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REVIEW

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Genetic aberrations involved in relapse of pediatric acute myeloid leukemia: A literature review

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Abstract

Globally, 15-20% of all children diagnosed with leukemia suffer from acute myeloid leukemia (AML), a rapidly progressive, clinically and biologically heterogeneous disease leading to the impaired differentiation of myeloid blast cells. Although 80% of patients achieve complete remission after induction chemotherapy, many relapse, negatively affecting overall out comes. The mechanisms underlying relapse have not been fully elucidated. This review aims to provide an overview of genetic aberrations involved in relapse of disease.

A literature review on molecular mechanisms implicated in pediatric AML relapse spanning from 2003 to 2017 was conducted. PubMed, Medline, and Google Scholar were interrogated using relevant search terms. Of note, we examined a total of final 10 research papers from four large study groups that have utilized whole genome sequencing and molecular targeting of trio or paired samples of initial diagnosis, remission, and relapse. Their findings reveal that the genomic landscape of pediatric AML varies from diagnosis to relapse in different populations. Pediatric AML relapse is a systemic evolutionary illness accompanied by synchronized mutational hits impairing differentiation function. The irregular proliferative function is a consequence of mutations in signal transduction genes such as *FLT3*, *RAS*, *PTPN11*, and c-*KIT* and genes that code for transcription factors such as CEBPα, WT1, SATB1, GFI1, KLF2, and TBP are associated with relapse of disease. Identification of molecular markers unique to different stages of the disease in distinct populations can provide valuable information about disease prognosis and management.

KEYWORDS

acute, gene expression, leukemia, myeloid, pediatrics, recurrence

1 | INTRODUCTION

Pediatric AML is a rapidly progressive disease, which is clinically and biologically heterogeneous. The abnormal gene expression due to genetic mutations and epigenetic changes impairs normal hematopoiesis. Cells harboring these changes may undergo clonal expansion and differentiation arrest at any specific stage; the condition is known as acute myeloid leukemia (AML). The global incidence of acute leukemia among all reported pediatric cancers is high with AML accounting for 15-20% of all acute leukemias.

Despite high remission rates in AML, improvement in overall survival has been marginal over the past decades, likely due to high relapse rates.[1,2] Globally, 80% of patients achieve complete remission after induction chemotherapy of which 30-40% subsequently relapse.[3] Approximately 50-60% of relapses occur within the first year after diagnosis and largely in the bone marrow.[4] Childhood AML relapse rates vary around the world with rates are as high as 40-80% in India, whereas a relapse rate of 29.4% has been documented in China.[5,6] The possible reasons for high relapse rates in developing countries could be incomplete treatment due to financial burden,[5] use of only conventional therapies,[7] and heterogeneity of disease.[8] Preventing or effectively treating relapse can result in improved outcomes.

Worldwide, the genomic landscape of pediatric AML varies from diagnosis to relapse. Studies of different population groups have identified various alterations in tyrosine kinases genes, transcription factors, nuclear transport genes, RAS/MAPK/MEK pathway, and deregulation of tumor suppressor genes in patients at diagnosis, remission, and relapse.[8] Molecular and genetic aberrations play an important role in pediatric AML relapse. Targeting the specific molecular aberration may increase remission rates and prevent relapse resulting in improved outcomes. Therefore, an in-depth knowledge of molecular mechanisms and factors involved in relapse development is critical.

TABLE 1 Gene expression and its prognosis in pediatric AML relapse

	Gene	Expression at relapse	Prognosis	References
Signal transduction genes	*FLT3*(*FLT3-ITD*, *FLT3-TKD*)	Both up- and downregulated	Poor	8, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20
	RAS(*N-RAS*, *K-RAS*)	Usually upregulated (*N-RAS* is downregulated)		8, 10, 11, 12, 13, 14, 19
	C-KIT	Retained		11, 12, 19
	PTPN11	Lost		12, 16, 18
Transcription factors	*WT1*	Both up- and downregulated		10, 11, 14, 16, 18
	CEBPα	Gene targets differentially regulated	Good	12, 19, 20
	GFI1			11
	SATB1			11
Nuclear transport gene	*NPM1*	Co-occurs with FLT3		10, 11

A narrative review of current literature on molecular mechanisms implicated in pediatric AML relapse is presented here. The prognostic correlation of molecular alterations identified in relapsed AML is provided in Table 1.

2 | METHODS

A narrative review of literature from 2003 to 2017 describing the prognostic implication of genetic and molecular markers found in relapse of AML children was conducted. The MeSH term "Leukemia, Myeloid, Acute" was used with "diagnosis," "recurrence," "relapse," "pediatric," "genes," and "gene expression" to search PubMed. Of the five articles retrieved, two were eliminated when filtered for full text articles within the applicable publication date range. One of these articles did not have paired or trio of samples from patients at initial diagnosis, remission, and relapse and was therefore excluded. Additional studies were hand-searched from the reference lists of relevant articles, including other related review articles and through a Google Scholar search. Figure 1 depicts the search strategy.

2.1 | Type I and II mutations in AML

Pediatric AML is a heterogeneous and dynamic disease, with the presence of multiple somatically acquired driver mutations, co-existing competing clones, and evolution of the disease over time. As part of the multistep and multilayered process of leukemogenesis, tyrosine kinase mutations, such as in FLT3, frequently occur in conjunction with other gene rearrangements and point mutations. Therefore, it appears likely that further mutations are required in addition to activating mutations for the development of AML, and alterations at multiple biological levels are associated with disease progression/relapse development (Figure 2).[9]

Four large study groups have utilized whole genome sequencing and molecular targeting of trio or paired samples of initial diagnosis, remission, and relapse to reveal a systemic pattern of acquisition and loss of mutations throughout disease (Table 2). The NCI/COG group studied samples taken at diagnosis, remission, and relapse (trio) from a large pediatric patient cohort (n = 1023) using whole exome sequencing (WES) and found mutations in several genes (including *FLT3*, *NRAS*, *PTPN11*, *WT1*, *KIT*, and *KRAS*). The most commonly altered pathways identified were tyrosine kinase and RAS/MAPK/MEK pathways in 30-90% of pediatric AML patients.[8] Additionally, mutations in transcription factors overlapped with the activated tyrosine kinase and RAS/MAPK variants and were found to be present at relapse.[8] Another group, Dutch Childhood Oncology and the AML-Berlin-Frankfurt-Münster, examined 69 paired pediatric samples collected upon initial diagnosis and relapse and also observed the persistence of *FLT3-ITD* (20.8%), *RAS* (23.8%), and *WT1* (17.8%) mutations (ie, type I/II) throughout disease.[10] These observations are consistent throughout all selected study groups and may indicate the importance of these genes and their underlying pathways.[8,10-20]

Sustained progression of the disease is required after leukemic transformation, which in addition to the role of multiple mutations also depends on adequate mutant allelic burden.[8,18,10] The high mutant allelic burden or variant allele fraction (VAF) provides the advantage to select more fit clones for proliferation.[8] This phenomenon is known as "fitness advantage" and provides resistance to apoptosis and therapy.[18] It also affects DNA repair mechanisms by the acquisition of the mutator phenotype, which has been described in ALL relapse cases and may be the reason for relapse in AML as well.[18] Farrar et al found adverse effect of high mutant allelic burden with relapse.[8] This observation also suggests the self-extinction of low variant alleles and supports the prognostic importance of a high allelic burden.

2.2 | FLT3 tyrosine kinase

Fms-related tyrosine kinase 3 (*FLT3*) gene encodes a class III receptor tyrosine kinase that regulates hematopoiesis. It is primarily expressed on hematopoietic progenitors where upon activation it phosphorylates cytoplasmic substrates.[21,22] The alteration in *FLT3* gene leads to the unregulated proliferation, which causes myeloid neoplasms.[22] Two types of *FLT3* mutations have been found in leukemic cells, internal tandem duplication (*ITD*) mutations of the juxtamembrane domain and point mutations such as in aspartic acid (D835) within the activation loop of the second tyrosine kinase domain (FLT-TKD).[23] The mutations in internal tandem of *FLT3* (ie, *FLT3-ITD*) are most commonly found in

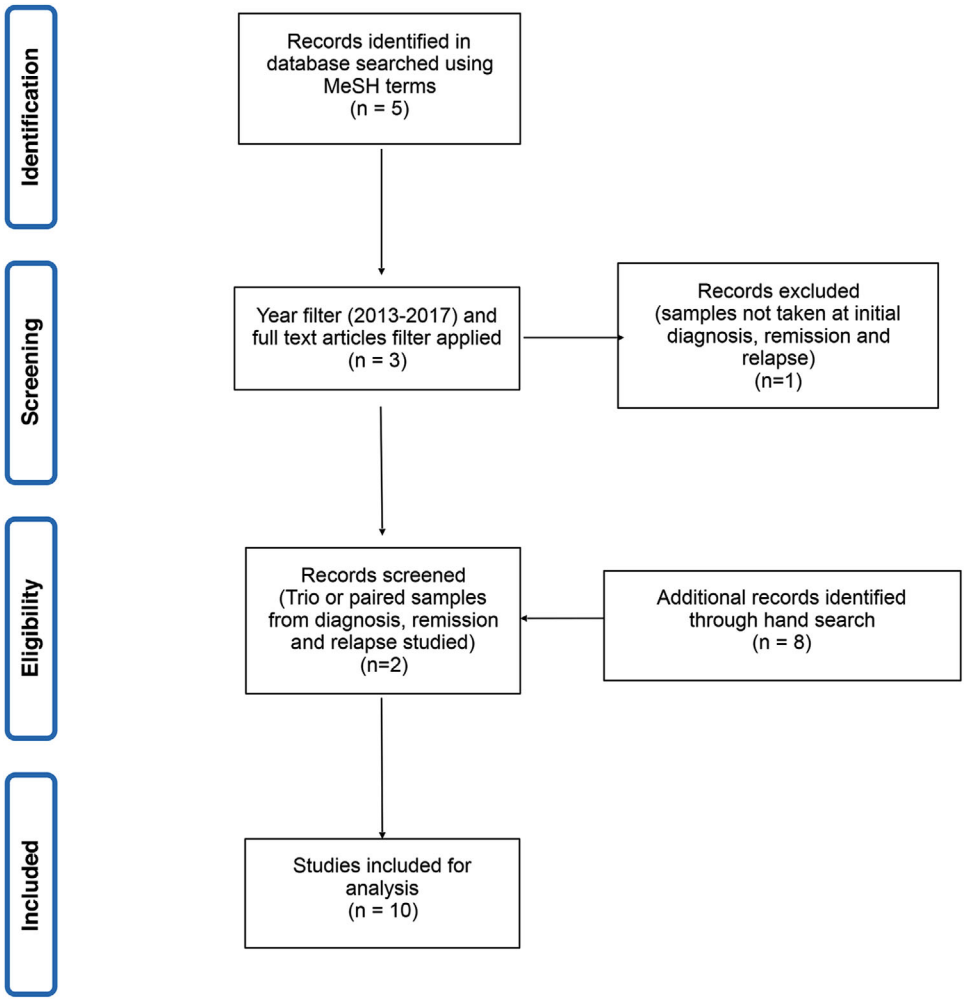

FIGURE 1 Search strategy [Colour figure can be viewed at wileyonlinelibrary.com]

pediatric AML.[8,10-14,18,19] *FLT3-ITD* indicates poor prognosis and predicts response to relapse therapy in pediatric population.[8,10-14,18,19]

A study conducted by Liang et al in which collected de novo AML samples (n = 91) from Taiwanese pediatric population identified *FLT-ITD* mutations in 15.4% and *FLT-TKD* mutations in 3.3% of patients, with none of the patients exhibiting both mutations. They further evaluated paired marrow specimens of the four patients who relapsed and found that none of them had *FLT3-ITD* or *FLT-TKD* at diagnosis, but at relapse one patient developed *FLT-ITD* wild-type mutation.[17] This has also been reported from other study cohorts.[10] The incidence of *FLT3-TKD* is low in both adult and children, and comparatively *FLT3-TKD* mutation is lower in children.[17] Similarly, another study by the Associazione Italiana Ematologia e Oncologia Pediatrica (AIEOP) group performed WES of four Italian children showing 25-30% expansion of the *FLT3-TKD* subclone at the time of relapse in one patient; this subclone had survived initial chemotherapy.[18] Despite the fact that therapy-endured small clones of *FLT3-TKD* underwent clonal expansion, the frequency of this mutation (ie, one out of four patients) is still low and is consistent with what has been described in other study groups.[17] Therefore, *FLT3* point (D835 residue) mutations (or *TKD*) are less likely to be involved in the development of pediatric AML relapse.[14]

The mutations in *FLT3-ITD* vary throughout diagnosis to relapse in all study groups.[10,11,13,14,18,17] To define the presence of *FLT3-ITD* mutations throughout diagnosis to relapse of pediatric population, Cloos et al examined Dutch pediatric (n = 42) and adult (n = 38) samples collected at initial diagnosis and at relapse. *FLT3-ITD* mutations found in mature leukemic cells were easily eradicated by therapy but the remaining *FLT3-ITD* mutation in leukemic stem cells may persist and cause relapse. Thus, in a few cases *FLT3-ITD* loss at the time of relapse maybe explained by eradication of this aberration in mature leukemic cells but not in stem cells.[14] The Dutch Oncology Group showed that mutations in small clones (stem cells) are biologically more stable than their ancestral clones and may undergo expansion at relapse due to the acquisition of therapy-induced alterations.[14]

The *FLT3-ITD* mutational shifts strongly influence the association of mutational status with time to relapse (TTR).[10] Although the risk of relapse was not statistically significant, when stratification of subgroups was done there was a strong trend for shorter TTR in patients with Type I/II mutations.[10] Children have a slightly longer time to relapse as compared with adults.[14] The median time to first relapse was 85 months for *FLT3-ITD* positive patients and 112 months for others.[11]

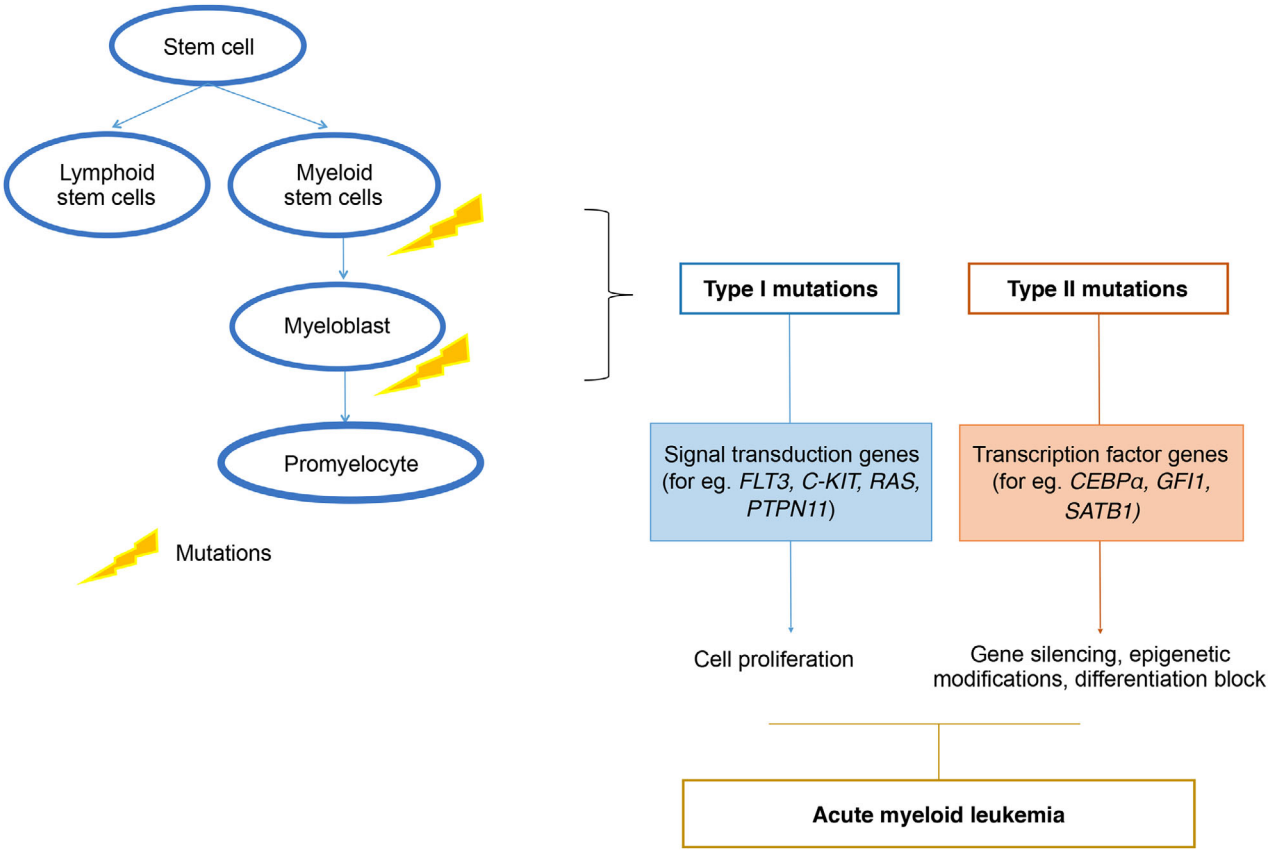

FIGURE 2 Tumorigenesis and types of mutations in select genes in pediatric acute myeloid leukemia. Left panel: Mutations impair normal hematopoiesis. Cells that harbor these alterations undergo clonal expansion and arrest at a specific stage of myeloid hematopoiesis giving rise to acute myeloid leukemias (AML). Right panel: Type I mutations drive abnormal cellular proliferation and type II mutations result in systemic block of differentiation leading to tumorigenesis [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Pediatric AML study groups (2003-2017). Paired refers to samples taken from the same patient at diagnosis and relapse; trio refers to samples taken from the same patient at diagnosis, remission, and relapse

Study groups	Year	Number of cases	Reference
Taiwanese Pediatric Oncology Group	2003	91 paired cases	17
	2005	117 paired cases	16
	2006	17 paired (+132 adult)	20
	2008	154 paired	19
Dutch childhood oncology group & AML Berlin-Frankfurt-Münster	2010	69 paired cases	10
	2014	198 paired cases	11
	2015	23 paired cases	12
AIEOP 2002/010	2016	4 trio cases	18
NCI/COG TARGET-AML	2016	20 trio cases	8
	2017	1000 trio cases	13

2.3 | *RAS* oncogene

Among signal transductions genes, *RAS* is the second most commonly mutated proto-oncogene. *RAS* mutations account for 20.8% of B-precursor acute lymphoblastic leukemia (ALL) pediatric patients and are found in 17.7% of pediatric AML relapse cases.[15] Based on data from the Taiwanese oncology group that collected 154 paired bone marrow samples from de novo AML children, a difference was noted between patients with core-binding factor (CBF) AML and non-CBF-AML. The findings showed that 7.3% (3/41) and 4.9% (2/41) had *N-RAS* and *K-RAS* mutations in patients with CBF-AML. However, in the non-CBF AML group, *N-RAS* mutations accounted for 10.7% (12/112), whereas *K-RAS* mutations were seen in 7.7% (8/110) of children.[19] Ras protein is located on the inner surface of the plasma membrane

and acts as molecular switch that transduces extracellular signals to the nucleus. Normally, Ras flips between the resting guanosine diphosphate (GDP)-bound state and active guanosine triphosphate (GTP)-bound state. Mutations block the hydrolysis of GTP to GDP, leading to constitutive signaling.[24] Ras is regulated by a protein known as Shp2 that is in turn regulated by PTPN11. The mutated *RAS* may transduce abnormal signals due to disrupted downstream proteins.[25] Farrar et al observed loss of *NRAS* and *PTPN11* at relapse in AML patients, as these genes were already initially very low (ie, low VAF).[8]

The *KMT2A* 11q23.3 rearrangement is one of the most common pediatric AML chromosomal alterations. Bolouri et al found mutations in *KRAS*, *NRAS*, *PTPN11*, and *NF1*, with these *KMT2A* translocations.[13] Bachas et al (the Dutch Childhood Oncology Group [DCOG] group), who initially studied 138 pediatric samples and then an additional 198 samples, found *RAS* mutations in children with cytogenetically normal AML, in a subgroup of other cytogenetic and some in the *MLL* rearrangement, AML-ETO1, and core binding factor AML.[10,11] Bachas et al also observed a strong trend toward shorter time to relapse of 17.4 and 9.4 months for wild-type *RAS* and mutant *RAS*, respectively.[11]

2.4 | Other type I gene mutations

C-KIT is a tyrosine kinase and stem cell factor (SCF) receptor more frequently found in pediatric CBF-AML.[11,19] As a surface protein that binds to SCF, it plays an important role in growth of certain blood cells. It may also be found in higher than normal amounts or in altered forms in some types of cancer cells, including gastrointestinal stromal tumors and melanoma.[26] Shih et al studied consecutive paired samples (n = 154) of patients with de novo AML and found a total of 27% (n = 41/154) of pediatric AML with core binding factor AML, out of which *c-KIT* mutations were found in 41.5% (n = 17/41).[19] In this study of paired patients, those who relapsed continued to retain *c-KIT* mutations suggesting their role in leukemogenesis of CBF-AML but no specific role in relapse.[19] Bachas et al assessed the frequency of molecular aberrations at first relapse in 198 non-French-American-British (FAB)-type M3 pediatric AML (age <18 years) and found 7.8% (15/192) of *c-KIT* mutations in their cohort.[11]

WT1 is another gene that plays an important role in cell cycle and apoptosis. It promotes tumor in osteosarcoma and could be potential therapeutic target.[27] *WT1* is also found to be associated with pediatric AML.[13,11,18] Bachas et al evaluated the clinical relevance of *WT1* using multivariate analysis for relapse-free survival (RFS). The analysis revealed that the presence of a *WT1* mutation was the only independent risk factor for shorter RFS.[11] The Cancer Genome Atlas (TCGA) pediatric AML cohort found that *FLT3-ITD* mutations with *WT1* mutations or NUP98-NSD1 fusions are associated with common induction failure and poorer outcomes in children with AML.[13] *WT1* may therefore also be a valuable marker to predict response to therapy.[11]

NPM1 is a nuclear transport gene, which has been found to be associated with cytogenetically normal AML. The COG/NCI TARGET AML group (n = 1023) also found mutations in the *NPM1* gene, which was more frequently mutated in older patients than in children.[13] However, in pediatric AML, this group found that the co-occurrence of *NPM1* and *FLT3-ITD* mutations was associated with better outcomes as compared to adults.[13]

2.5 | Role of transcription factors in pediatric AML relapse

In addition to driver mutations, type II mutations are also necessary for progression of AML.[20,16,8] The stepwise acquisition of these mutations gives genomic diversity within a cell lineage.[18] DCOG identified transcription factors that regulate differentially expressed genes in 23 pairs of samples (from diagnosis and relapse). In 20 out of these 23 pairs, CEBPα was identified as the transcription factor responsible for differences observed in gene expression between diagnosis and relapse. Of note, *CEBPα* mutation was only identified in one of the 23 patients, indicating that epigenetic or other alterations in *CEBPα* are responsible for the changes observed in *CEBPα*-regulated genes. Other transcription factors that were predicted to regulate differentially expressed genes in the paired samples included GFI1 (in 16/23 samples) and SATB1 (in 15/23 samples).[12] GFI1 is a growth factor independent 1 transcriptional repressor that encodes a nuclear zinc finger protein. This transcription factor is a key factor in histone modification that silences the promoter region of genes.[25] SATB1 is thought to be a main epigenetic modifier, linking higher order chromatin with gene regulation.[25]

In a study conducted in Taiwanese children (Taiwan Pediatric Oncology Group; TPOG), alterations in *CEBPα* were found in 6% (n = 7/117) of patients. Six out of seven patients had N-terminal frame shift mutations and in-frame insertions in the basic-leucine zipper (bZIP) domain of CEBPα, resulting in expression of a truncated protein.[16] A follow-up study of 17 children with paired samples of de novo and relapsed disease showed that the majority of *CEBPα* mutations were retained, but that there were changes in their allelic distribution at the time of recurrence.[20] In most instances, *CEBPα* confers good prognostic significance in pediatric AML with normal karyotypes.[12]

The AIEOP group studied pediatric AML patients (n = 4 trio samples at diagnosis, remission and relapse) without recurrent cytogenetics aberrations. The group detected highly penetrant bi-allelic mutations of *CEBPα* (biCEBPα), which showed a homozygous non-frame shift insertion of CEBPα involving the b ZIP domain in majority of tumor populated cells (Mutation Frequecy (MF) >80%) both at diagnosis and relapse.[18] The presence of *CEBPα* transcription factor-related gene mutations in the Italian, Dutch, and Taiwanese groups is comparable. To establish *CEBPα* mutations as molecular markers, there is a need to further study the role of *CEBPα* and other transcription factors in different and large populations.[16]

Of note, the data from the studies reviewed here show congruence between pre-next-generation sequencing (NGS) methodology and NGS data. For example, mutations in *FLT3*, *RAS*, *CEBPα* to name a few were identified using polymerase chain reaction (PCR)-based assays in older study cohorts and were also detected in large-scale whole exome and genome studies.[12,13,16] Moreover, type I mutations in *FLT3*, *RAS*, *WT1*, and *NPM1* have been reported to coincide with type II mutations, particularly in *CEBPα*,[12,13,16] indicating the role of multiple

alterations in the multilayered process of onset, progression, and relapse of disease.

2.6 | Clonal evolution after initial chemotherapy

Pediatric AML is a diverse disease with similar phenotypes despite molecular heterogeneity. This may explain repeated failure of randomized clinical trials in improving outcomes in recent years. No single treatment strategy is likely to be effective for all pediatric AML subtypes. Therefore, the careful assessment of emerging mutations is essential to counter relapse of the disease. The stepwise evolutionary tumor progression provides the genetic diversity within the cell lineage.[18] Microenvironmental conditions such as resource limitation and chemotherapy play a dynamic role in the acquisition of novel mutations, resulting in selection and expansion of biologically fit clones along with eradication or self-extinction of less fit clones.[18]

The NCI/COG TARGET AML group (n = 20 trios) used WES to show that therapeutic agents play a key role in evolutionary conservation of mutations at relapse. The obtained data of 141 verified diagnostic somatic, non-synonymous mutations showed that only 83 (58%) persisted and were identified at relapse. On the other hand, the group also reported 143 mutations at relapse of which 60 (42%) were novel and were not detected at diagnosis. Based on these observations, different scenarios for clonal evolution were suggested. For example, the selective pressure exerted by applied therapy can lead to evolution of distinct mutations at relapse.[8] This observation is also supported by work of the AIEOP group.[18] The AIEOP group found *ASXL3* mutation (novel mutation) at diagnosis with 1% of mutational frequency, which expanded to 60% at relapse.[18] As suggested by Farrar et al, therapy may be the reason of expansion of novel mutation at relapse.[8] The NCI/COG TARGET-AML observed the differences in conventional and targeted therapy with tyrosine kinase inhibitors (TKIs) with a particularly different pattern at relapse. For example, they observed that the treatment with (TKIs) selectively leads to secondary mutations in activation loop domain of the gene where those who relapse after exposure to TKI show evolution of secondary FLT3 mutations that are associated with TKI resistance.[8]

The biology of therapy-induced mutations may also explain the fitness advantage of emerging novel clones and may explain their survival from therapy. Masetti et al, in a study of four patients, found a clone with a deleterious point mutation in *TYK2*, a member of Janus tyrosine kinases family, which contributed to the clonal survival posttherapy in a relapse patient.[18] This may be due to activation of intracellular pathways through cytoplasmic kinases affecting cellular growth, differentiation, and survival. This clone constituted a third of the whole blast population at relapse.[18] The application of advanced techniques such as NGS on larger sample size from different population may provide a clear and more precise understanding of the process.

2.7 | Ethnical differences

The commonly mutated genes in all ethnic/regional groups include FLT3-ITD, RAS, and WT1. The Taiwanese population studies were pre-NGS and mutations were reported in signal transduction genes.[17] However, the NGS data reveal that there are some population-specific novel mutations as well, such as mutations in TLE4, MALAT1, NUMB, EIF4E3, HIST1H1C (Dutch study group)[12] in TET2, DHX15, DHX30, ETV6 (U.S. population)[8] and a novel point mutation of ASXL3 in Italian pediatric population.[18]

3 | CONCLUSION

Molecular and genetic aberrations play an important role in pediatric leukemia. The relapse of AML in children is a systemic and evolutionary process accompanied by abnormal proliferation and block of differentiation. Abnormal proliferation in AML is a consequence of mutations in signal transduction genes such as *FLT3*, *RAS* (*N-RAS*, *K-RAS*), *PTPN11*, and *c-KIT*, of which *FLT3* mutations are the most common. Block of differentiation is controlled by abnormal expression of transcription factors such as CEBPα. Some population-specific novel mutations are also of great relevance such as DHX15, DHX30, ASXL3, TLE4, MALAT1, NUMB, and EIF4E3. Relapse of childhood AML is a clonal evolutionary mechanism that requires both types of aberrations, that is, proliferative abnormality and block of differentiation. Mature leukemic cells can be eradicated by therapy; however, stem cells usually escape from therapy and may be the reason of relapse of disease. More work is needed to identify molecular markers unique to different stages of the disease in distinct populations that can provide valuable information about disease prognosis and management.

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