Mosaic Deletion of the *APC* Gene is Associated with an Increased Risk of Hematological Malignancy

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BACKGROUND

- The mosaic loss of the *APC* gene detected as part of multi-gene hereditary cancer panel testing on peripheral blood samples most likely reflects loss of the long arm of chromosome 5 (5q).
- Deletion of 5q is implicated in various hematological malignancies including therapy-related myelodysplastic syndrome (t-MDS) and acute myeloid leukemia (t-AML).[1]
- Therapy-related neoplasms are thought to be caused by treatment with cytotoxic agents, such as chemotherapy.[2,3]

OBJECTIVE

- To determine whether individuals with mosaic deletions of the *APC* gene are at increased risk of developing MDS/AML or t-MDS/AML.

METHODS

Cohort

- The patient cohort included individuals undergoing multi-gene hereditary cancer panel testing at a single laboratory over a 5-year period.

Analysis

- The frequency and type of hematologic malignancies in individuals with a mosaic *APC* deletion were evaluated.
- Personal cancer history was also evaluated, and included primary cancer type, age of diagnosis, age at time of genetic testing and secondary cancer (if applicable).
- Individuals were assessed according to whether or not they carried a mosaic deletion in *APC*.

Genetic Testing

- Primary identification of the deletion was performed using either next-generation sequencing (NGS) dosage analysis or comparative genomic hybridization (microarray-CGH).
- Confirmatory testing was performed using either microarray-CGH or multiplex ligation-dependent probe amplification (MLPA).
- Patients with certain hematological malignancies are typically ineligible for germline genetic testing because of the potentially confounding effect of these disorders on results. However, the cases of MDS presented in this study were either undisclosed or unknown at the time of genetic testing.

RESULTS

- Mosaic *APC* deletions were identified in 22 individuals.
  - All 22 individuals had a positive personal cancer history (Table 1).
  - 4/22 had t-MDS (Figure 1); 1/22 had thrombocytopenia.
  - All 4 with t-MDS had a personal history of breast cancer.
  - The 10-year incidence of t-MDS/AML in breast cancer patients overall is <2%.[2,4]

Table 1. Characteristics of individuals with mosaic *APC* deletions, by primary cancer diagnosis.

Primary Cancer	Secondary Cancer	MDS	*TP53* Mutation
Breast (n=13)	7	4	3
Ovarian (n=7)	0	0	3
Other (n=2)	1	0	1
Total (n=22)	8	4	7

Figure 1. Relationship between personal cancer history and MDS. Among patients with a mosaic deletion of the *APC* gene, those with a history of breast cancer were most likely to develop t-MDS.

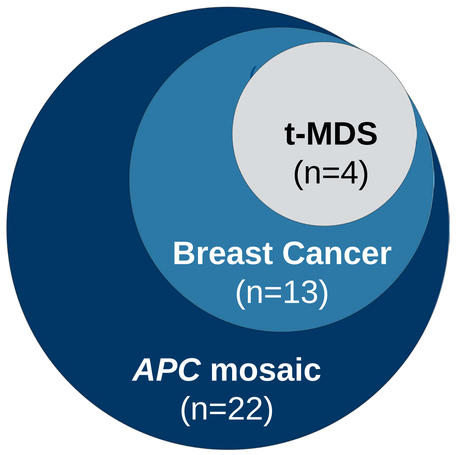
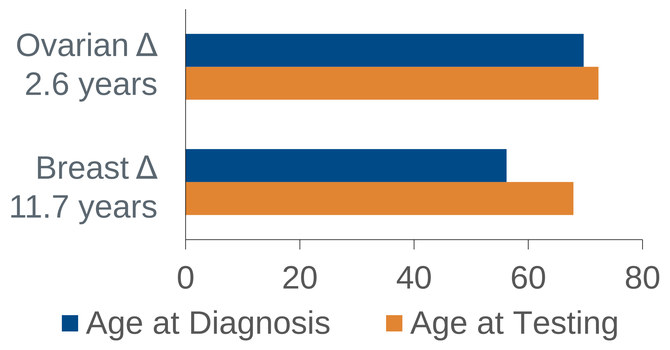


Figure 2. Timeline from a primary cancer diagnosis to the time of genetic testing.



- Co-occurring mutations were identified in 18/22 individuals.
  - A total of 24 co-occurring mutations were observed in these individuals.
  - 7/22 had *TP53* mutations (Table 1); 1/7 had t-MDS.
  - 7/22 individuals had *ATM* mutations (data not shown).
- The average age at the time of testing was 67.9 years for breast cancer patients and 72.3 years for ovarian cancer patients.
- The time elapsed between primary cancer diagnosis and genetic testing varied based on cancer type (Figure 2).

CONCLUSIONS

- Mosaic *APC* deletion was associated with an increased rate of t-MDS (18.2%), especially in breast cancer survivors (31%).
- All four patients with t-MDS had a personal history of breast cancer, two of whom had a history of multiple primary cancers.
- Evaluation for hematologic malignancy may be warranted for individuals with a mosaic *APC* deletion.
- This highlights the importance of follow-up by testing laboratories to ensure appropriate clinical interpretation of rare findings.

REFERENCES

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Presented at ACMG on April 13, 2018.