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Beyond *BRCA1/2*: Expanding Phenotypes for Probands with *CDH1, PTEN, STK11,* and *TP53* Mutations

BACKGROUND

- Clinical management and genetic testing guidelines currently exist for four hereditary breast cancer susceptibility genes beyond *BRCA1/2*: *CDH1*, *PTEN*, *STK11* and *TP53*.
- Although these genes are associated with defined genetic syndromes, testing criteria have broadened in scope as non-classic probands are found to harbor mutations. For example, the National Comprehensive Cancer Network (NCCN) has recently increased the early-onset breast cancer testing criterion in its *TP53* testing guideline from under age 30 to under age 36.
- We aimed to study whether individuals with a mutation in *CDH1*, *PTEN*, *STK11* or *TP53* identified by multi-gene panels met testing criteria or diagnostic criteria for their respective genetic syndromes.

METHODS

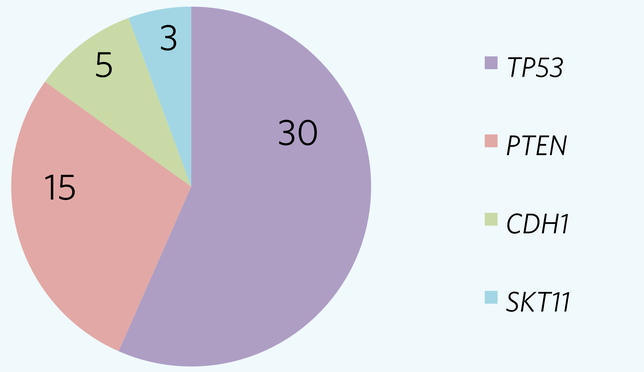
- 6215 probands underwent next generation sequencing with one of 5 hereditary cancer panels: *BRCA*plus, BreastNext, OvaNext, ColoNext or CancerNext.
- Sanger sequencing was performed to confirm reportable findings and regions with insufficient depth of coverage.
- Clinical information was obtained from test requisition forms submitted by clinicians to determine whether published clinical diagnostic/ testing criteria were met[1-4], with clinician follow-up for additional information when necessary.

Case Examples

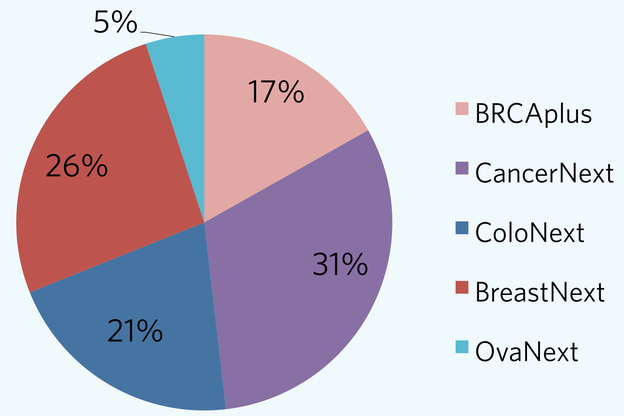
	Mutation Type	Panel Ordered	Proband History	Family History
CDH1 Case 1	Splice Site*	BreastNext	Bilateral breast cancer (ILC – 40)	Several paternal aunts with breast cancer (age unknown), father and paternal 1st cousin with sarcoma.
CDH1 Case 2	Splice Site*	ColoNext	Adenomatous polyps (54), CRC (54 & 59)	Mother breast cancer (63), sister renal cell carcinoma(65), brother with 10-99 pre-cancerous polyps (61) who also carries this *CDH1* mutation.
PTEN Case 1	Frameshift	BreastNext	Breast cancer (ILC- 37)	Mother with ovarian cancer (62), father with prostate cancer, paternal grandmother with breast cancer (70s).
PTEN Case 2	Promoter	OvaNext	Ovarian cancer (69)	Sister ovarian cancer (56), maternal grandfather stomach (70s), paternal uncle bone cancer (70s).
TP53 Case 1	Missense	*BRCA*plus	Breast cancer (IDC -44)	Mother diffuse gastric cancer (72), paternal cousin with ovarian cancer dx unknown age.
TP53 Case 2	Gross deletion	*BRCA*plus	Breast cancer (IDC - 42), DCIS (50)	Maternal great aunt 1 breast cancer (71), maternal great aunt 2 breast cancer (55).
TP53 Case 3	Missense	OvaNext	DCIS (38), *BRCA1/2, PTEN, CHEK2* previously negative	Sister breast (48), paternal cousin breast (29), paternal cousin breast (40s) & ovarian (age?), paternal aunt breast (40) paternal aunt colon (60s), mother endometrial (62), maternal aunt colon (60s), maternal cousin breast (50s), maternal cousin breast (40s) & leukemia (48), maternal grandmother breast (72).

*Individuals carried the same mutation

Mutation Distribution By Gene



Proportion of Mutations by Panel



Mutation Distribution By Panel *and* Gene

	TP53	*PTEN*	*CDH1*	*STK11*	Total
BRCAplus	11	4	2	1	18
CancerNext	7	1	0	1	8
ColoNext	3	4	2	1	10
BreastNext	7	4	1	0	12
OvaNext	2	2	0	0	4
Total	30	15	5	3	53

Interesting Observations Among Mutation Carriers

TP53:

- 9 individuals with a personal history of breast cancer diagnosed over age 35 without a family history sufficient to meet *TP53* testing criteria
- Multiple families presented with predominantly breast and ovarian cancer in the family

CDH1:

- Gastric cancer was seen in only 1 proband with a mutation

PTEN:

- Cancer histories were diverse, including 2 probands with ovarian cancer
- Strong potential for bias in information collected by clinician and/or reported on the requisition form to be specific to HBOC or colorectal cancer, rather than *PTEN*-related characteristics

STK11:

- All probands with *STK11* mutations met criteria for juvenile polyposis syndrome. This continues to be our experience.

OVERALL RESULTS

- 53 mutations in these four genes were identified among 6215 individuals tested (0.85%) across 5 panels, thus with variability in clinical presentation and reason for referral.
- 57% did not meet criteria for the related syndrome:
  - *TP53* – 53% (16/30)
  - *PTEN* – 80% (3/15)
  - *CDH1* – 80% (4/5)
  - *STK11* – 0% (0/3)
- *BRCA1/2* - 3.9% of individuals were found to carry a mutation in the *BRCA1/2* genes in the subset of these panels in which the *BRCA1/2* genes were included.

TAKE-HOME POINTS

- A substantial portion of mutation carriers will be missed if testing is restricted to individuals meeting current single-gene testing criteria.
- Results suggest that further research is needed, as broadening criteria for testing may be necessary.
- Clinical management guidelines differ dramatically between genes, making an accurate genetic diagnosis imperative for medical management.
- Results also suggest that multi-gene panels are an effective strategy for identification of individuals with a hereditary predisposition to cancer, yielding increased identification of mutation carriers compared to traditional testing methods.

REFERENCES

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