Genetic findings from a multi-gene panel for hereditary predisposition to leukemia

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Introduction

An estimated 5% to 10% of individuals diagnosed with leukemia have a hereditary predisposition. Genetic testing in this population is complicated by the need for a non-hematologic DNA source when malignancy is present, for which cultured skin fibroblasts are the gold standard.[1] Test results may impact treatment selection, screening management, and transplant donor selection. Despite clear clinical utility, few studies have reported on multi-gene panel testing for these individuals. This study characterizes the genetic results identified in a cohort of individuals with a suspected hereditary predisposition to leukemia.

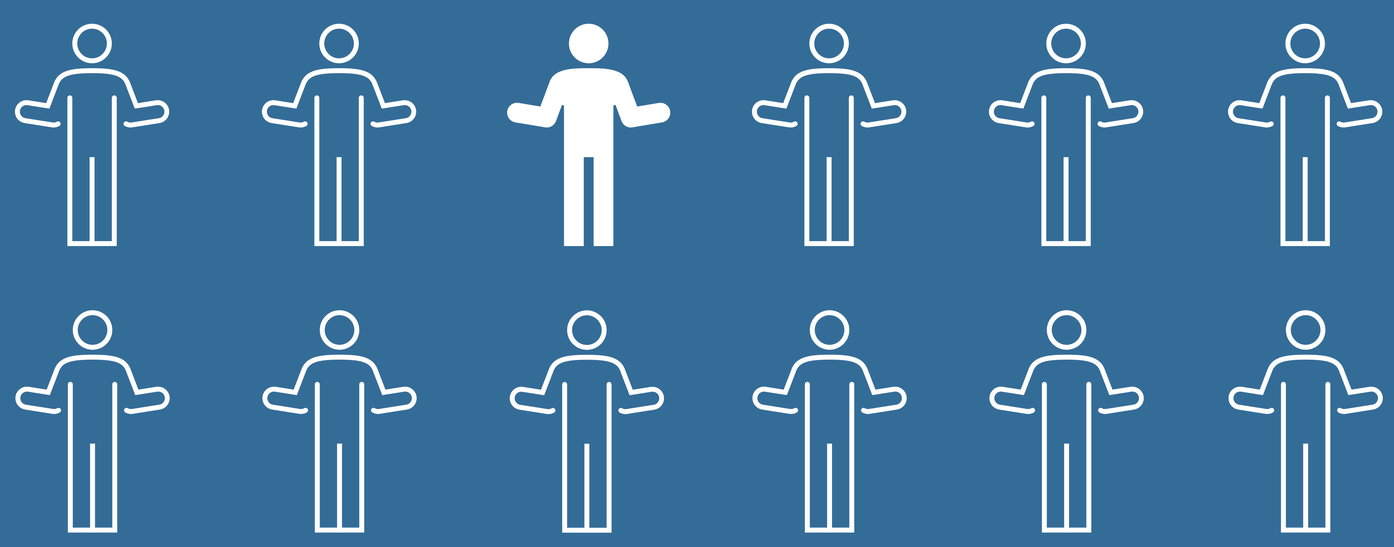
Methods

We performed a retrospective review of results for 126 consecutive patients referred for genetic testing with a suspicion of a hereditary predisposition to leukemia. Analysis included sequence and copy number variants via next-generation sequencing for 39-42 genes. Clinical and sample information was obtained from the test requisition. Variant interpretation and reporting utilized a modified ACMG/AMP guideline. A positive result was defined as the identification of pathogenic (P) or likely pathogenic (LP) variant(s) consistent with the individual's reported phenotype and disease mode of inheritance.

Results

Of the 126 individuals tested, 54% (68) were female, and the median age at time of testing was 20 years (range <1 to 91 years). Sample types provided for analysis included DNA of hematologic origin (blood, bone marrow, or saliva) in 33% (41) of individuals and nonhematologic origin in 67% (85) (Figure 1). Of patients who provided a sample of hematologic origin, 71% (29) had a personal history of an active hematologic disease noted in their clinical history.

A positive result was identified in 14% (18) of individuals, of which 61% (11) were germline variants across 8 genes: *CEBPA*, *DDX41*, *ETV6, FANCA*, *GATA2*, *SBDS*, and *TERC* (Table 1). Of the 18 positive results, 39% (7) were complicated by a possibly somatic or mosaic variant(s) across 5 genes: *DDX41*, *NRAS*, *PTPN11*, *RUNX1*, or *TP53,* or a mosaic genomic event: trisomy 21 or 17q11.2 deletion (Table 2). Variant allele fractions for these possibly somatic or mosaic results ranged from 10% to 68%. For all individuals with possibly somatic results, the sample type provided was DNA isolated from whole blood or bone marrow. Active malignancy was not indicated on the testing requisition; however, a personal history of a hematologic abnormality was documented in clinical notes for all these individuals.



One in 12 individuals undergoing NGS panel testing for hereditary predisposition to leukemia received a positive germline result

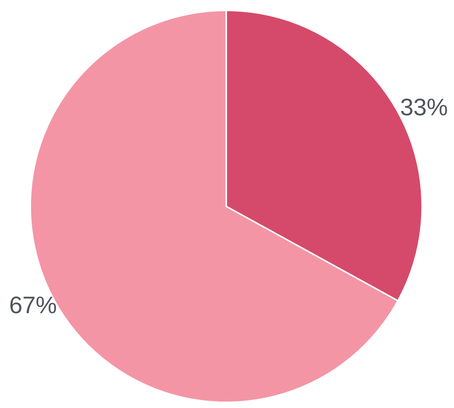


Figure 1. Sample types provided for genetic analysis. Hematologic sources include blood, bone marrow, and saliva.

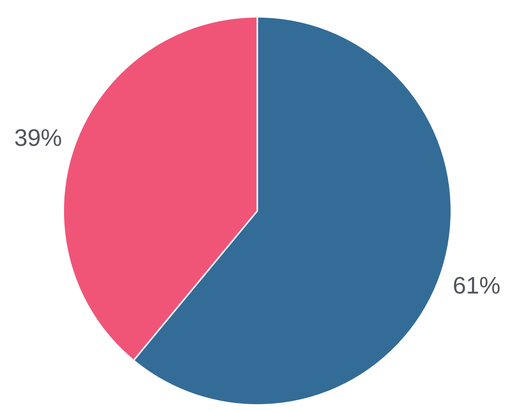


Figure 2. Germline and possibly somatic positive results (n=18).

Table 1. Genes with positive germline findings (n=11).

Gene(s)	MOI	% of Germline Results
ETV6	AD	27
DDX41, GATA2	AD	18 each
CEBPA, TERC	AD	9 each
FANCA, SBDS	AR	9 each

MOI - mode of inheritance; AD - autosomal dominant; AR - autosomal recessive

Table 2. Genes with possibly somatic or mosaic findings (n=7).

Gene(s)
TP53
NRAS
PTPN11
RUNX1
GATA2
Trisomy 21
2.5 Mb deletion of 17q11.2

Conclusions

- In this study, 14% of patients with a clinical suspicion of a hereditary predisposition to leukemia had a positive result, 61% of which were germline.
- For 39% of positive results, clinical interpretation may be limited due to a possibly somatic or mosaic variant(s) identified in DNA extracted from a hematologic source in individuals with hematologic disease.
- Most samples of hematologic origin came from individuals with a personal history of an active hematologic disease. Provider education is warranted.
- Multi-gene panel testing for hereditary predisposition leukemia can be informative if a non-hematologic sample type is provided.

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Reference:

1. Godley LA, DiNardo CD, Bolton K. Germline Predisposition in Hematologic Malignancies: testing, management, and implications. *Am Soc Clin Oncol Educ Book*. 2024;44(3):e432218. doi:10.1200/EDBK_432218

Conflict of interest statement: All authors are employed by Blueprint Genetics.