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Familial myelodysplastic syndrome/acute myeloid leukemia

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Abstract

A growing number of inherited genetic loci that contribute to myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) development in both children as well as adults are rapidly being identified. In recognition of the clinical impact of this emerging field, the World Health Organization, National Comprehensive Cancer Network, and European LeukemiaNet have all added consideration of inherited predisposition to MDS/AML classification and management. Study of these disorders is providing unique insight into the biology of both sporadic and familial MDS/AML. International collaborative efforts to store germline tissue, document family histories, and pool data are essential to progress in diagnosing and treating both hereditary and sporadic forms of MDS/AML.

Keywords

acute myeloid leukemia; AML; inherited; genetics; hereditary myeloid malignancy syndromes; MDS; myelodysplastic syndromes; predisposition

Introduction

Traditionally, the field of hereditary cancer genetics has been thought of as predominantly relevant to breast, ovarian, and colon cancer. However, with the hope of precision medicine has come expanding interest in cataloguing both the acquired as well as inherited genetic variants that contribute to diverse cancers occurring across the lifespan. Already, studies examining children with solid tumors and adults with various advanced solid tumors have shown that 8.6% and 14.3%, respectively, have inherited mutations in known cancer susceptibility genes [1, 2]. These data suggest that inherited susceptibility likely contributes to many cancer types, with proportions differing by cell of origin and disease features (eg, 4.6% with localized prostate cancer vs 11.8% with metastatic prostate cancer) [3]. Importantly, many of the individuals in these studies with inherited mutations would not have met traditional criteria for inherited genetic testing due to having a discordant tumor

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type and/or lack of family history suggestive of that syndrome. All of these data suggest that we must broaden our view of for whom and how inherited susceptibility contributes to cancer.

Inherited genetics in myelodysplastic syndrome and acute myeloid leukemia

Despite having exquisitely detailed acquired genetic information on large numbers of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) cases [4, 5], a deep understanding of the role of inherited genetics in MDS/AML has been hampered by several factors. Access to germ line tissue sources uncontaminated by tumor cells from large numbers of patients with MDS/AML, knowledge of which genes contribute to MDS/AML predisposition, and a general resistance to the idea that inherited genetics could play a role in MDS/AML outside the context of known inherited bone marrow failure syndrome presentations have all contributed. As a growing number of genes causing inherited forms of MDS/AML occurring across the lifespan have been identified, this resistance is beginning to be replaced by a growing interest and rapid pace of discovery in this field.

Already, estimates suggest that 4%-10% of children and young adults with MDS or AML [6–8] and 4% of adults with AML [9] carry inherited damaging mutations in cancer susceptibility genes. The genes implicated are diverse, including well-known hematopoietic transcription factors such as *CEBPA, GATA2,* and *RUNX1* as well as genes such as *BRCA1* and *MSH6*, more traditionally thought of as solid tumor risk genes [10]. The most recently identified genes, *DDX41, SAMD9* and *SAMD9L*, are revealing novel pathways involved in leukemogenesis and deepening our understanding of the basic biology of MDS/AML [11–13]. In recognition of the impact of this growing field on clinical care, the World Health Organization, European Leukemia Net, and National Comprehensive Cancer Network have all recently incorporated consideration of MDS/AML germ line predisposition syndromes into MDS/AML classification and clinical management guidelines, making knowledge of these syndromes now essential for clinicians and pathologists alike [14–16].

Clinical utility of familial MDS/AML detection and management

From a clinical perspective, understanding when and how to suspect germ line predisposition in a patient being evaluated for cytopenias and/or MDS/AML is critical for optimal care of the patient and his/her family [10]. Incorporating specific personal medical and family history questions about chronic cytopenias, aplastic anemia, MDS/AML, a bleeding propensity, or specific organ system features such as pulmonary fibrosis or immunodeficiency are key components for clinical detection. Attention to the specific acquired mutations in a patient's MDS or leukemia cells may also suggest the diagnosis (eg, a RUNX1 p.R204Q mutation in MDS cells from a young patient with a prior unexplained bleeding propensity is highly suspicious for familial platelet disorder). Further, about 7% of patients with AML featuring biallelic *CEBPA* mutations AML will carry one of the two *CEBPA* mutations in the germline [17]. Lastly, evaluation of allogeneic stem cell donors is also an important encounter for the detection of a hereditary MDS/AML syndrome.

Specifically, unexplained cytopenias or failure to mobilize stem cells well in related donors of patients with MDS/AML require further evaluation [18, 19].

Recognition of an inherited cause provides a specific molecular diagnosis, helping to understand unique disease features, prognosis, other organ systems that may be involved, and identify others in the family who may be at risk. Further, a molecular diagnosis helps avoid unnecessary and potentially harmful treatments, such as treatment with steroids or splenectomy for a misdiagnosis of immune thrombocytopenia in individuals with inherited thrombocytopenia due to mutations in *RUNX1, ANKRD26*, or *ETV6.* Knowledge of a specific inherited syndrome also guides stem cell transplant decision making including: (1) stem cell donor selection (ie, to avoid use of a related stem cell donor carrying the same germ line mutation, which may result in adverse transplant outcomes such as failure to engraft or donor cell leukemia) [20]; (2) timing (eg, early stem cell transplant in a young patient with a germline *GATA2* mutation with low grade MDS but multiple syndrome-related infectious complications) [21]; and (3) preparative regimen (eg, avoiding the fatal toxicity that can result from busulfan use in those with a short telomere syndrome) [22]. Recent observations in familial AML due to *CEBPA* mutation illustrate the prognostic relevance. Individuals with an inherited *CEBPA* mutation acquire a second *CEBPA* mutation at the time of leukemia development, presenting similarly to those with sporadic biallelic *CEBPA* mutated AML, but have later, sometimes multiple, chemosensitive relapses with an 8 year vs 16 month median post relapse survival as compared to those with biallelic sporadic disease [23]. This work further demonstrated that AML relapses in this familial context were actually second, independent AML occurrences originating from the predisposed stem cell pool, likely explaining the chemosensitivity.

Unique research opportunities

From a research perspective, familial MDS/AML syndromes offer a unique opportunity to dissect the multistep pathways in leukemogenesis from a single inherited MDS/AML predisposition mutation to overt disease. For example, we found that 67% of a small group of healthy individuals with germ line *RUNX1* mutations developed clonal hematopoiesis of indeterminate potential (CHIP) by the age of 50 [24], a number much higher than the approximately 2% of individuals in the general population with CHIP by the same age [25]. Further, investigation of the role of inherited genetics in therapy-related leukemogenesis identified inherited cancer susceptibility gene mutations in 21% of women who developed therapy-related leukemias post breast cancer treatment, suggesting a possible gene×environment interaction in risk for this lethal complication [26]. Studies are also beginning to delineate the perturbations that occur in normal hematopoiesis in some of these disorders, providing rationale for future mechanism-based interventions. For example, Bluteau et al demonstrated that the pro-platelet forming defect observed in individuals with a germ line *ANKRD26* mutation, which causes thrombocytopenia and predisposition to various leukemias, results from increased MAPK/ERK pathway signaling and that a MAPK inhibitor could partially restore pro-platelet formation in patient samples in vitro [27]. These are just a few examples of the many exciting discoveries facilitated by partnering with patients and their families affected by monogenic familial MDS/AML predisposition. Long

term, the hope is to find better ways to treat both familial and sporadic cases, and ultimately, how to prevent MDS/AML.

Conclusion

Patients with inherited predisposition to MDS/AML are more common than previously recognized. Identification in real time impacts the clinical care of these patients and their families. Partnering with these families and international collaborators to determine the mechanisms and multi-step processes from the carrier state to overt disease has enormous potential to improve the outcomes of patients with both familial and sporadic forms of MDS/AML. Incorporating collection of ideal germ line tissue along with family histories to the already robust international MDS/AML registries and data sharing are all essential to future progress in this field.

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