Received: 14 September 2019 | Accepted: 13 November 2019

DOI: 10.1002/iub.2204

CRITICAL REVIEW

IUBMB LIFE WILEY

GATA2 mutations in myeloid malignancies: Two zinc fingers in many pies

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Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Numbers: SFB1243 A08, A08

Abstract

The GATA family of transcription factors are zinc finger (ZF) DNA-binding proteins that regulate transcription during development and cell differentiation. *GATA2* plays an essential role in the regulation of hematopoiesis. As a result, mutations in this gene or alterations in its expression level or function have been linked to a variety of human hematologic disorders. In this review, we summarize the findings and developments over the recent years regarding the clinical correlations and functional properties of distinct *GATA2* mutations in hematopoietic malignancies, with particular focus on the mutational hotspots in the ZF domains.

KEYWORDS

GATA2, genetics, leukemia, myeloid malignancy, transcription factors

1 | INTRODUCTION

GATA binding protein 2 (GATA2) belongs to the GATA family of transcription factors that regulate hematopoietic stem cell self-renewal and differentiation.[1] *GATA2* is crucial for the proliferation and maintenance of hematopoietic stem cells and multipotent progenitors and plays important roles in the development of eukaryotic organisms.[2] The name of the gene is derived from the ability of its protein product to bind the consensus DNA sequence (A/T)GATA(A/G) through two highly conserved zinc finger (ZF) domains.[3] Both somatic and hereditary *GATA2* mutations have been reported in myeloid neoplasia, including chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML).[4–7] The incidence of *GATA2* mutation in AML varies depending on the patient cohort and disease subtype considered.[8–10]

Germline *GATA2* mutations underlie an autosomal dominant predisposition to early onset MDS/AML often with an aggressive disease course and poor outcome.[4] Accordingly, constitutional *GATA2* alterations were recently reported in pediatric MDS frequently representing de novo germline events.[5] Heterozygous pathogenic germline *GATA2* mutations also cause a complex immunodeficiency disorder with variable degree of multilineage cytopenias and different clinical manifestations. Initially, they were identified as different entities, like Monocytopenia and mycobacterial infection syndrome, Dendritic cell, monocyte, B and NK lymphoid deficiency (DCML), and Emberger syndrome,[6,11,12] and are now referred to as GATA2 deficiency.[13] Patients with GATA2 deficiency have an

Abbreviations: AEL, Acute erythroid leukemia; AML, Acute myeloid leukemia; ATRA, All-trans-retinoic acid; CEBPA, CCAAT/enhancer-binding protein alpha; CFU-G, Colony forming unit granulocyte; CFU-M, Colony forming unit monocyte; CML, Chronic myeloid leukemia; DCML, Dendritic cell, monocyte, B and NK lymphoid; del, Deletion; DFS, Disease-free survival; EFS, Event-free survival; FAB, French-American-British; GATA2, GATA-binding factor 2; GOF, Gain of function; inv, Inversion; LOF, Loss of function; MDS, Myelodysplastic syndrome; MonoMAC, Monocytopenia and mycobacterial infection; OS, Overall survival; RFS, Relapse-free survival; t, Translocation; WT, Wild-type; ZF, Zinc finger.

increased propensity to develop MDS/AML, which, among other explanations, may arise due to the impaired immune capacity and bone marrow stress. Nevertheless, pediatric patients with germline *GATA2* mutation can present MDS without a recognized immunodeficiency.[5,14] On a functional level, these mutations often possess compromised transcriptional activity and may have dominant-negative characteristics.[15] *GATA2* germline mutations predominately cause amino acid substitutions in the C-terminal ZF2-domain or truncations throughout the protein.

Somatic *GATA2* mutations mainly cluster in the two ZF domains and are associated with specific leukemia subtypes, like CML progression to blast crisis, or AML with CCAAT/enhancer-binding protein alpha (CEBPA) mutations.[8,16] Phenotypic correlations and defined mutational clustering distinguish ZF1 and ZF2 *GATA2* mutations, indicating that they may represent fundamentally different leukemogenic mechanisms.[17] In this review, we summarize the current understanding and controversies of *GATA2* ZF mutations in the context of their clinical correlations and functional consequences.

2 | GATA2 ZF MUTATIONS: INCIDENCE AND CLINICAL CORRELATIONS IN HEMATOLOGICAL MALIGNANCIES

Zhang et al. identified the somatic ZF2 mutation L359V in CML patients with blast crisis (Figure 1). They described L359V to be a gain-of-function (GOF) mutation, which led to enhanced DNA binding and coactivator recruitment when compared to GATA2 wild-type (WT).[18] In a subsequent publication, the group also confirmed that this mutation is exclusively associated with CML progression but not with other hematological malignancies.[16] Because of the unfavorable outcome of patients with the GATA2 L359V mutation, they suggested that this mutation might also serve as adverse prognostic marker.[16,18] A summary of the discussed articles is provided in Table 1.

Hahn et al. described the germline ZF2 mutant T354M, as loss-of-function (LOF) mutation, which correlates with an early onset MDS/AML. T354M mutations in GATA2 were not found in a cohort of sporadic AML patients, although they could not completely rule out possible mutations due to the presence of samples with

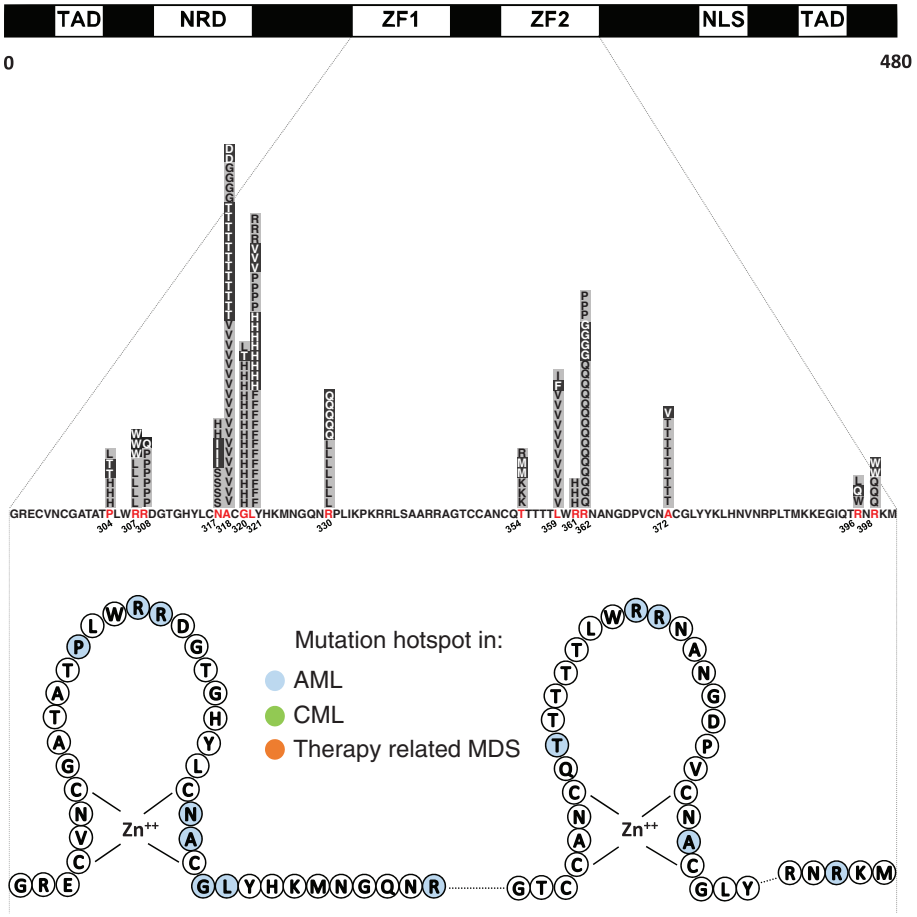

FIGURE 1 Schematic representation of mutation hotspots in the ZF region of *GATA2*. Only missense mutations occurring in the same position in three or more patients with myeloid malignancies are represented. Data from the Catalogue of Somatic Mutations in Cancer (COSMIC v90). AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; NLS, nuclear localization sequence; NRD, negative regulatory domain; TAD, transactivation domain, ZF1, zinc finger 1; ZF2, zinc finger 2

TABLE 1 Summary of the clinical data of the cited studies

Publication	Cohort and patient number	Key finding
Zhang et al.,[18]	85 unselected CML patients with blast transformation	L359V: GOF, exclusively associated with CML, adverse prognostic marker
Dickinson et al.[12]	Four unrelated patients with MonoMAC	*GATA2* ZF2 mutations cause MonoMAC syndrome
Hahn et al.[4]	Five four pedigrees with predisposition to MDS/AML, prescreened for absence of *RUNX1* or *CEBPA* germline mutations	T354M: LOF, associated with early onset of MDS/AML
Yan et al.[10]	Nine paired samples of AML-M5 cases	Found P304H, C319S, and R362Q
Fasan et al.[9]	98 cases of GATA2 mutations in intermediate-risk karyotype AML with biallelic CEBPA mutations	GATA2 mutations in biCEBPA and association with female sex and favorable survival
Greif et al.[8]	160 adult AML patients with a normal karyotype (diagnostic bone marrow or peripheral blood samples)	Recurrent *GATA2* ZF1 mutations associated exclusively with bi*CEBPA* mutations in AML
Green et al.[19]	153 sporadic AML patients, 3 members of a germline *CEBPA*-mutant family	GATA2 mutation do not impact favorable outcome of bi*CEBPA* patients
Hou et al.[20]	192 adult patients who were newly diagnosed as having de novo AML	GATA2 mutations second hit, FAB M1 and M4, better OS and RFS
Gröschel et al.[21]	32 AML (including 2 cell lines MUTZ-3 and UCSD-AML1), 4 CML-BC (including 2 cell lines HNT-34 and MOLM-1), and 5 MDS cases	Negative correlation with RUNX1 mutations, co-occurrence with SF3B1 mutations, most commonly mutated transcription factor in inv(3)/t(3;3)
West et al.[22]	48 patients with GATA2 deficiency	29% had ASXL1 mutations with earlier onset of myeloid transformation
Theis et al.[23]	202 AML patients with CEBPA single or CEBPA double mutations	GATA2 mutations in moCEBPA, no impact on outcome
Ping et al.[24]	158 AEL patients	ZF1 mutations in AEL
Chong et al.[15]	98 patients (clinical information correlated with common germline GATA2 mutations from) gathered in studies from 27 confirmed kindreds and 7 individuals with de novo mutations	T354M, R396Q, and R398W show no difference in leukemia-free survival
Al Seraihi et al.[25]	Five-generation family with *GATA2* T354M MDS/AML	*GATA2–ASXL1* mutation insufficient for leukemia, allele-specific expression of mutant allele
Tien et al.[17]	693 newly diagnosed de novo non-M3 AML	L359V in BCR-ABL negative AML, longer OS, better DFS, acquired ZF1 mutations at relapse

Note: Pubmed search criteria: GATA2, leukemia, ZF, hematopoiesis, AML, and CML.
Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia; DFS, disease-free survival; GOF, gain of function; LOF, loss of function; MDS, myelodysplastic syndrome; OS, overall survival; RFS, relapse-free survival; ZF1, zinc finger 1; ZF2, zinc finger 2.

low percentage blasts. Additionally, they analyzed global gene expression and observed that the T354M mutation lead to a complete LOF while L359V led to a GOF and partial loss (1,253 newly regulated and 457 no longer regulated genes) when compared to GATA2 WT.[4]

Interestingly, Dickinson et al. described disruptive germline mutations in GATA2 ZF2 (including T354M and R398W) as the cause for DCML, which predisposed to myelodysplasia and leukemia.[12]

Chong et al. reported recurrent germline ZF2 mutations. T354M, R396Q, and R398W, which all predisposed to myeloid malignancies, with different phenotypical tendencies (T354M: MDS/AML; R396Q: immunodeficiency; R398W: MonoMAC syndrome) and showed no difference in leukemia-free survival of the affected patients. In their study, they concluded that variable DNA-binding affinity alone was not enough to explain an association between specific ZF2 mutations and hematological malignancy subtypes. The authors summarized that, although those ZF2 mutations broadly predispose to MDS/AML, they appeared to confer unique characteristics regarding differential GATA2 DNA-binding affinity, protein–protein interactions, transactivation potential, colony formation, and differentiation. These results may

explain the differences in age of onset and disease subtypes described by the authors.[15]

Greif et al. found a specific association of biallelic *CEBPA* mutations in cytogenetically normal AML with recurrent somatic mutations in the ZF1 of *GATA2*. In this study, the authors did not observe any significant difference in clinical parameters, like age or sex, between biallelic *CEBPA*-mutated patients with and without mutations in *GATA2*. The presence of *GATA2* mutations did not negatively affect the favorable overall survival (OS) and event-free survival (EFS) of biallelic *CEBPA* patients but there was a trend toward a better OS and EFS for biallelic *CEBPA* patients with additional *GATA2* mutations. This study shows that *GATA2* mutations were mutually exclusive with *NPM1* mutations suggesting alternative mechanisms of leukemogenesis. Moreover, *GATA2* mutations led to a reduction of transcription of CEBPA target genes, pointing toward an oncogenic cooperativity.[8] They also showed that there were genes enriched in the *GATA2*-mutated subgroup being *MYC*, *JUNB*, *FOS*, and *CEBPB* among others.[8]

The striking association of somatic *GATA2* mutations with biallelic *CEBPA* mutations was confirmed by Fasan et al. in a large set of intermediate-risk AML patients. In addition, they provided data on *GATA2* mutations in *CEBPA* WT AML at a frequency of 3.3%. The group demonstrated that *GATA2* mutations were secondary events, were associated with female sex, and had a favorable impact on clinical outcome.[9] In contrast, Green et al. showed that *GATA2* mutation does not impact the favorable outcome of biallelic *CEBPA*-mutated patients.[19]

Hou et al. observed that in all patients with somatic *GATA2* mutations, there were concurrent mutations of other genes, mostly *CEBPA*. Additionally, they showed that the mutations might be lost or gained during disease progression. In their cohort, the mutations were closely associated with younger age and FAB M1 subtype but were mutually exclusive with *NPM1* mutation and FAB M4 subtype. In their study, mutations in *GATA2* correlated with better OS and relapse-free survival (RFS).[20]

Theis et al. confirmed a high incidence of somatic *GATA2* mutations in the subgroup of patients with biallelic *CEBPA* mutations. Moreover, the authors also detected *GATA2* mutations in AML with monoallelic *CEBPA* mutations at a low frequency. In their study, mutations in *GATA2* did not impact clinical outcome, neither in the overall AML patient cohort nor in distinct patient subgroups. Therefore, they stated that the mutational *GATA2* status does not allow to further refine risk stratification of this disease category.[23]

In a study by Gröschel et al., *GATA2* was the most commonly mutated transcription factor in inv(3)/t(3;3) myeloid malignancies with 15% prevalence and all occurred in ZF1 or ZF2. Furthermore, *GATA2* mutations were negatively correlated with RUNX1 mutations, but enriched in samples with *SF3B1* mutations. All mutations found in that study were confirmed to be somatic.[21]

Ping et al. identified somatic *GATA2* mutations in acute erythroid leukemia (AEL) patients. Most of the observed mutations were missense and among them, 9 out of 12 were located in ZF1. They detected *GATA2* mutations in 5.5% of non-AEL AML and in 15% of CML in blast crisis and reported that the frequency of *GATA2* mutations in AEL (22.4%) is significantly higher than in non-AEL AML.[24] Iacobucci et al. confirmed that these data with a cohort of 159 child and adult AEL cases presenting a mutational prevalence of 14.4%.[26]

Tien et al. analyzed *GATA2* mutations in non-M3 AML patients and identified 44 *GATA2* mutations in 43 (6.2%) of their 693 patients, two-thirds of those mutations located in the ZF1 domain. In their cohort, ZF1 mutations were closely associated with FAB M1 subtype and biallelic *CEBPA* mutations but not associated with FAB M4 subtype, *NPM1* mutations and *FLT3*-ITD. They found that AML patients with ZF1 mutations had a significantly longer OS than patients with *GATA2* WT or ZF2 mutations. ZF1 mutations also predicted better disease-free survival (DFS) and a trend for better OS in patients with biallelic *CEBPA* mutations. Consistent with the previous studies of adult AML, *GATA2* mutations localized predominantly in the ZF1 region. In addition, the authors reported two novel AML missense somatic mutations, one of them being the ZF2 mutant L359V, and that some patients acquired *GATA2* ZF1 mutations at relapse being R307L, G320D, L321P, and L321H.[17]

West et al. proposed that somatic alteration of *ASXL1* on the ground of *GATA2* germline mutation is a mechanism driving the onset and severity of disease symptoms.[22] In a subsequent study, Seraihi et al. suggested that a combination of *GATA2* and *ASXL1* mutation alone is not sufficient to promote clonal expansion and leukemic transformation, as this secondary somatic hit may not reliably represent disease progression or identify when treatment is indicated. They did not detect other acquired mutations in the 33 myeloid genes assessed in their affected individuals. The authors proposed allele-specific expression of the *GATA2* mutant allele as an alternative leukemogenic mechanism. Moreover, they suggested that monosomy 7 may be acquired following the acquisition of *ASXL1* mutations, therefore contributing to the malignancy but not initiating symptoms.[25]

3 | GATA2 ZF MUTATIONS: FUNCTIONAL IMPLICATIONS

Zhang et al. reported that GATA2 L359V ZF2 somatic mutant exhibited a higher transactivation potential, compared to GATA2 WT and therefore suggested that L359V is a GOF mutation. Hence, they claimed that GATA2 L359V may recruit coactivators more effectively, thus resulting in an increased transactivation of its target genes. Moreover, they showed that GATA2 L359V presents an enhanced binding to PU.1. Additionally, they observed that at the cellular level, *GATA2* mutations disturbed all-trans-retinoic acid (ATRA)-induced differentiation of HL60 cells, which would be a scenario similar to the block of differentiation in blast cells. Therefore, they stated that the GOF of GATA2 L359V may underline the blast crisis with the myelomonocytic phenotype observed in CML patients.[16,18]

Hahn et al. observed that the germline GATA2 ZF2 mutation T354M dramatically reduced the ability of GATA2 to bind its consensus DNA motif. Using Luciferase reporter assays in HEK 293T cells, they showed that T354M had significantly reduced transactivation ability compared to WT on known *GATA2* responsive enhancer elements of *RUNX1*, *CD34*, and the *LYL1* promoter. Although the transcription assay in HEK 293T is rather artificial, this model has been frequently used and yielded conclusive data in the study of transcription factors.[4,8,27] Under nondifferentiating conditions, they found that T354M acted as LOF mutant unlike WT and L359V, which inhibited proliferation and promoted apoptosis. However, they also observed that in the presence of ATRA, T354M alone enabled HL60 cell proliferation and survival while simultaneously inhibiting differentiation and apoptosis.[4]

In a study of Chong et al., the group tested several somatic and germline mutants. They showed different DNA-binding capabilities: L359V displayed no significant reduction in binding, in contrast to T354M, R362Q, R398W, and the ZF1 mutant L321F that showed reduced but still detectable binding. The mutants T355del, R361L, C373R, and R396Q displayed little or no detectable binding. They reported that all mutants displayed a reduced capability to transactivate transcription from at least one *GATA2*-responsive element compared to WT. L359V displayed activity similar to WT or a mild GOF. The mutants with the lowest DNA-binding affinity (T355del, R361L and C373R) showed the most prominent reduction in transactivation, including complete abrogation in some instances, whereas the mutants T354M, R362Q, R398W, and L321F displayed residual transactivation potential. Furthermore, they observed that all GATA2 mutants, except for L359V, showed reduced synergistic transactivation with PU.1. Interestingly, T354 M and C373R showed enhanced affinity to PU.1. Based on those findings, the group claimed that despite transactivation via *GATA2*-responsive elements was seen to correlate with DNA-binding activity, the interaction and coactivation with PU.1 varied between the tested mutants. The group observed a striking derepression of colony formation for most of the mutants. In the case of L359V, the described de-repression of colony-forming ability could not be explained by its effect on DNA binding and transactivation ability. Due to these findings, the group suggested that there are both DNA-dependent and independent effects of *GATA2* mutations on differentiation. In that study, T354M, L359V, and R362Q but not others were able to repress colony forming unit monocyte differentiation.[15]

Greif et al. observed that the ZF1 somatic mutants A318T and L321F showed a reduced transactivation upon cotransfection with a GATA-responsive reporter. The G320D mutant showed an increased activation, whereas the L359V mutant did not show a significant difference when compared to GATA2 WT. In coimmunoprecipitation experiments, the GATA2 mutants A318T, G320D, L321F, and L359V were still able to interact with CEBPA WT. *CEBPA*-dependent activation was enhanced by the coexpression of GATA2 WT, but this enhancement was reduced for all the GATA2 ZF1 mutants associated with AML with biallelic *CEBPA* mutations, but not for the CML-associated L359V mutant.[8]

Another study by Cortés-Lavaud et al. reported that the GATA2 ZF2 germline mutations T354M, T355del, and R396Q impair the transcriptional activity of GATA2. The group furthermore described R396Q to be a LOF mutation due to its abrogation in promoter binding, loss of DNA binding ability and inability to retain a progenitor phenotype. They found that R396Q increased the proportion of colony forming unit granulocyte.[28]

Ping et al. showed that upon coexpression of GATA2 WT with the ZF1 somatic mutant R330X, the transcriptional activity of *GATA2* WT was significantly affected and therefore concluded that R330X had a dominant-negative effect over GATA2 WT. The authors did not observe such a dominant-negative effect in ZF1 mutants P304H and L321P. Additionally, in their study, the overexpression of GATA2 mutants in the mouse myeloid progenitor cell line 32D had no effect on proliferation or colony-forming ability.[24]

Katsumura et al. analyzed the functional consequences of *GATA2* ZF1 somatic mutations from AML patients in a mouse aortic endothelial cell assay. They showed that while GATA2 WT activated specific target genes, ZF1 leukemia mutations impaired the transcriptional response. Using a genetic complementation assay, they discovered that the *GATA2* ZF1 mutant R307W, which was predicted to be inactive or to have diminished

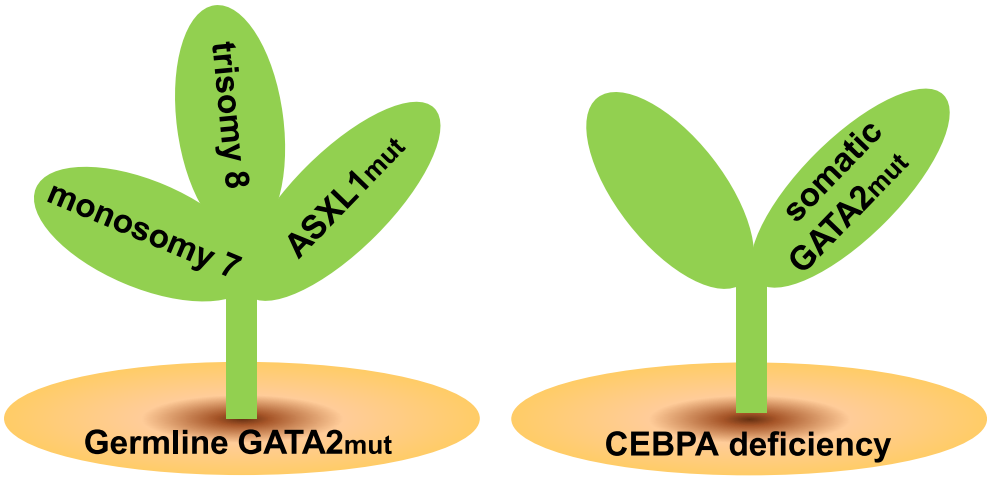

FIGURE 2 Evolutionary patterns of GATA2 mutations in myeloid leukemia. Left panel: *GATA2* germline mutation provides a fertile ground for the appearance of *ASXL1* mutation, monosomy of chromosome 7 and trisomy of chromosome 8. Right panel: *CEBPA* deficiency provides a fertile ground for the emergence of *GATA2* somatic mutations

activity, retained activity in primary cells. Of particular interest to the group was its capacity to induce granulocytic differentiation and cell cycle progression, which they showed to exceed that of *GATA2* WT. In their study, they were able to highlight several functional differences between ZF mutants: Although ZF1 mutations resembled the effect of ZF2 mutations with respect to the disruption of chromatin binding and target gene activation; ZF1 mutants were more efficient to activate target genes.[29]

4 | DISCUSSION AND CONCLUSIONS

Germline mutations in *GATA2* are either missense in the ZF2, frameshift or stop spread across the gene. Generally, they are associated with reduced DNA binding ability and transactivation potential, consistent with a LOF phenotype.[4,15] Of note, the only reported missense ZF1 germline mutation affects a cysteine, which likely critically disrupts the ZF structure, resulting in a complete LOF.[5] The lack of germline mutations in ZF1 can be explained by the assumption that ZF1 mutations may be embryonic lethal. Another possible explanation could be that ZF1 mutations can only contribute to leukemogenesis on the specific transcriptional context of cells with *CEBPA* deficiency. The link between *GATA2* germline mutations and higher MDS/AML incidence is a well-established fact.[4] These patients present a high proportion of *ASXL1* mutations, monosomy 7 and trisomy 8,[22,25] which suggest that *GATA2* mutation provides a specific fertile ground which selects for these lesions (Figure 2, left panel). Based on the existing literature it remains controversial if *SETBP1* mutations are associated with *GATA2* related MDS[30] or are rather associated with monosomy 7.[31]

Somatic *GATA2* mutations show overall reduced transactivation potential with a few exceptions[8,24,29] and skew the differentiation of hematologic progenitors towards the granulocytic linage.[29] So far, somatic mutations in *GATA2* ZF1 have been shown to co-occur with mutations in *CEBPA* and *SF3B1*, FAB M1 subtype, AEL and t(3;3) AML and to be mutually exclusive with mutations in *NPM1*, *RUNX1*, and *FLT3*-ITD and FAB M4 AML.[8,17,21,24] The L359V mutant was earlier described to be exclusively associated with CML,[16] whereas more recent studies show an association with BCR-ABL-negative AML.[17] The prognostic value of somatic *GATA2* mutations remains controversial. The discrepancies between the aforementioned studies may arise from confounders such as the higher prevalence of *GATA2* mutation in females, patient age and the favorable prognostic of *CEBPA* double mutations.[9] Beyond AML with biallelic *CEBPA* mutations, we and others recently found *GATA2* mutations in t(8;21) AML.[32–34] In fact, AML1-ETO represses CEBPA transcription,[35] indicating that *GATA2* mutations arise on the fertile ground of *CEBPA* deficiency—due to either *CEBPA* mutation or downregulation (Figure 2, right panel). Another example for this correlation is AML with 3(q21;q26) aberrations,[21] where the overexpression of *EVI1* (MECOM) represses *CEBPA*,[36] thus providing the basis for acquisition of *GATA2* mutations. Additionally, somatic *GATA2* mutations are either lost or acquired as the disease progresses.[20] The fact that somatic *GATA2* mutations frequently arise during AML relapse suggests a role of *GATA2* in chemotherapy resistance.[17]

Another layer of complexity when navigating the existent *GATA2* mutational data is the fact that some reported somatic mutations have not been tested for germline status. This may result in typical *GATA2* germline mutations, for example T354M, being reported as somatic without assurance that those patients did not have a germline mutation.

Although *GATA2* has been in the spotlight of hematological research for several years, the exact mechanism of leukemic promotion through *GATA2* mutation remains elusive. To date, it is clear that mutations in ZF1 and ZF2 have different functional consequences and co-occur with specific leukemic lesions. The collaboration of *GATA2* mutations with these lesions is likely to be the missing piece in this puzzle. We can expect a much greater understanding of the prognostic value of these mutations as patient cohorts expand, as well as a better functional characterization as more specific leukemia models are developed in the years to come.

ACKNOWLEDGMENTS

P.A.G. acknowledges support by the Deutsche Forschungsgemeinschaft (DFG), Collaborative Research Centre (CRC) 1243 "Cancer Evolution," Project A08.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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How to cite this article: Leubolt G, Redondo Monte E, Greif PA. *GATA2* mutations in myeloid malignancies: Two zinc fingers in many pies. *IUBMB Life*. 2020;72:151–158. https://doi.org/10.1002/iub.2204