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Hereditary Hematologic Malignancies: A Canadian Perspective

Introduction
When a patient is newly diagnosed with a malignancy, two common questions are often asked: 1) why did I get this cancer and 2) are my children or other family members at risk? In the case of hematologic malignancies, the standard response has been that the cause is unknown and family members are not at increased risk. However, hereditary predisposition to hematologic malignancies, especially myeloid malignancies, is becoming increasingly recognized, necessitating a change to this dogma.[1] Hereditary hematologic malignancies are not as rare as previously believed, with an ever-increasing number of predisposition genes and alleles being discovered. Since the initial discovery of familial platelet disorder with associated myeloid malignancy (FPDMM) due to deleterious germline variants in *RUNX1* in 1999,[2] the list of predisposition genes, such as *CEBPA, DDX41, ETV6, GATA2*, and others continues to grow.[3–6]

What are Hereditary Hematologic Malignancies?
Hereditary hematologic malignancy is a heterogenous term used to describe a hematologic malignancy that arises in the setting of a deleterious (pathogenic or likely pathogenic) germline variant. These predisposing variants can be inherited or can occur *de novo*, as is the case for the majority of GATA2 deficiency syndrome variants.[6] To date, predisposition alleles have been identified in over 40 different genes, resulting in a variety of predisposition syndromes **(Table 1)**.[1] Most germline predisposition syndromes are autosomal dominant (e.g. *ANKRD26, DDX41, RUNX1, TP53*, and many others), however others are autosomal recessive in their inheritance (e.g. *SBDS* and *FANCA*). Phenotype and penetrance vary depending on the particular gene as well as the individual variant involved. Some predisposition variants, like those in *CEBPA*, predispose to myeloid malignancies only, whereas others, like those in *RUNX1*, predispose to both myeloid and lymphoid malignancies as well as a pre-existing platelet disorder, and those in *TP53* predispose to both myeloid and lymphoid malignancies as well as numerous solid tumours.[1] Hereditary hematologic malignancies can be broken down into categories based on the predominant type(s) of hematologic malignancy to which they predispose as well as by the presence or absence of other features such as thrombocytopenia and/or platelet dysfunction, solid organ dysfunction, or additional predisposition to solid tumours **(Table 1)**.

Why is Recognition of Hereditary Hematologic Malignancies Important?
Knowledge of hereditary hematologic malignancies is becoming more commonplace and their importance is underscored by the incorporation of germline predisposition to myeloid neoplasms in the 2016 WHO update on myeloid neoplasms as well as the 2022 ELN Acute Myeloid Leukemia (AML) recommendations.[7,8] Within the 2022 ELN AML recommendations, "germline predisposition" is now included as a qualifier for the diagnostic classification of AML and related neoplasms.[7]

Recognition and identification of a predisposing germline variant has important implications for patients as well as their family members. The penetrance varies depending on the gene involved, but for some, such as 5' *CEBPA* variants, it is nearly 100% for development of AML.[3] For these and other germline predisposed patients, the risk of relapse after chemotherapy alone is high and an allogeneic hematopoietic stem cell transplant (HSCT) is recommended, but donor selection must be approached carefully.[9] Most predisposition variants are

Gene(s)	Inheritance	Predisposition to:
Myeloid neoplasms with germline predisposition without pre-existing platelet disorder or organ dysfunction		
CEBPA	AD	AML
DDX41	AD	Most common: MDS, AML Less common: MPNs, lymphoid neoplasms
Myeloid neoplasms with germline predisposition and pre-existing platelet disorders		
RUNX1	AD	Life-long mild/moderate thrombocytopenia and qualitative platelet defects Most common: MDS, AML, T-cell ALL Less common: HCL, CMML, B-cell malignancies
ANKRD26	AD	Thrombocytopenia and variety of platelet function defects MDS, AML, other myeloid neoplasms
ETV6	AD	Life-long thrombocytopenia ALL > myeloid malignancies
Myeloid neoplasms with germline predisposition and potential organ dysfunction		
GATA2	AD	GATA2 deficiency syndrome Lymphedema, immunodeficiencies, warts, NTM infections, pulmonary alveolar proteinosis, and many other phenotypes. MDS, AML (often with monosomy 7 and/or trisomy 8)
ELANE, GFI1 CSF3R, HAX1, G6PC3	AD, AR	Severe congenital neutropenia BMF, MDS, AML
SDBS, DNAJC21, EFL1, SRP54	AR	Shwachman-Diamond Syndrome BMF, MDS, AML, ALL
FANCA – FANCW	AR	Fanconi anemia BMF, MDS, AML
ACD, CTC1, DKC1, RTEL1, TERC, TERT, TINF2, NHP2, NOP10, PARN, WRAP53	AD, AR, X-linked	Telomere biology disorders BMF, mucocutaneous triad, pulmonary fibrosis, liver cirrhosis, squamous cell carcinoma, MDS, AML
SAMD9, SAMD9L	AD	MIRAGE syndrome, Ataxia-Pancytopenia syndrome BMF, MDS, non-syndromic monosomy 7
CBL, KRAS, NRAS, PTPN11	AD	Noonan syndrome or Noonan syndrome-like JMML, AML
NF1	AD	Neurofibromatosis 1 JMML, AML
Multiple myeloma with germline predisposition		
ARID1A, DIS3, POT1, TNFRSF13B, USP45	AD	MM, lymphoid neoplasms
Hodgkin lymphoma with germline predisposition		
DICER1, NPAT, POT1	AD	HL, other lymphoid neoplasms
Germline predisposition causing multiple cancer types including hematologic malignancies		
CHEK2	AD	Clonal hematopoiesis, myeloid neoplasms, lymphoid neoplasms, solid tumours
RECQL4	AR	Aplastic anemia, myeloid neoplasms, lymphoid neoplasms, solid tumours
BRCA1, BRCA2	AD	Hereditary breast and ovarian cancer syndrome Myeloid and lymphoid neoplasms, solid tumours
MLH1, MSH2, MSH6, PMS2	AD, AR	Lynch Syndrome Myeloid and lymphoid neoplasms, solid tumours
NBN	AR	Nijmegen Breakage Syndrome Aplastic anemia, lymphoid neoplasms (ALL > lymphoma), solid tumours
TP53	AD	Li-Fraumeni syndrome Myeloid and lymphoid neoplasms, numerous solid tumours
WAS	X-linked	Wiskott-Aldrich Syndrome Microthrombocytopenia, lymphoma, myeloid neoplasms, solid tumours (glioma, acoustic neuroma, testicular carcinoma)

***Table 1**. List of genes for which deleterious variants predispose to hematologic malignancies*

Myeloid neoplasm classifications are adapted from the 2022 European Leukemia Net AML recommendations.[7] ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BMF, bone marrow failure; CMML, chronic myelomonocytic leukemia; HCL, hairy cell leukemia; HL, Hodgkin lymphoma; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NTM, nontuberculous mycobacteria.

autosomal dominant and since the preferred donors for HSCT are matched-related donors, there is high risk of giving back the same predisposing variant if the related donor's germline status is unknown. Devastating complications including graft failure, donor-derived leukemia, and leukemia development in the donor following stem cell mobilization have all been reported when donors who carry deleterious germline variants have been used for HSCT.[10–12] It is therefore recommended to test potential related donors and to avoid their use as a hematopoietic stem cell donor if they carry the same predisposition variant.[1,9]

The identification of deleterious variants in genes associated with thrombocytopenia such as *ANKRD26*, *ETV6*, and *RUNX1* are important as these patients often get misdiagnosed as having immune thrombocytopenia. Without proper recognition, these patients may be subject to unhelpful and potentially harmful immunosuppressive therapies. In the case of other genes, such as *TERT* and *TERC*, deleterious variants are associated with organ dysfunction, most notably pulmonary fibrosis, and solid tumours in addition to hematologic malignancies. The identification of such variants enables informed treatment decisions, screening for occult organ dysfunction, and solid tumour screening.[13]

For hereditary hematologic malignancy patients being considered for HSCT, careful assessment for gene-specific organ dysfunction is important in order to better evaluate and mitigate the risk of severe transplant-associated morbidity or mortality. For example, GATA2 deficiency syndrome patients are at high risk of atypical mycobacterial infections and antimicrobial prophylaxis with a macrolide is recommended.[14] Although evidence-based guidelines for each individual predisposition gene do not exist, expert opinion recommendations suggest using standard preparative regimens for myelodysplastic syndrome (MDS)/AML patients with germline variants not associated with bone marrow failure or severe organ dysfunction. For those with germline variants in bone marrow failure or telomere biology disorder genes, a fludarabine-based reduced intensity conditioning regimen similar to that used for Fanconi anemia patients is recommended to avoid excessive toxicity and poor survival observed with fully myeloablative conditioning.[13,15]

Surveillance for asymptomatic carriers of a hereditary hematologic malignancy predisposition variant is based upon expert opinion recommendations and includes universal recommendations as well as gene/syndrome-specific recommendations.[13] Individual gene-specific surveillance recommendations for carriers with and without hematologic malignancies are beyond the scope of this article and readers are referred to previously published reviews.[13,16–19] Universal screening recommendations for those currently without hematologic malignancies include a CBC with differential every 6-12 months, HLA typing at baseline, and a bone marrow biopsy and aspirate including cytogenetics and molecular if any abnormalities on the CBC develop, such as new cytopenia(s) or macrocytosis. Some experts advocate for a bone marrow biopsy and aspirate to be conducted at baseline, however this remains controversial for patients with no hematologic abnormalities.

How Common are Hereditary Hematologic Malignancies?

Among patients between the ages of 18-40 years, a deleterious germline variant was found in 19% of those with MDS/AML and 15% with aplastic anemia.[20] *DDX41* is the most frequently germline-mutated gene among adults with myeloid neoplasms. Studies examining unselected, unrelated adults with MDS/AML have found 2-6% harboured a germline predisposing variant in *DDX41*.[21,22] These patients often did not have a family history of hematologic malignancy and the median age at diagnosis was 68-69 years, similar to that of sporadic MDS/AML. In a recent CIBMTR study, 7% of all MDS patients (ages 11-71 years) undergoing related HSCT were found to have a deleterious germline variant.[23] Therefore, older age at diagnosis and lack of family history cannot be used to exclude the possibility of an underlying germline predisposition.

As shown in **Table 1**, several genes have also been found to predispose to lymphoid neoplasms and/or plasma cell dyscrasias, including many that also predispose to a variety of solid tumours.[1,24,25] However, in comparison to myeloid neoplasms there are much fewer data available on germline predisposition to lymphoid neoplasms and this is an area of active research.

Who and How to Test for Hereditary Hematologic Malignancies?

Germline predisposition should be considered as a possibility for all patients with hematologic malignancies given the relatively high frequency of occurrence. **Figure 1** depicts an approach for selection and testing of suspected hereditary hematologic malignancy patients. Suggestive features can include: a personal history of multiple malignancies, long standing cytopenias and/or bleeding diatheses, family history of hematologic malignancy and/or younger than average age onset of solid tumours within two generations of the patient, physical phenotype consistent with a known germline predisposition syndrome, and/or the identification of a potential germline variant on tumour-based molecular testing. In addition to testing those with suggestive features, given the high frequency of predisposition variants in patients with MDS of all ages undergoing HSCT as well as those with AA, MDS, and AML under the age of 40 years, routine germline testing at the time of diagnosis for these patients should be considered.

For patients with myeloid or lymphoid neoplasms with bone marrow or peripheral blood involvement, DNA derived from cultured skin fibroblasts should be obtained as the gold standard to eliminate possible malignant cell contamination. A 3 mm punch skin biopsy is easily performed and sufficient for this purpose. Culturing of the skin fibroblasts can be conducted at most Canadian cytogenetics laboratories. Hair follicles are an alternative source of germline DNA; however,

DNA yield is often low. Clinical testing is typically performed using next-generation sequencing (NGS) platforms. Knowledge of the panel used for testing is important to ensure it is sufficiently comprehensive in terms of the genes captured and the ability to detect single nucleotide variants as well as copy number variants, which are often not detected by standard NGS-based assays. Results of genetic testing and genetic counseling (both pre- and post-testing) should be provided by personnel with expertise and dedicated training in this field.

In order to learn more about existing predisposition syndromes and to uncover new syndromes, all patients with suspected hereditary hematologic malignancy should be offered participation in research, where available. Unfortunately, clinical germline genetic testing is not currently available at most major academic centres within Canada. However, testing options do exist via shipment to commercial labs or to a limited number of academic laboratories, such as the IWK Clinical Genomics Laboratory in Halifax, which have validated clinical germline testing panels for hematologic malignancies.

Conclusions and Future Directions

Hereditary hematologic malignancies are more common than previously appreciated and may be accompanied by unique phenotypic characteristics and cancer risks. The identification of patients harbouring these germline predisposing variants is vital to ensure optimal care, to reduce risk of relapse, to institute screening for possible associated solid tumors or organ dysfunction, and to avoid unnecessary treatments or interventions. As these predisposition syndromes gain increasing attention and have begun to be incorporated in major diagnostic and management guidelines, there will be an increasing demand for clinical germline testing. As Canadian hematologists, we need to collaborate with and encourage our local molecular laboratories and/or genetics centres to incorporate germline testing for hereditary hematologic malignancies for optimal patient care.

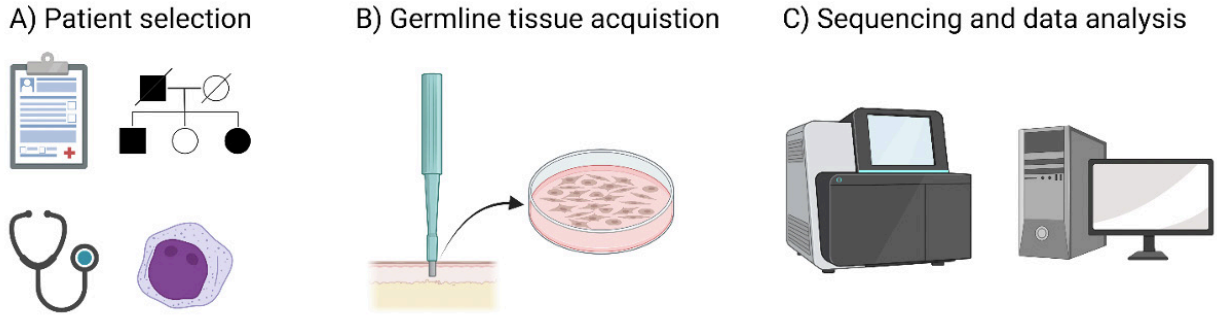

Figure 1. *Approach for selection and testing of patients with suspected hereditary hematologic malignancy. A) Suspicious features that would prompt recommendations for germline genetic testing and pre-test counseling include: a personal history of multiple malignancies; long standing cytopenias and/or bleeding diatheses; a diagnosis of aplastic anemia, myelodysplastic syndrome, or acute myeloid leukemia under the age of 40 years; a diagnosis of myelodysplastic syndrome and plans to undergo allogeneic hematopoietic stem cell transplant; a family history of hematologic malignancy and/or younger than average age of onset of solid tumours within two generations of the patient; physical phenotype consistent with a known germline predisposition syndrome; and/or the identification of a potential germline variant on tumour-based molecular testing. B) For patients that decide to undergo testing, the recommended source for germline DNA is cultured skin fibroblasts, which can easily be obtained with a 3mm punch biopsy. C) Next-generation sequencing is performed on the germline DNA, variants are analyzed and classified according to their pathogenicity,[26] and a clinical report is generated. A comprehensive testing panel with capabilities to call single nucleotide variants and copy number variants is recommended.*

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