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Next-Generation Sequencing (NGS)-Based Clinical Testing is Recommended for the Detection of Gene Mutations Associated with Familial Myelodysplastic Syndrome and Acute Myeloid Leukemia Predisposition Syndromes

Ryan S Robetorye*

Department of Laboratory Medicine and Pathology, Mayo Clinic Hospital, Phoenix, Arizona, USA

***Corresponding author:** Ryan S. Robetorye, Department of Laboratory Medicine and Pathology, Mayo Clinic Hospital, Phoenix, Arizona, USA, Tel: +(480)301-8000; E-mail: Robetorye.Ryan@mayo.edu

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Commentary

Individuals with Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) usually present later in life, but infrequent MDS/AML cases may exhibit early onset and may also show aggregates within families. However, individuals with inherited forms of hematologic malignancies are currently underappreciated and underdiagnosed due to the low frequency of such cases and a general lack of clinical awareness of familial MDS/AML predisposition syndromes. The recent development of next-generation sequencing (NGS)-based testing using targeted gene panels provides an efficient and cost-effective strategy to identify clinically significant variants in families with suspected MDS/AML predisposition syndromes.

Individuals with myelodysplastic syndromes (MDS) and acute myeloid leukemias (AML) usually present later in life, with a median age of onset greater than 70 years of age; however, infrequent MDS/AML cases may exhibit early onset and may also show aggregates within families. Moreover, familial clusters of MDS and AML occur much more frequently than expected by chance, suggesting that inherited factors play a role in the development of these diseases [1]. However, an inherited basis is frequently not considered when cases of MDS and AML occur in biological relatives, and individuals with inherited forms of hematologic malignancies are currently underappreciated and underdiagnosed due to the low frequency of cases and a low level of clinician awareness of these syndromes.

The expensive and time-consuming process of serially testing single genes and a lack of commercially-available clinical testing of appropriate genes may also play a role in some cases. However, clinicians must increasingly recognize the possibility that certain gene mutations may represent pathogenic germline mutations that may predispose to MDS/AML and initiate appropriate follow-up germline genetic testing. The increasing importance of recognition of such mutations is evidenced by the inclusion of a new category in the 2016 revision of the WHO classification of myeloid neoplasms and acute leukemia designated "Classification of myeloid neoplasm with germline predisposition" [2].

Although a given cancer predisposition syndrome is rare, recent studies have shown that germline cancer predisposition mutations in general may not be as rare as previously presumed. For example, a recent study from St. Jude Hospital of 1120 patients with pediatric cancers identified germline mutations in cancer predisposing genes in 8.5% of the patients with cancer [3]. Another study of adult patients seen at a hereditary hematologic malignancy clinic identified germline mutations in 18% of the patients [4]. Similarly, a study of individuals from 17 families with two or more biological relatives with MDS/AML detected a pathogenic germline variant in five of the families (29%) [5]. Familial MDS/AML may occur in the context of bone marrow failure diseases such as *GATA2* spectrum disorders, Fanconi anemia, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, and dyskeratosis congenital/telomere biology disorders, as well as in association with germ line mutations in the *ANKRD26, CEBPA, DDX41, ELANE, ETV6, HAX1, RUNX1, SAMD9, SAMD9L, SRP72, and TP53* genes (Table 1) [6,7].

Sanger sequencing for detection of single gene mutations or a small series of genes may be practical when a clear clinical phenotype suggests a specific diagnosis, and this approach may also be effective for screening additional family members when a mutation has been previously identified in a proband. However, in most families with a suspected cancer predisposition syndrome, a previously identified gene mutation will not be available for subsequent family member screening, and the choices for gene mutation testing may also be complicated by the variable penetrance observed in many of the germline MDS/AML disorders.

This phenomenon may result in some family members carrying the same gene mutation developing different clinical symptoms and different myeloid malignancies, while other family members might remain completely unaffected. This heterogeneity in clinical presentation even among members of the same families can also result in overlapping clinical and phenotypic features between multiple possible syndromes. When the diagnosis is unclear, serial single-gene testing for all possible related genes can be expensive, time-consuming, and impractical, but the recent development of next-generation sequencing (NGS)-based testing can provide a much more efficient and cost-effective strategy to identify clinically significant variants in families with suspected MDS/AML predisposition syndromes using targeted gene panels.

For example, a recent study of pediatric and young adult patients with idiopathic bone marrow failure or MDS identified pathogenic germline mutations in eight of 71 patients (11.3%) who lacked a diagnosis after clinical evaluation and standard clinically-directed genetic testing using a custom targeted NGS gene panel [8]. Another retrospective analysis of pediatric and young adult patients that had undergone bone marrow stem cell transplantation for aplastic anemia or MDS using a multiplexed targeted NGS gene panel identified a pathogenic mutation in five of 98 (5.1%) aplastic anemia patients and 15 of 110 (13.6%) MDS patients, with all of the mutations present in the germline except for one somatically acquired *RUNX1* gene

mutation found in the peripheral blood of one of the MDS patients [9]. An additional study of 83 patients with unclassified inherited bone marrow failure syndromes using a 72-gene NGS panel identified causal mutations and established the diagnosis in 15 (18%) of the patients.

Syndrome	Gene	Inheritance	Marrow Failure	MDS	AML
GATA2 Spectrum Disorders	GATA2	AD	X	X	X
Fanconi Anemia	21 genes, including FANCA through FANCV	Mostly AR	X	X	X
Dyskeratosis Congenita	13 genes, including TERC, TERT	Mixture of AD and AR	X	X	X
Shwachman- Diamond Syndrome	SBDS	AR	X	X	X
Diamond-Blackfan Anemia	22 genes, including GATA1	Mostly AD	X	X	X
Severe Congenital Neutropenia	ELANE And HAX1	AD (ELANE) AR (HAX1)	X	X	X
Thrombocytopenia 2	ANKRD26	AD	-	X	X
Familial AML with CEBPA Mutation	CEBPA	AD	-	X	X
Familial AML with mutated DDX41	DDX41	AD	-	X	X
Thrombocytopenia 5	ETV6	AD	-	X	X
Familial Platelet Disorder with propensity to myeloid malignancy (FPD/AML)	RUNX1	AD	-	X	X
MIRAGE Syndrome	SAMD9	AD	-	X	X
Ataxia-Pancytopenia Syndrome	SAMD9L	AD	-	X	X
Bone Marrow Failure Syndrome-1	SRP72	AD	X	X	X
Li-Fraumeni	TP53	AD	-	X	X
AD: Autosomal Dominant; AR: Autosomal Recessive					

Table 1: Genes involved in hereditary MDS and AML predisposition disorders.

For the purposes of clinical diagnostic testing, NGS-based clinical testing using custom targeted gene panels is recommended for screening and identification of pathogenic mutations associated with familial MDS/AML syndromes [8-11]. However, once gene mutations associated with specific genetically defined hereditary MDS/AML syndromes have been identified using NGS gene panels, additional confirmatory clinical germline testing is recommended to be performed using DNA samples obtained from cultured skin fibroblasts obtained from skin punch biopsy or skin ellipse biopsies [11].

Peripheral blood specimens should be avoided for germline mutation confirmation testing as this specimen is potentially an affected tumor-containing tissue, and all other tissues potentially contaminated by peripheral blood should also be avoided, including bone marrow, saliva, and buccal cells [11]. The importance of avoiding peripheral blood as a specimen for confirmatory germ line testing is underscored by the finding of a *RUNX1* gene mutation with a variant allele fraction of 51% (well within range for a heterozygous germline variant) that was confirmed to actually be a somatically acquired mutation in a MDS patient [9].

The recognition of individuals carrying germline gene mutations associated with MDS/AML predisposition syndromes is important for several reasons. Asymptomatic carrier relatives should be identified and excluded as possible donors for bone marrow stem cell transplantation, and such carriers should also be closely followed for early detection of clonal progression and management of associated clinical symptoms such as bleeding disorders, cytopenias, and other organ dysfunction [5].

The recent development and dissemination of more affordable NGS technologies has greatly expanded the field of hereditary myeloid malignancy syndromes, and it appears that hematopoietic neoplasms may have an important hereditary component similar to that of other solid tumors such as breast cancers. Targeted NGS panels are therefore recommended for the detection of germline variants that predispose to development of MDS/AML as these panels represent a practical, highly efficient, and cost-effective method to identify such variants. However, there is still a great need for knowledgeable researchers, physicians, nurses, and genetic counselors to help identify, manage, and treat the growing number of patients that will be diagnosed with these disorders in the future [11].

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