Mutations in *STK11* identified exclusively in individuals with clinical histories suggestive of Peutz-Jeghers syndrome

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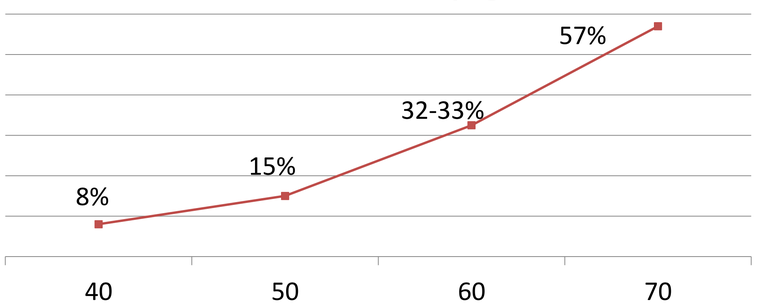
BACKGROUND

- Pathogenic mutations in *STK11* are detected in approximately 80% of individuals clinically diagnosed with Peutz-Jeghers syndrome (PJS).
- Due to the risk of early onset breast cancer, it has been proposed that family members could develop breast cancer prior to polyposis symptomatology.[1] Thus, *STK11* has been included on a number of commercially available and academic research hereditary breast cancer (HBC) multigene panel tests.
- In this study, we sought to identify individuals with a *STK11* mutation detected on HBC multigene panels offered by Ambry Genetics. We hypothesized that some individuals with HBC in the absence of other PJS features will harbor a STK11 pathogenic mutation.

Clinical Features of PJS

- **Hamartomatous polyps (PJS-type)**
  - Interdigitating smooth muscle bundles in a characteristic arborizing (branching tree) appearance throughout the polyp. Bundles extend into the submucosa, muscularis propria, and even the bowel wall.[1]
- **Cutaneous pigmentation**
  - Particularly on the lips and other oral mucosa, hands, and feet.
- **Cancer predisposition**
  - 9-11 fold increased risk for cancer compared to general population.[1]
  - Increased risk for breast, colorectal, gastric, pancreatic, and ovarian cancers.

Breast Cancer Risk by Age[2,3]



METHODS

- Between March 2012 and May 2014, 12,928 individuals underwent panel testing with BRCAplus (*BRCA1*, *BRCA2*, *CDH1*, *PTEN*, *STK11*, *TP53*) or BreastNext (BRCAplus genes and *ATM*, *BARD1*, *BRIP1*, *CHEK2*, *MRE11A*, *MUTYH*, *NBN*, *NF1*, *PALB2*, *RAD50*, *RAD51C*, *RAD51D*).
- Clinical data submitted via test requisition form and subsequently verified by the clinician was assessed for individuals with a *STK11* pathogenic mutation.
- Clinical data from an additional 75 individuals with a pathogenic mutation or variant, likely pathogenic (ie pathogenic findings) in *STK11* identified through single gene testing or another multigene panel was also assessed.

Figure 1. Pathogenic Finding by HBC Panel in Genes with Syndromic Features

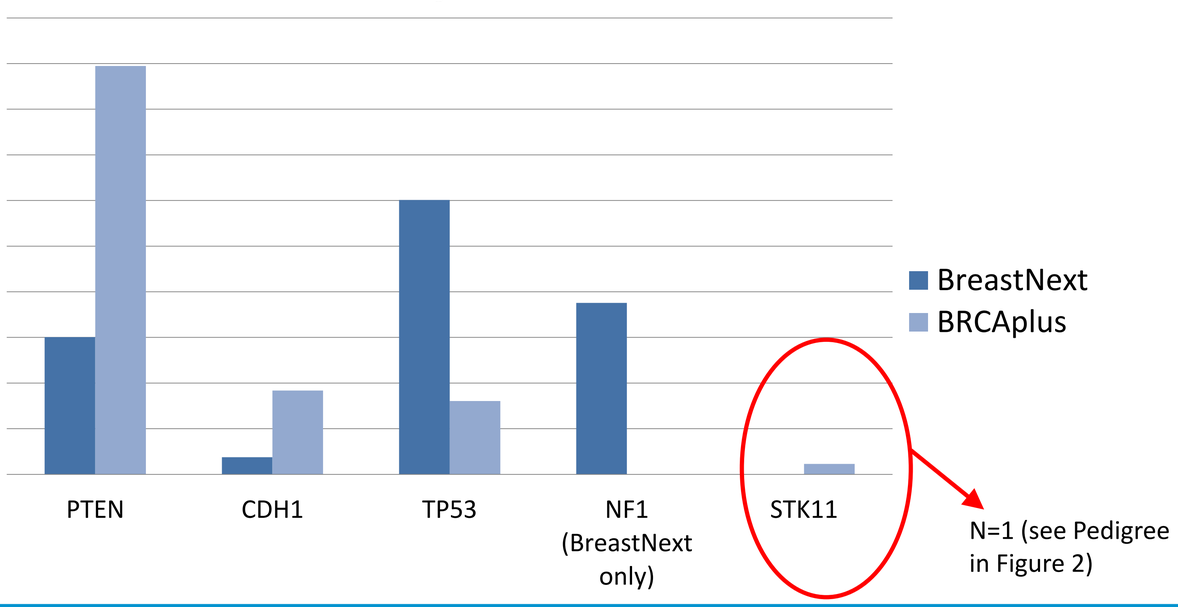
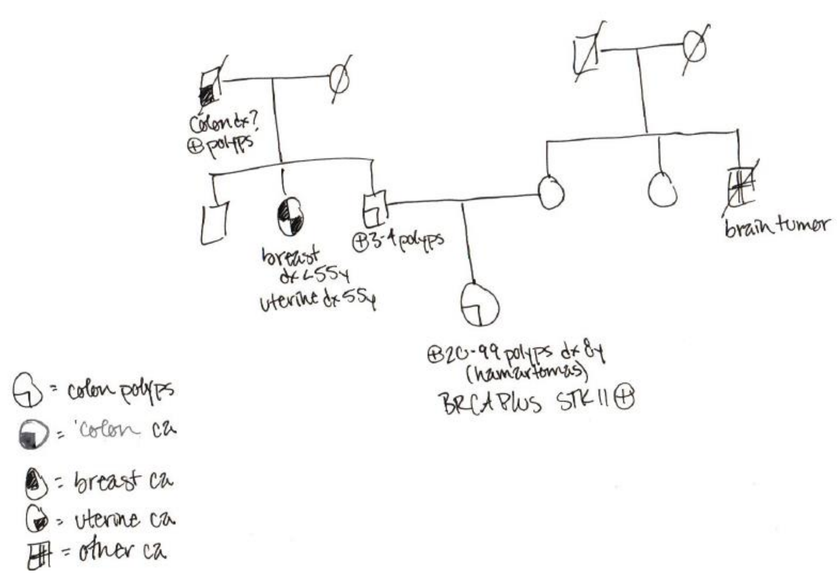


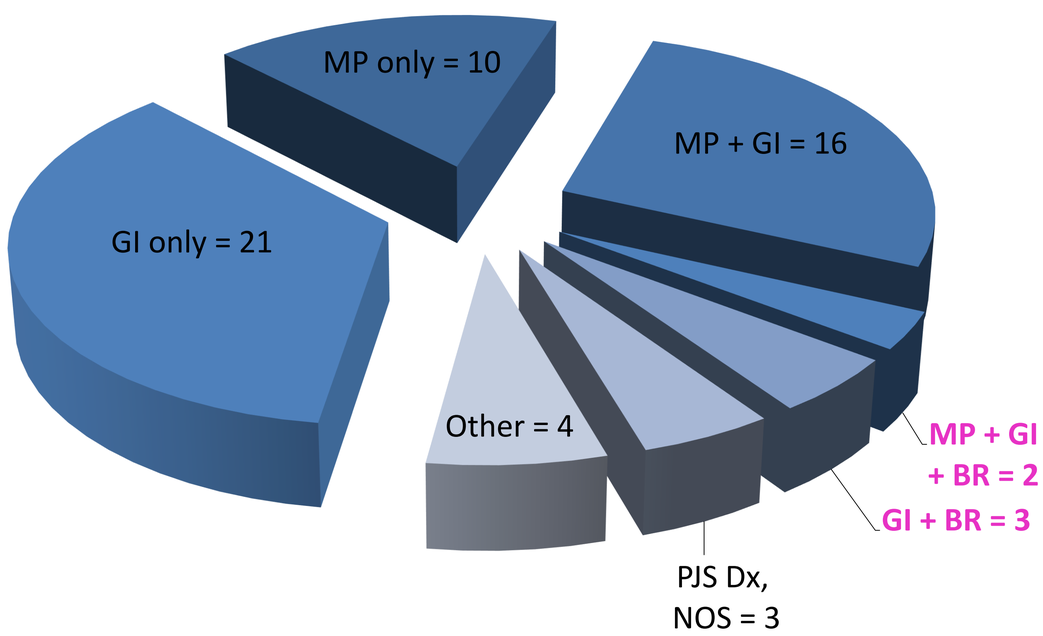
Figure 2. HBC Panel *STK11* Positive Family



RESULTS

- Only 1/12,928 referred for HBC multigene panel testing carried a *STK11* pathogenic mutation.
- 75 additional *STK11* pathogenic findings have been identified in our cohort, including 3 on hereditary colon cancer panels, 1 on a hereditary cancer panel, and 71 on *STK11* single gene analyses.
- Individuals with a *STK11* pathogenic mutation had a clinical diagnosis of PJS and/or features consistent with PJS. Those without clinical data submitted were 23 years old or younger.
- Of the 5 individuals with breast cancer (see Figure 3), all had additional features consistent with a PJS diagnosis.
- Variants of unknown significance (VUS) in *STK11* were identified in 0.44% of the HBC multigene cohort.
  - There are significantly more VUS than mutations identified in *STK11* on HBC panels ($p<0.001$).
- 12/76 (15.8%) of all mutations identified were gross deletions/duplications.

Figure 3. Clinical Features of *STK11* Positives



Legend:
GI, Gastrointestinal; MP, Mucocutaneous Pigmentation; BR, Breast Cancer; PJS Dx NOS, Clinical Diagnosis of Peutz-Jeghers syndrome without specific features provided; other – individuals without clinical information provided, but young ages (2, 15, 15 and 23 years of age).

TAKE-HOME POINTS

- *STK11* testing should include gross deletion/duplication and gene sequencing analysis.
- Breast cancer alone is not an indication for *STK11* testing; however, individuals with breast cancer plus hamartomatous polyps and/or mucocutaneous pigmentation should undergo *STK11* evaluation.
- Inclusion of *STK11* is not appropriate on multigene HBC panels, introducing more uncertain results (VUS) without improving diagnostic yield.
- *STK11* testing should be reserved for broad spectrum hereditary cancer or polyposis panels or for single gene analysis in individuals with a history suggestive of PJS.

REFERENCES

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