REGULAR ARTICLE

blood advances

Somatic GATA2 mutations define a subgroup of myeloid malignancy patients at high risk for invasive fungal disease

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Key Points

- *GATA2* mutations are more common than expected in patients with myeloid malignancy who develop invasive aspergillosis.
- Myeloid malignancy patients with somatic *GATA2* mutations have a high risk of invasive fungal disease with antineoplastic treatment.

Invasive fungal disease (IFD) can be a severe treatment complication in patients with myeloid malignancies, but current risk models do not incorporate disease-specific factors, such as somatic gene mutations. Germline *GATA2* deficiency is associated with a susceptibility to IFD. To determine whether myeloid gene mutations were associated with IFD risk, we identified 2 complementary cohorts of patients with myeloid malignancy, based on (1) the diagnosis of invasive aspergillosis (IA), or (2) the presence of *GATA2* mutations identified during standard clinical sequencing. We found somatic *GATA2* mutations in 5 of 27 consecutive patients who had myeloid malignancy and developed IA. Among 51 consecutive patients with *GATA2* mutations identified in the evaluation of myeloid malignancy, we found that IFD was diagnosed and treated in 21 (41%), all of whom had received chemotherapy or had undergone an allogeneic stem cell transplant. Pulmonary infections and disseminated candidiasis were most common. The 90-day mortality was 52% among patients with IFD. Our results indicate that patients with somatic *GATA2* mutations are a vulnerable subgroup of patients with myeloid malignancy who have high risk for treatment-associated IFD and suggest that a focused approach to antifungal prophylaxis be considered.

Introduction

The *GATA2* gene encodes a transcription factor and is mutated recurrently in sporadic myeloid malignancies and in patients with GATA2 deficiency syndrome.[1-5] Missense mutations affecting the *GATA2* zinc finger DNA-binding domains (ZF1 and ZF2) cause loss of function by impairing binding to GATA-DNA motifs, whereas nonsense or frameshift mutations reduce the overall abundance of GATA2 protein.[4] Patients with germline *GATA2* mutations can have a primary immunodeficiency and an elevated risk of recurrent infections that are, in part, caused by myeloid dendritic cell, monocyte, and natural killer cell dysfunction.[4-6] These defects in immune cells confer susceptibility to invasive fungal disease (IFD), particularly invasive aspergillosis (IA).[7,8]

GATA2 is mutated somatically in 1% to 4% of patients with sporadic myeloid malignancies.[1-3] One study found that 5 of 9 patients with myeloid malignancies and somatic *GATA2* mutations had clinical and flow cytometric features of immunodeficiency, suggesting that somatic mutations exert pleiotropic effects in terminal immune lineages in addition to their effects on hematopoietic stem and progenitor cells.[9] A case report identified a patient with a somatic *GATA2*-mutated myeloid neoplasm who developed mycobacterial and invasive pulmonary fungal infections.[10] These reports raise the possibility

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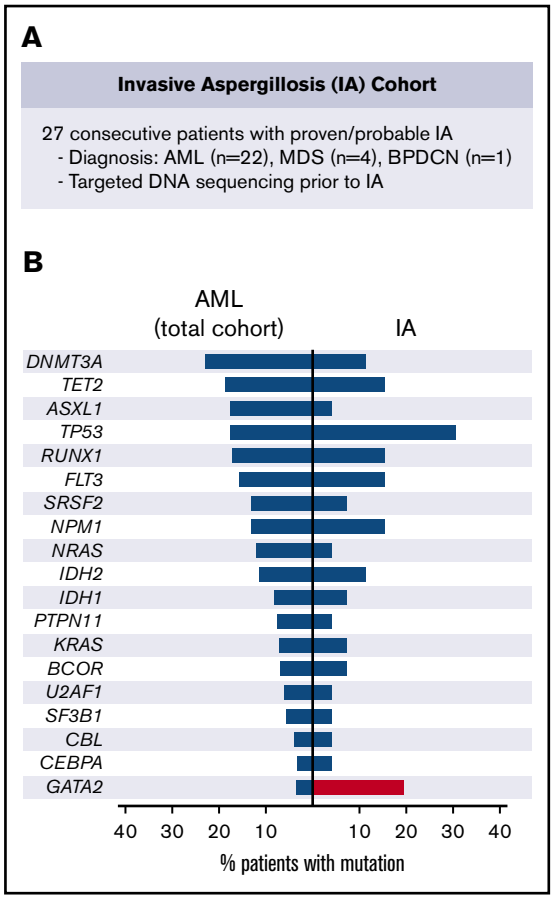

Figure 1. IA cohort. (A) Description of the IA cohort. (B) Frequency of recurrent driver mutations in patients with AML at our institution (left) and observed frequency in the IA cohort (right). BPDCN, blastic plasmacytoid dendritic cell neoplasm.

that somatic *GATA2* deficiency confers a risk of infection similar to that of germline mutations. We therefore sought to define the prevalence and spectrum of IFD in a consecutive series of adult patients with myeloid malignancy who harbored somatic *GATA2* mutations.

Study design

Genetic analysis

Gene mutations were identified by targeted DNA sequencing of blood or bone marrow specimens,[11] and variants were interpreted for pathogenicity, as previously described.[3] The *GATA2* coding region, implicated in sporadic myeloid disease,[12] is targeted by this panel.

IA cohort

Twenty-seven consecutive adult patients had clinical sequencing in an evaluation of myeloid malignancy and were diagnosed with proven or probable IA from March 2015 through December 2017 (Figure 1A).[13]

GATA2 cohort

Seventy-six patients with *GATA2* mutations were identified among 2383 consecutive adult patients who had clinical sequencing for evaluation of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), or MDS/MPN overlap from July 2014 through September 2019. Seven patients with proven germline *GATA2* mutations were excluded from the analysis. Fifty-one patients were considered evaluable for IFD based on (1) documentation of death at any time, or (2) at least 90 days of follow-up after identification of *GATA2* mutation by sequencing. In the remaining 51 patients, *GATA2* mutations were defined as either somatic or likely somatic based on genetic characteristics and clinical history obtained by a detailed review of personal and family history of myeloid malignancies, immunodeficiency, and recurrent infections (Figure 2A).

Annotation of fungal disease

IA and IFD were categorized as proven, probable, or possible based on the revised guidelines from the European Organization for the Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG).[14] Patients with possible IFD were separated into those who received antifungal agents (possible-treated) and those who did not. See supplemental Methods for further details. Based on the low baseline rate of IFD, antifungal prophylaxis during treatment of myeloid malignancies is not standard practice at our institution. This study was conducted with the approval of the Dana-Farber/Harvard Cancer Center and Massachusetts General-Brigham and Women's Institutional Review Boards.

Results and discussion

To identify potential associations between myeloid genetic alterations and risk of IFD, we first analyzed 27 consecutive patients with myeloid malignancies who developed IA (supplemental Table 1) and compared the frequency of somatic gene mutations in this cohort to the frequency of myeloid mutations in patients with AML and MDS at our institution (supplemental Table 2). The most commonly mutated genes in patients with IA were *TP53* (29%; 8 of 27) and *GATA2* (19%; 5 of 27), in contrast with their frequencies in patients with AML in the overall cohort of 17.3% and 3.2%, respectively (Figure 1B; supplemental Table 2). *TP53* and *GATA2* were not concurrently mutated in individual patients, indicating that they reflect independent markers of IA risk. Whereas *TP53* mutations are associated with factors previously linked to increased risk of IA, such as adverse cytogenetics and treatment resistance,[15,16] *GATA2* mutations, typically in the context of normal karyotype AML, have had no adverse impact on outcomes.[17] In this cohort, the number of lines of prior therapy was not significantly different between the *GATA2* mutant and wild-type cases (Mann-Whitney, $P = .25$).

Germline *GATA2* mutations have been linked to an increased risk of fungal infections,[4,6-8] raising the possibility that somatic *GATA2* mutations mediate a similar effect. To test this hypothesis, we determined the incidence of IFD in a larger cohort of consecutive patients with *GATA2* mutations. Among 51 evaluable patients with *GATA2* mutations, diagnoses included AML (n = 27), MDS (n = 8), MDS/MPN overlap syndromes (n = 13), and MPN (n = 3). Most of these patients (43 of 51; 84%) received myelotoxic treatments, including intensive induction chemotherapy, hypomethylating agents, and allogeneic hematopoietic cell transplantation (HCT) (supplemental Tables 3 and 4). Consistent with the reported spectrum of pathogenic *GATA2* mutations,[4] the mutations in our cohort included truncating mutations located throughout the coding

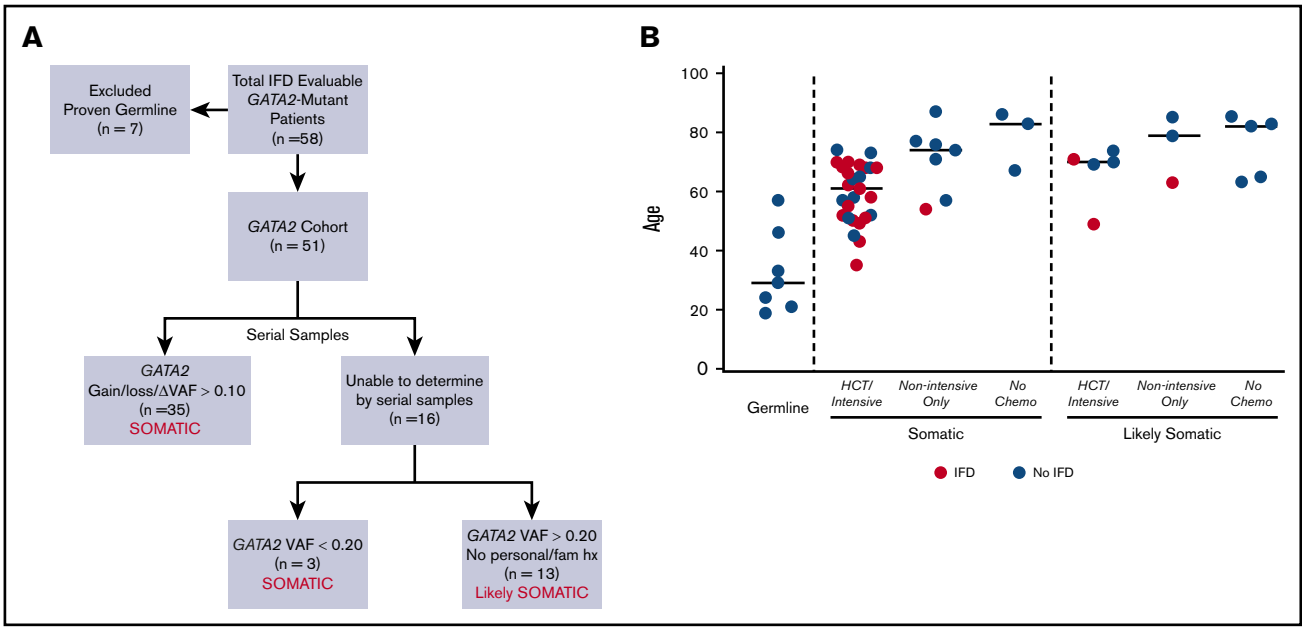

Figure 2. *GATA2* cohort. (A) The approach to defining *GATA2* mutations as somatic or likely somatic. (B) Age distribution comparing patients with proven germline *GATA2* mutations (n = 7) and patients with definitive (n = 38) or likely (n = 13) *GATA2* mutations, based on the framework outlined in panel A. Red points indicate proven, probable, or possible-treated cases of IFD. VAF, variant allele frequency.

region and missense substitutions or in-frame indels located within ZF1 or ZF2 (supplemental Figure 2).

In total, 21 of 51 (41%) evaluable patients with *GATA2* mutations developed proven (n = 5), probable (n = 10), or possible-treated (n = 6) IFD (Table 1). Of the 21 patients, 18 had definitively somatic and 3 had likely somatic *GATA2* mutations (Figure 2B). There was no significant association between the diagnosis of IFD and the type, zinc finger distribution, or variant allele frequency of the *GATA2* mutation or the presence of specific cooccurring gene mutations (supplemental Table 5; supplemental Figure 3). In all 21 patients with proven, probable, or possible-treated IFD, the development of IFD followed treatment with chemotherapy or HCT (Figures 2B and 3; Table 1). By contrast, there were no cases of IFD in the 8 patients with *GATA2*-mutated disease who did not receive chemotherapy or undergo HCT, because of their lower risk disease or fitness, despite similar follow-up periods. IFD diagnoses occurred evenly across the 5-year study period, with no temporal clustering of cases suggestive of environmental outbreaks (supplemental Figure 4).

Pulmonary infection was the most common manifestation of IFD (18 of 21 patients). There was no evidence of preexisting pulmonary alveolar proteinosis, which is associated with germline GATA2 deficiency syndrome,[18] in the patients with pulmonary IFD. Five patients with pulmonary consolidation had concurrently elevated serum or bronchoalveolar lavage (BAL) galactomannan levels. Disseminated candidiasis with positive blood culture isolates occurred in 3 patients. One patient developed invasive fungal sinusitis and another had a fungal brain abscess. Culture isolates included *Aspergillus fumigatus*, *Rhizopus* sp., *Scedosporium* sp., *Candida albicans*, and *Candida tropicalis*. All 6 patients with possible-treated IFD had concern for isolated pulmonary infection, including a patient with a BAL culture that grew *Doratomyces* sp.

All 21 patients received treatment with mold-active antifungals, including triazoles or liposomal amphotericin B. The 90-day mortality after diagnosis of IFD was 52%. Complete descriptions of the clinical, genetic, and mycological characteristics of patients with IFD are shown in Table 1.

The depth and duration of neutropenia are established risk factors for development of IFD.[15] Therefore, we evaluated the characteristics of neutropenia in this cohort to determine whether *GATA2* mutations were associated with severe or prolonged treatment-induced neutropenia. As expected, most patients (19 of 21) were severely neutropenic (ANC $<0.5 \times 10^3/\mu L$) at the time of the IFD diagnosis. In the subset of 13 patients with *GATA2*-mutated AML who received intensive induction chemotherapy at diagnosis or relapse, the median duration from the start of chemotherapy to ANC recovery ($>0.5 \times 10^3/\mu L$) was 27 days. This was consistent with the median duration of severe neutropenia reported in a cohort of 205 consecutive patients with AML treated with 7+3 therapy (23 days; interquartile range, 19-28).[19] Further, in our *GATA2* cohort, there was no difference in the median duration of severe neutropenia between patients with AML who did and those who did not develop IFD after induction (28 vs 25 days; $P = .67$). Similarly, because patients with germline GATA2 deficiency can also have quantitative reduction in monocytes, we examined the absolute monocyte count (AMC) at the index time point. We found absolute monocytopenia (AMC $<0.5 \times 10^3/\mu L$) in 31 of 51 patients (61%), but there was no difference in AMC between patients who did and those who did not develop IFD. Together, these observations suggest that the effect of *GATA2* mutations on IFD risk is not primarily mediated by a selective quantitative defect in neutrophils or monocytes.

We found that 21 of 43 patients (49%) with *GATA2*-mutated myeloid malignancy who were treated with chemotherapy or HCT developed proven, probable, or possible IFD and received antifungal

Table 1. Clinical, genetic, and IFD characteristics in the *GATA2* Cohort

		Disease/treatment			*GATA2*			IFD			
Patient ID	Age, y	Diagnosis	HCT	Proximal chemotherapy	Mutation	VAF	Somatic confidence	Category	Infection site	Mycology	ANC <0.5 × $10^3/\mu L$
G1	51	AML	Yes	MEC	N317H	0.12	Definite	Proven	Brain	Pathology with invasive fungal forms, culture with *Scedosporium* sp.	Yes
G2	68	AML	No	MEC	R398W	0.30	Definite	Proven	Pulmonary, disseminated candidiasis	Elevated serum galactomannan, *C tropicalis* bloodstream infection	Yes
G3	58	MDS	Yes	—	R398W	0.37	Definite	Proven	Pulmonary, disseminated candidiasis	Elevated serum galactomannan, *C albicans* bloodstream infection	Yes
G4	72	AML	Yes	—	G320D	0.37	Likely	Proven	Disseminated candidiasis	*C tropicalis* bloodstream infection	Yes
G5	51	MDS/MPN	Yes	—	R396Q	0.08	Definite	Proven	Pulmonary	Pathology with invasive fungal forms, BAL culture with *Rhizopus* sp.	No
G6	49	AML	Yes	Decitabine	G320D	0.44	Definite	Probable	Sinus	Elevated serum galactomannan	Yes
G7	70	AML	Yes	Clofarabine, cytarabine	T301K	0.31	Definite	Probable	Pulmonary	Elevated serum β-D-glucan	Yes
G8	35	AML	Yes	Decitabine	L321P	0.16	Definite	Probable	Pulmonary	BAL culture with *A fumigatus*	Yes
G9	53	AML	Yes	MEC	A12fs*	0.44	Definite	Probable	Pulmonary	Elevated BAL galactomannan	Yes
G10	68	AML	No	CPX-351	M388_K390del	0.31	Definite	Probable	Pulmonary	Elevated serum β-D-glucan	Yes
G11	63	AML	No	Decitabine/venetoclax	G320D	0.41	Likely	Probable	Pulmonary	Elevated serum galactomannan	Yes
G12	61	MDS	No	CPX-351	G82fs*	0.08	Definite	Probable	Pulmonary	Elevated serum β-D-glucan	Yes
G13	50	AML	Yes	—	N297S	0.45	Likely	Probable	Pulmonary	Elevated serum galactomannan/β-D-glucan	Yes
G14	68	MDS/MPN	Yes	Decitabine	P385R	0.13	Definite	Probable	Pulmonary	BAL culture with *A fumigatus*	No
G15	62	AML	Yes	—	V16fs*	0.38	Definite	Probable	Pulmonary	Elevated serum β-D-glucan	Yes
G16	54	AML	No	αCD123 ADC	K282fs*	0.21	Definite	Possible-treated	Pulmonary	—	Yes
G17	66	AML	No	Daunorubicin, cytarabine	T354M, P121fs*	0.44, 0.36	Definite	Possible-treated	Pulmonary	—	Yes
G18	66	AML	No	Daunorubicin, cytarabine	D99fs*	0.18	Definite	Possible-treated	Pulmonary	—	Yes
G19	70	AML	No	MEC	M388_E391del	0.44	Definite	Possible-treated	Pulmonary	—	Yes
G20	55	AML	No	Daunorubicin, cytarabine	G274fs*	0.13	Definite	Possible-treated	Pulmonary	—	Yes
G21	43	MDS/MPN	Yes	—	L321F	0.15	Definite	Possible-treated	Pulmonary	—	Yes

αCD123-ADC, αCD123-targeting antibody-drug conjugate; ANC, absolute neutrophil count; MEC, mitoxantrone, etoposide, and intermediate-dose Ara-C; VAF, variant allele frequency (VAF at initial index detection).

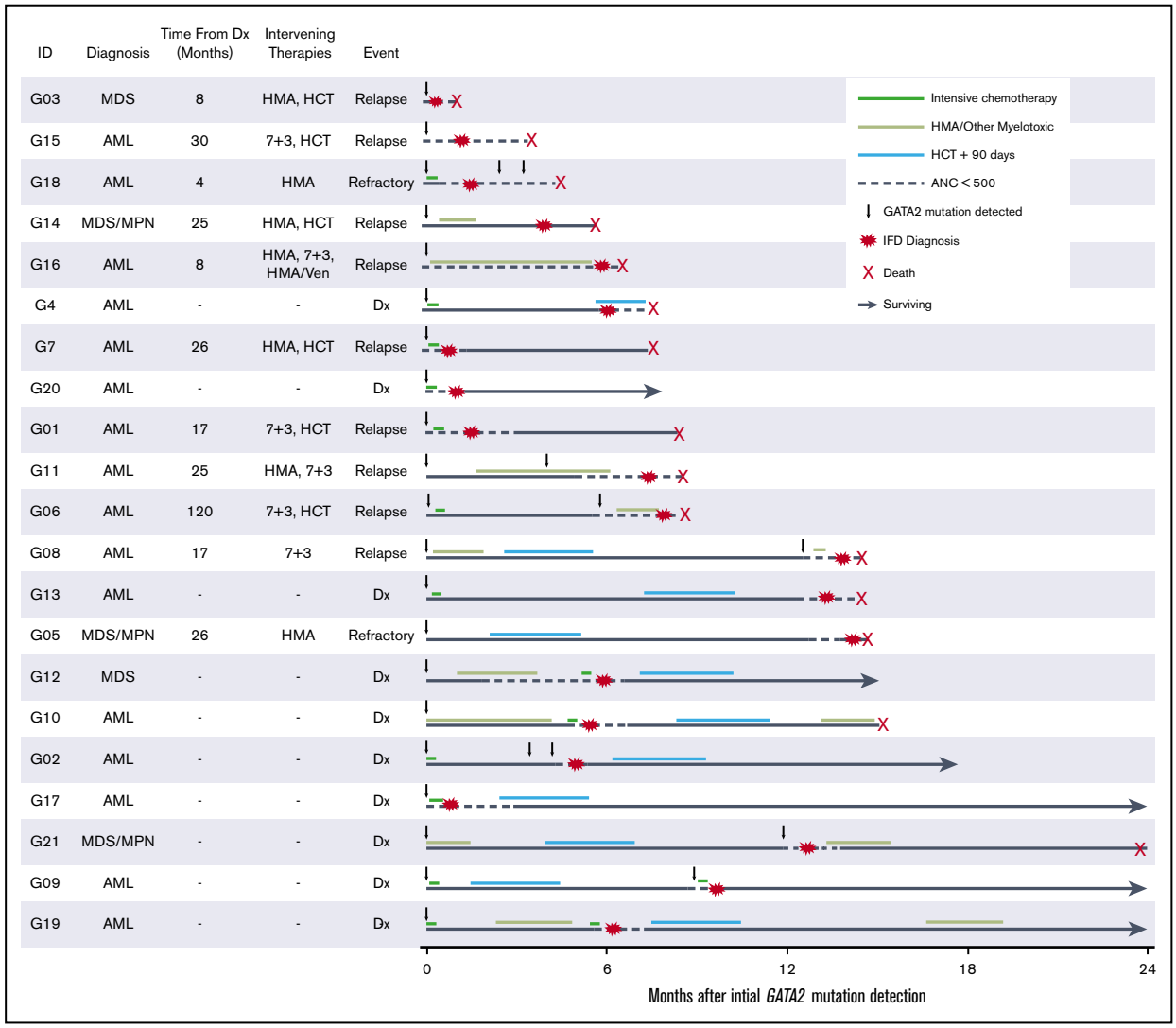

Figure 3. Disease, treatment, and IFD timeline. Swimmers plot detailing timeline of disease and treatment relative to initial *GATA2* detection in patients with proven, probable, or possible-treated IFD in the *GATA2* cohort. Dx, diagnosis; HMA, hypomethylating agent.

therapy. IFD developed in 10 of 26 (38%) treated patients with *GATA2* mutations identified at diagnosis and in 11 of 17 (65%) patients with *GATA2* mutation identified in the setting of relapsed or refractory disease. The high incidence of IFD in patients with *GATA2* mutations contrasted sharply with the rate of IFD in patients with myeloid malignancy in multiple treatment contexts. Specifically, we observed a 6% cumulative incidence of IFD at 1 year in 901 patients with myeloid malignancy who underwent allogeneic HCT at our institution, and the incidence of IFD in patients with *GATA2*-mutated myeloid malignancy in our cohort was higher than reported in patients who received induction chemotherapy for acute leukemia (10% within 100 days and 13% overall),[20] during treatment with hypomethylating agents (9.6%)[21] and after HCT (10% within 1 year).[22] These data indicate that the presence of somatic *GATA2* mutations may define a specific subgroup of patients who have an elevated risk of developing IFD in the context of myelotoxic or immunosuppressive therapy.

Randomized, placebo-controlled trials have demonstrated a reduction in IFD in patients who undergo HCT and receive antifungal prophylaxis, compared with those with no prophylaxis after HCT.[23,24] However, these studies evaluated patients in uniform disease cohorts, without the ability to analyze the magnitude of effect in genetically defined subpopulations. Recent studies have demonstrated that mutations in MDS/AML driver genes can exert pleiotropic effects in terminal hematopoietic lineages in addition to promoting clonal expansion of stem and progenitor cells. For example, the *JAK2*-V617F mutation has been linked with increased formation of neutrophil extracellular traps and increased thrombotic risk in myeloproliferative neoplasms,[25] and *TET2* mutations have been associated with potentiated immune/inflammatory signaling and cardiovascular risk in individuals with clonal hematopoiesis.[26,27] Our results suggest that acquired *GATA2* deficiency causes immune alterations that are similar to those defined in patients with germline *GATA2* deficiency, thereby exposing them to a similarly increased risk of developing IFD. This increased risk appears to manifest particularly in the context of myelosuppressive chemotherapy and HCT, but not in the absence of treatment, suggesting that GATA2-dependent fungal conidial surveillance by mature

innate immune cells suppresses overt IFD in the absence of treatment-related myelosuppression. Our findings indicate that somatic *GATA2* mutations define a vulnerable subgroup of patients with myeloid malignancy for whom antifungal agents should be considered to be a part of the infection prophylaxis regimen.

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Authorship

Contribution: R.S.V., M.P.C., F.M.M., T.D.B., and R.C.L designed the study; R.S.V., M.P.C., C.E.R., D.F., V.T.H., S.K., and T.D.B. performed the data analysis; R.S.V., T.D.B., and R.C.L. wrote the manuscript; and all authors reviewed the manuscript during its preparation and approved the submission.

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