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509.BONE MARROW FAILURE AND CANCER PREDISPOSITION SYNDROMES: CONGENITAL

Germline Predisposition in Myeloid Neoplasms Aged ≥50: A Novel Approach for Allogeneic Stem Cell -Transplantation Decision-Making

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Introduction

Patients aged 50 or older (≥50) with myeloid neoplasms (MNs), non-affected relatives, and no previous platelet or organ disorder are routinely not tested for germline predisposition. However, approximately 70% of myelodysplastic neoplasms (MDS) patients undergoing an allogeneic hematopoietic stem cell transplantation (alloHSCT) from familial donors, in 2021, were ≥50 years old (y.o.) (EBMT). Given the significant frequency of pathogenic/likely pathogenic (P/LP) germline variants in these patients (about 8%) along with the risk of transplanting cells with the same variant, it seems reasonable to perform universal germline testing in hematological neoplasms although challenging due to labor and cost constraints.

Aims

To address this, we developed a pragmatic approach incorporating a specific gene list to the diagnostic myeloid somatic panel to identify patients and exclude relatives with shared germline variants. To do that we: (1) Conducted a literature review to assess the gene-disease association's validity in this specific context. (2) Designed a germline-augmented virtual somatic panel (GASP) based on our findings. (3) Tested the virtual panel's performance in 133 MNs cases, aged ≥50, with matched germline-tumor exome sequencing, and no prior organ or platelet disorders.

Methods

We considered those genes included in the WHO Classification and NCCN Clinical Practice Guidelines as myeloid predisposition genes. For autosomal recessive disorders, heterozygous carriers were not considered. We analyzed the relation of these genes with MNs diagnosed ≥50 y.o. without prior organ or platelet dysfunction: To establish a valid association for a gene, we required the presence of P/LP variants in at least two peer-reviewed studies in the subset of interest. GASP combined genes with recurrent somatic mutations in myeloid disorders, as proposed by Duncavage et al. (Blood 2022), and those associated with the specific cohort of interest.

WES was performed on paired tumoral-germline samples on a HiSeq 2000/Novaseq6000 instrument (Illumina Inc) with a target of 100x depth coverage.

Results

From 2018 to 2023, we collected samples from 133 patients (121 MDS and 12 CMML cases -FAB myelodysplastic variant) diagnosed with WHO-established MDS, aged ≥50, without prior organ or platelet disorders. Among the main characteristics at baseline, we highlight a median age at diagnosis of 57 years old (range, 50-88), and the presence of a first-degree relative with a myeloid neoplasm diagnosis in 7% of the cases.

The literature search revealed 11 genes associated with germline predisposition within the cohort of interest. Seven were WHO/NCCN genes: *DDX41*, *TERT*, *GATA2*, *CEBPA*, *SAMD9*, *ERCC6L2*, and *TP53*. Additionally, four "recently associated genes" were incorporated based on recent descriptions in germline MNs ≥50 y.o. and reported at least in two peer-reviewed articles: *CHEK2*, *DNAH9*, *ATM*, and *SH2B3* (Table 1).

Next, we tested the accuracy of both the GASP and Duncavage's recommended somatic panel in our cohort of 133 myeloid neoplasms characterized by WES. Among these cases, we identified 15 (11%) P/LP germline variants in both WHO/NCCN and recently associated genes. Duncavage's somatic panel could only detect 8 out of 15 (53%) cases, while the expanded GASP detected 13 out of 15 (87%) variants (Figure 1). The GASP showed a C-index of 0.933, outperforming Duncavage's panel, which scored 0.767.

Conclusions

Eleven genes have been found to harbor P/LP germline variants in patients with MNs diagnosed ≥50 y.o. and no previous organ or platelet disorder. In our cohort, 11% of patients carried a P/LP germline variant in a MNs predisposition gene. Such a finding would have gone undetected as germline predisposition testing is not typically advised for these patients. Expanding the myeloid somatic panel (GASP) allows the identification of 87% of P/LP variants during the diagnosis process, enabling clinicians to exclude carrier relatives as potential allo-SCT donors.

Disclosures Bernal Del Castillo: *AbbVie:* Consultancy; *Jazz:* Consultancy; *Otsuka:* Consultancy. **López-Andrade:** *Jazz Pharmaceuticals:* Consultancy. **Tazon:** *Bristol Myer Squibb:* Honoraria. **Diez-Campelo:** *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Gilead Sciences:* Other: Travel expense reimbursement; *BMS/Celgene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Advisory board fees; *GSK:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Bosch:** *Gilead:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *Karyospharm:* Other; *Celgene:* Consultancy, Honoraria; *Roche:* Consultancy, Honoraria; *Mundipharma:* Consultancy, Honoraria; *Lilly:* Consultancy; *Roche:* Honoraria; *BeiGene:* Consultancy. **Jerez:** *Novartis:* Consultancy; *GILEAD:* Research Funding; *Astrazeneca:* Research Funding; *BMS:* Consultancy.

Table 1. The one panel. Myeloid neoplasms predisposition genes with presence of P/LP germline variants cases in adults with an MDS onset ≥50_y.o without previous organ or platelet disorder in main published series.

Gene	Feurstein S. et al. Blood 2022 n=404	Yang F. et al., Blood 2022 n=391	Rio-Machin A et al., Nat Commun. 2020 n=168	Studies on specific genes / case reports / small cohorts	Current study n=119	Already included in recommended somatic panel (Duncavage et al)	WHO/NCCN gene
DDX41	5 cases	8 cases	4 cases	Makishima et al., Blood 2023 (293/1350). Guijarro F. et al., Blood advances 2023 (2/47). Molteni E. et al., Blood 2023 (9/402).	2 cases	yes	yes
TERT	4 cases	2 cases	1 case	NF	1 case	No	Yes
TP53	2 cases	NF	1 case	NF	NF	Yes	Yes
GATA2	NF	NF	NF	Weinberg OK Am J Clin Pathol 2019. (1/51). Churpek et al. Blood 2015 (1/59).	1 case	Yes	Yes
CEBPA	NF	NF	NF	Bak A. et al. Hereditary Cancer in Clinical Practice 2021 (1/103). Taskesen E. et al. Blood 2011 (1 case).	1 case	Yes	Yes
SAMD9	NF	1 case	NF	Nagata et al., Blood 2022 (12/680).	NF	Yes	Yes
CHEK2	1 case	5 cases	NF	NF	NF	No	No
DNAH9	NF	2 cases	1 case	NF	3 cases	No	No
ATM	NF	2 cases	NF	Guijarro F. et al., Blood advances 2023 (2/47).	1 case	No	No
*ERCC162**	NF	NF	NF	Douglas et al. Blood 2019 (3 cases). Hakkarainen et al., Blood 2023 (1 case).	1 case	No	Yes
SH2B3	NF	NF	NF	Rumi et al., Blood 2016 (1/149). Rotz et al. Am. J. Hematol. 2016 (1/26). Coltro et al. Am J Hematol 2019 (1 case).	NF	Yes	No

**ERCC6L2* is considered only in its biallelic configuration.
NF= not found

Figure 1. Accuracy of Duncavage's and GASP panels. Percentage of cases harboring a P/LP germline variant in 133 MNs (MDS and CMML) cases without previous organ or platelet disorders diagnosed ≥50 y.o.; (upper graph), percentage of those cases identified by Duncavage's somatic panel. Down right, Percentage of those cases identified by the germline-augmented somatic panel.

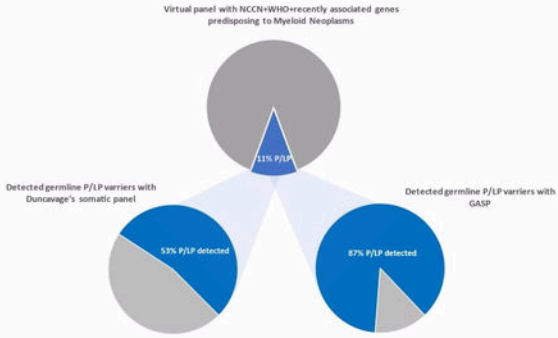

Figure 1

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