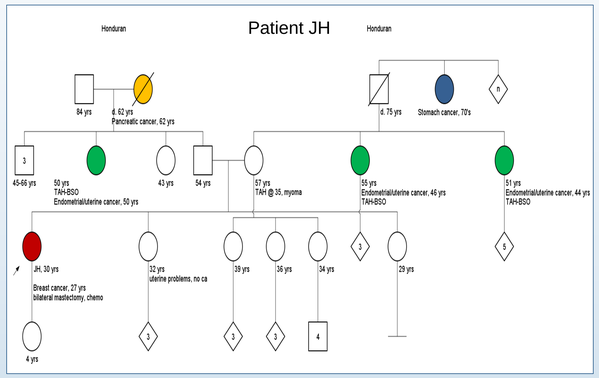
- A chart review was performed to determine personal and family history characteristics of patients who tested positive for a deleterious *TP53* mutation on pan-cancer (broad spectrum) multi-gene testing for twenty five or more genes
- Utilized NCCN Guidelines to determine testing eligibility for Li-Fraumeni Syndrome
- Reviewed recommended screenings

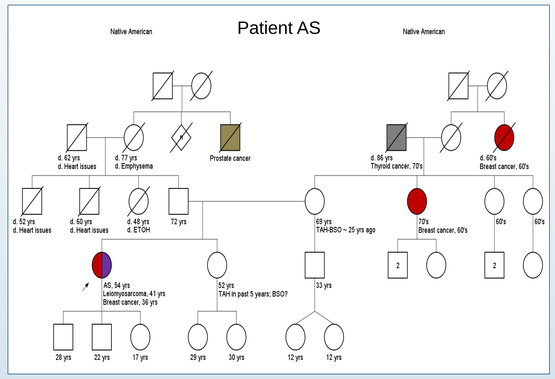
Results:

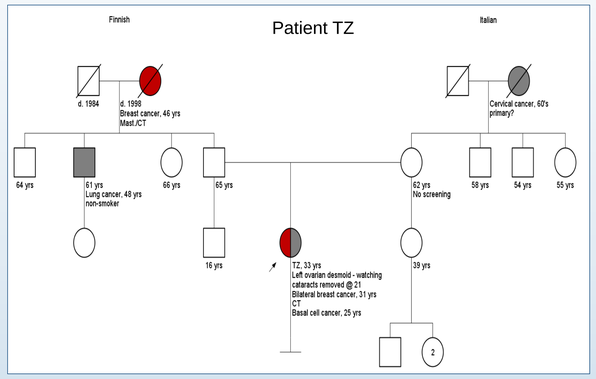
- Between April 1, 2014 and March 31, 2015, 441 patients received results from pan-cancer multi-gene testing
- Five patients tested positive for a deleterious *TP53* mutation of whom:
  1) Four patients did not meet recognized clinical diagnostic criteria (classic or Chompret) for a diagnosis of LFS at the time of testing
  2) Three patients met NCCN clinical testing guidelines for LFS
  3) Two patients did not meet clinical diagnostic criteria or NCCN clinical testing guidelines
- All mutations identified were previously described pathogenic mutations
- All mutations were previously identified in at least one individual who met classic LFS or Chompret criteria

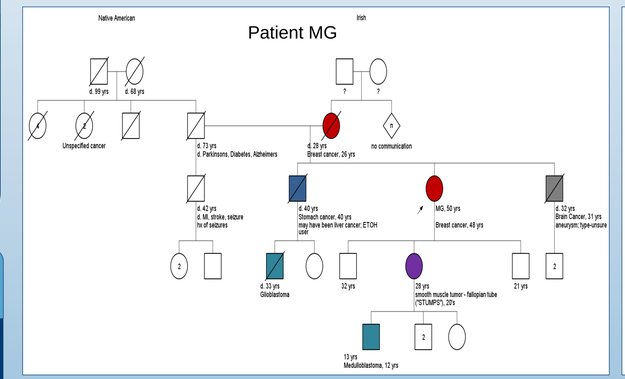
Testing Ordered and Li-Fraumeni Testing Criteria

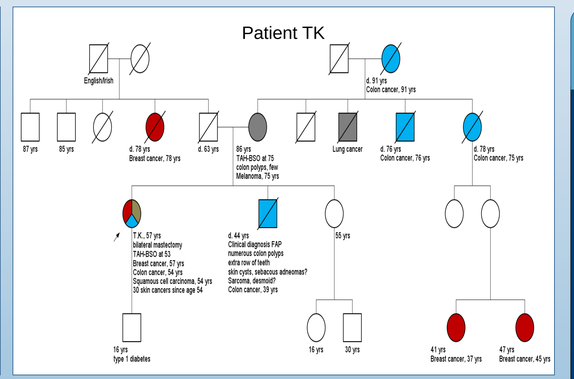
Patient	Test	Classic LFS Criteria	Chompret Criteria	NCCN Testing Guidelines	None
JH	CancerNext™ (28 genes)			X	
AS	CancerNext™ (28 genes)		X		
TZ	myRisk™ (25 genes)			X	
MG	Hereditary Cancer Syndromes (29 genes)				X
TK	CancerNext™ (28 genes)				X











Mutation Description

Patient	Mutation	Classification	Novel vs Previously described	Comments
JH	c.-2G>A	Pathogenic	Previously described	• Described/detected in numerous LFS families
AS	5'UTR_3'UTRdel	Pathogenic	Previously described	• One report in literature: female with breast cancer at 46, leiomyosarcoma at age 49
TZ	c.542G>A	Pathogenic	Previously described	• Reported in the literature in one family with LFS and in an individual with early onset breast cancer • Studies indicate disruption of protein function
MG	c.584T>C	Pathogenic	Previously described	• Reported as de novo in a patient with glioblastoma and colon cancer • Studies have shown the missense change causes functional inactivation
TK	c.817C>T	Pathogenic	Previously described	• Reported in multiple families who met classic LFS/Chompret criteria • Reported to have loss of transactivation capacity and dominant negative phenotype • Position is a mutation hot spot

Discussion:

- This series highlights the high variability in expressivity of what is historically considered a highly penetrant inherited cancer predisposition syndrome
- Given the majority of our families did not meet clinical diagnostic criteria for LFS, it is clear that multi-gene testing is leading to widening of the disease phenotype
- Identification of families who do not meet clinical diagnostic criteria presents many unanswered questions:
  - existence of genotype/phenotype correlations
  - the presence of genetic or environmental modifiers
  - refinement of quantifying cancer risks
- In this series mutations identified are all previously described in LFS families leading to recommending classic LFS screening guidelines even though some of these families didn't meet testing criteria
- There is a need to more broadly assess genotype/phenotype correlations, cancer risks, risk modifiers, and ultimately be able to advise these patients about cancer risk management

References:

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