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MYELOID NEOPLASMS WITH GERMLINE PREDISPOSITION ARE NOT UNCOMMON AMONG COHORT OF PATIENTS WITH BONE MARROW FAILURE.

AML-668

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INTRODUCTION

- The recognition of germline variants predisposing to myeloid neoplasms has grown alongside increased genetic study utilization, particularly in hematopoietic malignancies. Germline mutations have been described in acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS)
- These disorders often present with bone marrow failure, cytopenias, and symptoms secondary to cytopenias.
- Identifying these variants is crucial for accurate diagnosis and management.
- While somatic alterations have provided crucial diagnostic and prognostic information, comprehensive sequencing of non-tumor or germline material has revolutionized our understanding of how germline variations contribute to cancer development.
- 5-15% cancers are due to germline predisposed variants.

AIM

This study aimed to evaluate the prevalence of germline variants predisposing to myeloid malignancy, by whole exome sequencing, in young and middle-aged adults (aged 18-50 years) presenting with cytopenia(s) and bone marrow failure

METHODS

- A retrospective analysis was conducted on young and middle-aged adults (aged 18-50 years), who presented with cytopenias and bone marrow failure, at a single center in a tertiary care public teaching hospital in North India.
- Comprehensive clinical evaluations, imaging studies, complete blood counts, peripheral smear evaluations, and biochemical studies were performed in all patients.
- Bone marrow examination was performed to assess cellularity and morphology across all cell lineages.
- Chromosomal breakage study and testing by flow cytometry were used to rule out Fanconi anemia (FA) and paroxysmal nocturnal hemoglobinuria (PNH) respectively. Patients with classical syndromic bone marrow failure (FA), Diamond-Blackfan anemia, etc.) and with alternative explanations for their cytopenia(s) (eg: PNH) were excluded.
- Next-generation sequencing (NGS), primarily whole exome sequencing was performed with DNA extracted from peripheral blood.
- Standard bioinformatic pipelines facilitated quality checks, read alignment, and pathogenicity testing, adhering to ACMG/AMP guidelines for variant reporting.

RESULTS

- Total of 82 patients were included in the final analysis.
- Pancytopenia was seen in 51 (62.2%) patients, with others exhibiting single lineage cytopenia or bicytopenia. Anemia was noted universally. Bicytopenia was seen in 20(30.5%) cases
- Mean age is 32 years
- Male-to-female ratio was 1.8:1
- Mean Hb was 8.2 g/dl (Range: 4.7g/dl-11.2 g/dl)
- 80% had received at least one blood transfusion
- Ten patients (12.2%) exhibited germline variants with predisposition to myeloid neoplasms
- Identified variants included ANKRD26 (2), RUNX1 (2), DDX41 (1), SAMD9 (3), SAMD9L (2)
- Heterozygous mutation was noted in all positive cases with an autosomal dominant pattern of inheritance
- Point mutations were noted in all cases
- The number of each individual variant was small to analyse the characteristics of the variants individually.

Fig.1: Proportion of germline variants with predisposition to myeloid neoplasms in adult bone marrow failure

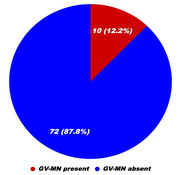


Fig.2 : Germline variants in BMF

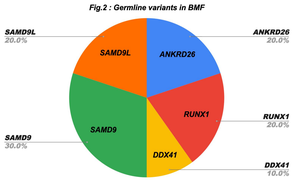


Table 1: Shows results of clinicopathological parameters of all cases

Gene	Gene ID	Variant	Inheritance pattern/Zygosity
ANKRD26	ENST00000376087.5	c.3059G>A (p.Arg1020His)	Autosomal dominant/Heterozygous
DDX41	ENST00000330503.12	c.1100G>A c.860A>T (p.Asp287Val)	Autosomal dominant/Heterozygous
RUNX1	ENST00000300305.3	c.592G>A	Autosomal dominant/Heterozygous
SAMD9	ENST00000379958.3	c.3751A>C (p.Lys1251Gln) c.2297A>G (p.Lys766Arg)	Autosomal dominant/Heterozygous
SAMD9L	ENST00000318238.9	c.4547dup (p.Asn1516LysfsTer2) c.2297A>G (p.Lys766Arg)	Autosomal dominant/Heterozygous

DISCUSSION

- Detecting a germline variant with predisposition to myeloid neoplasms carries significant implications for both the patient and their family.
- GV-MN need to be differentiated from immune disorders like immune aplastic anemia, immune thrombocytopenia and other immune cytopenias. GV-MN respond poorly to immunosuppression as these are not primarily immune disorders.
- Genetic testing aids in selecting an appropriate related donor for allogeneic hematopoietic stem cell transplantation by ensuring that the donor does not share the same genetic risk factors, thereby reducing the risk of disease recurrence.
- The patient's genetic profile is essential for tailoring the preparative regimen for transplantation, as hereditary conditions can influence the patient's response to treatment and the likelihood of side effects.
- For family members, understanding the hereditary risk enables cascade genetic testing and targeted genetic counseling and personalized cancer surveillance, which can facilitate early detection and intervention for those at increased risk.
- Knowledge of specific genetic variants allows for the implementation of targeted therapies, resulting in more precise and effective treatment plans.
- Early identification of AML predisposition is crucial for optimizing clinical care and ensuring a tailored management approach for both the patient and their family.

CONCLUSION

- This study reveals germline variants with genetic predisposition is not uncommon in patients presenting with unexplained bone marrow failure.
- Our study shows that 12% of patients with bone marrow failure without an alternative cause show germline variants with genetic predisposition to myeloid neoplasms.
- Identification of GV-MN is crucial for appropriate clinical management and to avoid unnecessary immunosuppression
- The presence of GV-MN can lead to organ dysfunction and myeloid neoplasms, emphasizing the critical importance of early identification to prevent misdiagnosis and ensure appropriate management.
- Screening family members for these variants is recommended due to their autosomal dominant inheritance, which can also aid in donor selection for hematopoietic stem cell transplantation.
- This study underscores the significance of NGS in identifying individuals with GV-MN.

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