Cancer and Metastasis Reviews (2020) 39:189–209
https://doi.org/10.1007/s10555-020-09846-1

The genomics of acute myeloid leukemia in children

Shannon E. Conneely[1] · Rachel E. Rau[1]

Published online: 10 January 2020

Abstract
Acute myeloid leukemia (AML) is a clinically, morphologically, and genetically heterogeneous disorder. Like many malignancies, the genomic landscape of pediatric AML has been mapped recently through sequencing of large cohorts of patients. Much has been learned about the biology of AML through studies of specific recurrent genetic lesions. Further, genetic lesions have been linked to specific clinical features, response to therapy, and outcome, leading to improvements in risk stratification. Lastly, targeted therapeutic approaches have been developed for the treatment of specific genetic lesions, some of which are already having a positive impact on outcomes. While the advances made based on the discoveries of sequencing studies are significant, much work is left. The biologic, clinical, and prognostic impact of a number of genetic lesions, including several seemingly unique to pediatric patients, remains undefined. While targeted approaches are being explored, for most, the efficacy and tolerability when incorporated into standard therapy is yet to be determined. Furthermore, the challenge of how to study small subpopulations with rare genetic lesions in an already rare disease will have to be considered. In all, while questions and challenges remain, precisely defining the genomic landscape of AML, holds great promise for ultimately leading to improved outcomes for affected patients.

Keywords Acute myeloid leukemia · Pediatric · Genomics · Risk stratification · Targeted therapies

1 Introduction

It has long been recognized that acute myeloid leukemia (AML) is a heterogeneous group of malignancies. Perhaps the first way in which this heterogeneity was appreciated was morphologically, when astute pathologists recognized that AML can take many forms, often with features resembling a normal myeloid cell counterpart, offering a useful way to classify these diseases. Then the cytogenetic era came, with identification of a multitude of underlying structural chromosomal aberrations. Along the way, important clinical correlates were made, with the recognition that certain cytogenetic changes strongly correlated with outcome, many of which remain the cornerstone of AML risk stratification to this day. Now, we are in the midst of the genomics age, and through large-scale sequencing efforts of large cohorts of patients, the extent of the diversity of AML is coming to light.

While each individual AML genome is relatively quiet, comprised of a surprisingly small number of critical genetic changes, the spectrum of genetic changes that can give rise to AML is vast. This mapping of the genomic landscape of AML has led to a number of significant advancements. Much has been learned about the biology of AML development through elegant molecular investigations dissecting the mechanisms by which specific genetic changes drive or contribute to leukemia development. Linking clinical data with genetic information has identified a number of genetic lesions with prognostic impact, allowing for a refinement of risk adapted therapy for patients. Finally, the identification of genetic lesions or downstream effects of genetic changes that are targetable has opened the door to improving outcomes through the incorporation of targeted therapies into treatment regimens.

Herein, we will review the current landscape of pediatric AML. We will review a number of recurrent cytogenetic and molecular lesions, highlighting what is known about the biology of these lesions, their associated clinical features, including prognostic impact, and targeted approaches to specific genetic alterations.

✉ Rachel E. Rau
rerau@bcm.edu

[1] Division of Pediatric Hematology/Oncology, Texas Children's Cancer Center, Baylor College of Medicine, 1102 Bates Avenue, Feigin Tower, Suite 1025, Houston, TX 77030, USA

2 Major cytogenetic subsets of AML

In AML, a number of specific recurrent structural cytogenetic lesions define disease entities and inform prognosis (Table 1). The identification of these lesions has also provided insights into the mechanisms by which AML develops.

2.1 Acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) is a distinct disease entity typically characterized by the fusion of promyelocytic leukemia (*PML*) gene with the retinoic acid receptor alpha (*RARA*), most commonly due to the balanced translocation t(15;17)(q24.1;q21.2) [1–4]. APL constitutes approximately 5–10% of pediatric AML cases, and the frequency increased with age to a peak from 30 to 40 years of age [5] (Fig. 1).

A predominant mechanism by which the PML-RARA fusion causes APL is the repression of RARA target genes as well as certain non-RARA target genes, leading to blocked differentiation at the promyelocytic stage. More recently, the role of PML in APL genesis has been elucidated [6–9]. The PML-RARA fusion protein prevents the formation of nuclear structures called PML nuclear bodies (NBs). Among the cellular functions of nuclear bodies is the activation of the P53 tumor suppressor pathway and induction of cell senescence in response to stress [7]. Therefore, disruption of these critical macromolecules by the PML-APL fusion protein inhibits cell death and senescence with a net effect of increased self-renewal [6–9].

With the exception of relatively high early death rates due to severe coagulopathy and differentiation syndrome, APL is a highly curable disease. The cornerstone of therapy for APL has long been all-trans-retinoic acid (ATRA), which is capable of inducing differentiation. ATRA should be initiated once the diagnosis of APL is suspected, even before confirmatory cytogenetic testing is finalized, to reduce the risk of bleeding due to coagulopathy. Most current pediatric APL regimens employ ATRA plus an anthracycline with remission rates over 95% and greater than 80% overall survival [10–15]. Interestingly, arsenic trioxide (ATO) also has particular therapeutic activity APL and has proven safe and efficacious in adult and pediatric APL [16–18]. The mechanism by which ATO leads to the destruction of APL cells is *via* binding to and causing degradation of the PML-RARA fusion protein [1, 2]. ATRA and ATO (intravenous or oral) alone without cytotoxic chemotherapy has proven efficacious and well tolerated in adults with APL and a small series of children with APL, and similar studies of non-chemotherapy treatment regimens for the treatment of larger cohorts of children with APL are ongoing (NCT02339740) [15, 19–25].

While the vast majority of APL patients have the classic t(15;17) apparent on chromosomal analysis, rare patients can have cryptic rearrangements or complex cytogenetic changes resulting in *PML-RARA* fusion [26]. Thus, the most recent version of the World Health Organization classification of myeloid neoplasms has refined the nomenclature of APL to APL with PML-RARA [4]. Variant RARA fusions also occur in a minority of cases with the morphologic and clinical characteristics of APL. These include zinc finger and BTB domain containing 16 (*ZBTB16*, also known as promyelocytic leukemia zinc finger (*PLZF*)), signal transducer and activator of transcription 5B (*STAT5B*), and nucleophosmin (*NPM1*) among rare additional fusion partners [26, 27]. Identification of these variants is of clinical importance, as some are resistant to ATRA (e.g., STAT5B-RARA and ZBTB16-RARA) [26]. While less characterized in rare variants, sensitivity to ATO may also differ, particularly as a mechanism of action of ATO is *via* binding to the PML portion of the PML-RARA fusion [1, 2]. Therefore, use of additional assays such as *RARA* break-apart FISH and/or next-generation sequencing in patients with clinical features of APL lacking the classic PML-RARA fusion by conventional methods should be pursued. Additionally, there are also case reports of fusions involving retinoic acid receptors beta (*RARB*) and gamma (*RARG*) in APL; the prognostic and therapeutic impact of such rare translocations is not yet known [28, 29].

2.2 Core binding factor AML

Core binding factor (CBF) AML is a cytogenetically defined subtype of AML characterized by the presence of either t(8;21)(q22;q22) or inv(16)(p13q22) structural chromosomal aberrations, hereafter referred to as t(8;21) and inv(16), respectively. CBF AML accounts for approximately 20–25% of pediatric AML cases and is classified as a favorable risk subtype [30–32]. Nearly 90% of patients achieve complete remission with chemotherapy alone and bone marrow transplant is typically not required for cure [30, 31]. With an event-free survival of 70% and overall survival near 80%, patients with CBF AML have improved prognosis compared to most other AML subtypes; however, approximately 30% of patients will still relapse [30, 31, 33, 34]. CBF AML occurs in all age groups but is uncommon in infants less than 1 year of age [5, 32]. Following infancy, the prevalence of CBF AML quickly rises and then maintains a steady rate until adulthood, when it decreases to roughly 15% of adult AML [5, 32, 35].

Inv(16) and t(8;21) AML are collectively termed CBF AML due to their similar effects on the CBF transcription factor complex as well as their similar outcome profiles. In both inv(16) and t(8;21), the chromosomal rearrangement leads to a fusion gene involving one of the components of the CBF complex and attendant fusion protein expression [36, 37]. The normal CBF complex is a heterodimer composed of a DNA binding alpha subunit from the Runt-related transcription factor gene family and a non-DNA binding beta subunit, CBFβ, which allosterically enhances DNA

Table 1 Select recurrent structural chromosomal aberrations in childhood AML

Genetic lesion	Incidence in pediatric AML	Outcome	Potential for targeted therapy	Common co-occurring lesions
t(15;17)(q22;q12) and other rare variants; *PML-RARA* or other RARA fusion	~5%	Favorable	ATRA, arsenic	*FLT3*-ITD; *WT1* mutations
t(8;21)(q22;q22); *RUNX1-RUNX1T1*	~15%	Favorable	Dasatinib (targeting KIT kinase)	–X/-Y, mutations of activated signaling; most commonly *KIT* and *NRAS/KRAS*; mutations of chromatin modifiers and cohesin complex members
Inv(16)/t(16;16)(p13.1;q22); *CBFβ-MYH11*	10–15%		Dasatinib (targeting KIT kinase)	Mutations of activated signaling, most commonly *KIT* and *NRAS/KRAS*
t(11;v)(q23;v);t(v;11)(v;q23); *KMT2A* rearrangements; *KMT2A-AF9* most common	10–15% children and adolescents; 35–60% infants	Overall neutral, but fusion specific impact on prognosis	Hypomethylating agents, DOT1L inhibitors, Menin-KMT2A protein--protein interaction inhibitors, PRMT5 inhibtors, LSD1 inhibitors	Ras pathway mutations; activating *FLT3* mutations
Monosomy 7, del(7q)	1–3%	Unfavorable		Relatively common in CBF AML but not associated with worse outcome in that subset
Monosomy 5, del(5q)	1–2%	Unfavorable		
12p anomalies	2–4%	Unfavorable		
11q15 cryptic translocations; NUP98 fusions most commonly *NUP98-NSD1,* in AMKL *NUP98-KDM5A* most frequent	4–5%	Possibly unfavorable; combined *FLT3*-ITD and *NUP98-NSD1* fusion associated with poor prognosis		*FLT3*-ITD and *WT1* mutations; HOX overexpression; *NUP98-KDM5A* common in AMKL where it is highly associated with monoand bi-allelic *RB1* deletion;
t(1;22)(p13;q13); *RBM15-MKL1* fusion	~10% of AMKL	Intermediate		
Inv(16)(p13.3q24.3); *CBFA2T3-GLIS2 fusion*	15–20% AMKL	Unfavorable	GLI inhibitors (GANT61)	
HOX gene fusions	~15% AMKL	Intermediate		Associated with CTCF/cohesin, *MPL*, and activated signaling pathway lesions
t(6;9)(p22;q34); *DEK-NUP214*	1–2%	Unfavorable		FLT3 mutations in ~70%
3q26.2 rearrangements (MECOM); most commonlyinv(3)(q21;q26.2) or t(3;3)(q21;q26.2)	<1%	Unfavorable in adults		*NRAS* mutations
t(7;12)(q36;p13); *ETV6-MNX1*	~1% overall; 30% infant AML	Unfavorable	KAT inhibitors, C646, I-CBP112, CCS1477	
t(8;16)(p11;p13);t(8;22)(p11;q13); other rare t(8;v)(p11;v); *KAT6A-CREBBPA*; *KAT6-EP300*;other rare KAT6A fusions	<1% pediatric AML	Unfavorable; cases of regression of congenital *KAT6A-CREBBPA* AML		
ETS TF fusions; *FUS*, *ERG*, *ETV6*		Unfavorable	Fusion proteins bind RARA target genes inhibiting expression; ATRA may induce differentiation	Possibly preceding epigenetic regulator mutations; *BCOR, ASXL1* and *DNMT3A* mutations

ATRA, all-trans retinoic acid; *M4Eo*, monocytic AML with eosinophilia; *CBF*, core binding factor; *AMKL*, acute megakaryoblastic leukemia; *ITD*, internal tandem duplication; *TKIs*, tyrosine kinase inhibitors; TF, transcription factor

binding and stability of the complex. When CBFβ dimerizes with RUNX1, the CBF complex drives gene expression programs promoting myeloid cell differentiation. In t(8;21), the fusion gene *RUNX1-RUNX1T1*, composed of exons 1–5 of *RUNX1* and exons 2–11 of *RUNX1T1*, produces the chimeric protein RUNX1-CBFA2T1, formerly called AML1-ETO. RUNX1-CBFA2T1 retains the DNA binding and dimerizing domains of RUNX1 but adds the transcriptional corepressor function of CBFA2T1. In inv(16) and the less common t(16;16)(p13q22), the fusion gene *CBFB-MYH11*, composed of exons 1–5 of *CBFB* and exons 12–41 of *MYH11*, produces the chimeric protein CBFβ-SMMHC [38]. Here, CBFβ retains its ability to dimerize with the alpha subunit, but the addition of smooth muscle myosin component, SMMHC, leads to inhibition of the CBF complex and sequestering of CBFβ away from chromatin [39]. In both cases, the resultant fusion proteins act in a dominant negative manner to inhibit the normal function of the core binding factor complex leading to maturation arrest in the myeloid cell lineage.

Despite similar effects on the function of CBF, t(8;21) and inv(16) have several differences. Using historical French-American-British (FAB) classifications, t(8;21) is more commonly associated with the M2 subtype, AML with maturation, whereas inv(16) is associated with M4Eo, myelomonocytic AML with aberrant eosinophils, though a variety of FAB types can be seen in either [4]. The age distribution also differs, with inv(16) prevelance relatively constantfrom infancy to adulthood, t(8;21) is far more common in older children and adolescents [5] (Fig. 1). Adult data has suggested even the prognostic impact of t(8;21) and inv(16) may differ, with patients with inv(16) having a worse prognosis than those with t(8;21) [40]. While additional cytogenetic changes can occur in either CBF AML subtype, loss of a sex chromosome and deletion of chromosome 9q occurs almost exclusively in t(8;21), whereas trisomy of chromosome 22 occurs much more commonly in inv(16) [30–32]. In both cases, the fusion gene almost never occurs in isolation, as additional mutated pathways or cytogenetic changes typically occur, suggesting these fusions are necessary but not sufficient for leukemic transformation.

2.3 *KMT2A*-rearranged AML

Rearrangements involving the histone methyltransferase, *KMT2A* (Lysine (K)-specific methyltransferase 2A, previously *MLL1*), at chromosome 11q23 are common in childhood leukemias, including over 75% of infant B lymphoblastic leukemias (B-ALL), 3% of non-infant B-ALL, approximately 5% of T lymphoblastic leukemias, and are associated with a poor prognosis in these diseases [41–44]. They are also recurrent in the poor prognosis mixed phenotype acute leukemia, thus the former name of the gene, mixed lineage leukemia 1(*MLL1*), and are recurrent lesions in therapy related acute leukemias [4, 45]. In childhood AML, *KMT2A* rearrangements are also common, particularly in infants (35-60%) with decreased frequency in childhood and adolescence (~ 10–15%) and adults (~10%) [5, 30–32, 45–47].

Wild-type KMT2A is a histone methyltransferase that mediates the addition of methyl groups to lysine 4 on the tail of histone 3 (H3K4) and broadly speaking H3K4 methylation is associated with activation of gene transcription. Under normal conditions, KMT2A is part of the large multi-protein, MLL1 complex, which regulates KMT2A target gene expression not only by H3K4 methylation but *via* recruitment of additional factors that regulate gene expression [45].

Fusions, predominantly in frame, of the *N*-terminal portion of *KMT2A* with nearly 100 different fusion partners, have been identified in *KMT2A* rearranged (*KMT2A*r) leukemias to date [48]. In all of the identified fusions, KMT2A retains its *N*-terminal portion harboring the DNA binding domains, nuclear localization domains, and the domain mediating the interaction between KMT2A and Menin/LEDGF, which binds demethylated histone 3 lysine 36 (H3K36). The *C*-terminal portion containing the catalytic SET domain as well as a transcriptional activation domain is lost. Despite the diversity of fusion partners, nine fusions account for approximately 90% of all *KMT2A* rearrangements encountered in acute leukemias [48]. The common fusion partners all appear to, at least in part, mediate leukemia development by aberrant activation of KMT2A target genes through recruitment of factors associated with target gene transcription and elongation (see review by Winter and Bernt [45]). Aberrantly activated KMT2A target genes including stem cell associated HOX cluster genes and HOX co-factor *MEIS1*, which are often expressed in leukemias and are thought to play a prominent role in driving *KMT2A*r leukemia [45, 49, 50]. Interestingly, despite some likely common mechanistic pathways, the distribution of *KMT2A* rearrangements differs by disease phenotype and by age suggesting the fusion partner impacts disease phenotype. In B-ALL, *AF4* (resulting from t(4;11)(q21;q23)) is by far the most common *KMT2A* fusion partner, accounting for approximately 40% of all pediatric, nearly 50% of infant, and 80% of adult *KMT2A*r B-ALL. Conversely, less than 5% of *KMT2A*r AML cases regardless of age are *KMT2A-AF4* fusions. In pediatric AML, AF9 is the most common fusion partner (t(9;11)(p22;q23)), found in approximately 40% of *KMT2A*r AML cases, followed by roughly 20% with *AF10* (t(10;11)(p12;q23)), 8% with *AF6* (t(6;11)(q27;q23)), 7% with *ELL* (t(11;19)(q23;p13.1)), and 6% with *ENL* (t(11;19)(q23;p13.3)). In infants with *AML*, *AF9*, and *AF10* each account for around 25% of all *KMT2A* fusions and *ELL* another 15% with all others being far less common.

In most clinical studies, *KMT2A*r in AML has been associated with inferior outcome; however, the relative impact on outcome is likely dependent upon which fusion is present [31, 46]. One international study including data from 11 different pediatric cancer consortia reviewed over 750 *KMT2A*r

pediatric AML cases. The authors found that certain *KMT2A* rearrangements were independent predictors of outcome in a multivariable analysis. In particular, t(6;11)(q27;q23) and t(10;11)(p11.2;q23) (fusion partners *AF6* and *ABI1*, respectively) were associated with dismal outcomes whereas patients with t(1;11)(q21;q23) (fusion partner *MLLT11/AF1Q*) had an excellent prognosis [46]. While the numbers of patients with each specific *KMT2A* rearrangement were inherently small, the data are compelling enough to warrant consideration of inclusion as risk stratification criteria for children with AML, including consideration of best available HSCT in first complete remission (CR) for patients with poor prognosis *KMT2A* lesions. Therefore, it is important to characterize the specific fusion present in patients with AML. Nearly a third of the *KMT2A* rearrangements in leukemia are not detectable by conventional karyotype assessment. Therefore, FISH or molecular methods should be used to determine the precise *KMT2A* rearrangement in patients with AML [4].

Given the overall poor response to standard chemotherapy and inferior outcomes associated with most *KMT2A*r leukemias, much research over the last few decades has aimed to identify novel effective therapeutic approaches. Given what has been learned about the epigenetic drivers of *KMT2A*r leukemias, several epigenetic modifying agents have been explored for therapeutic efficacy. Disrupter of telomere silencing 1-like (DOT1L), the histone methyltransferase responsible for the transcription elongation mark H3K79 methylation, was found to be critical to *KMT2A*r leukemia initiation and maintenance [51]. Based on this finding, small molecule inhibitors of DOT1L were developed and showed promise in pre-clinical studies of *KMT2A*r leukemia [52], but the clinical compound, pinometostat, failed to show a strong efficacy signal in a single agent, phase I clinical trial of relapsed/refractory pediatric *KMT2A*r leukemia patients [53]. Currently, a phase 1b/2 study in patients 14 year and older with newly diagnosed *KMT2A* rearranged AML in combination with standard induction chemotherapy is ongoing (NCT03724084). Additional strategies targeting the epigenetic aberrations that underlie *KMT2A*r leukemia are being investigated including agents targeting the menin-KMT2A interaction [54] (NCT04065399, NCT04067336), the H3K27 methyltransferase polycomb repressive complex [55], the argining methyltransferase, PMRT5 [56], the histone demethylase, LSD1 [57], and bromodomain inhibitors [58]. *KMT2A*r leukemias are also characterized by aberrant DNA hypermethylation [59, 60], thus incorporation of the hypomethylating agent azacitidine into standard chemotherapy is being explored in a clinical trial of infant *KMT2A*r leukemia (NCT02828358) and if effective, could be used in other *KMT2A*r leukemias. Additional studies have found that histone deacetylase inhibitors [61] and proteasome inhibitors [62] may have specific therapeutic efficacy against *KMT2A*r leukemias, and a clinical trial studying the addition of the HDAC inhibitor, vorinostat, and the proteasome inhibitor, bortezomib, to standard chemotherapy for the treatment of children with relapsed/refractory *KMT2A*r leukemias was undertaken, but terminated early due to inability to meet accrual goals (NCT02419755).

2.4 Aneuploidy and segmental chromosomal alteration in AML

Aneuploidy is common across all childhood leukemias including AML. However, only the rare loss of chromosome 5 (-5) (or -5q) and chromosome 7 (-7) are prognostic in AML. Like in adult AML, -7 and -5 or -5q are associated with a poor prognosis in children with AML, though are quite rare, occurring in < 5% of children with AML [5]. Such patients are generally considered candidates for best available HSCT in first CR [5, 30, 35]. Complex karyotypes (≥ 3 structural chromosomal lesions without favorable cytogenetics and without *KMT2A*r) are relatively common in pediatric AML, but in contrast to adult disease is not consistently correlated with outcome and therefore is not routinely incorporated into risk classification for children [5, 30, 35].

Other numeric chromosomal changes in pediatric AML are relatively common but most are not generally associated with outcome. Abnormalities of 3q (< 5%), trisomy 8 (10–15%), acquired trisomy 21 (~ 5%), and rare trisomies of chromosome 4, 6, 13, and 19 are recurrent in pediatric AML, but are not consistently associated with outcome [30]. A study by the Berlin-Frankfurt-Munster (BFM) group found that aberration of 12p, on the other hand, was associated with a poor prognosis, though was only present in 2% of their patients [31], similar finding were reported by the United Kingdom Medical Research Council in analysis of their AML10 and AML12 trials [30]. Thus, AML with aberration of 12p is a rare, poor prognosis subset.

3 Additional fusions in pediatric AML

3.1 NUP98 fusions

The gene nucleoporin 98kD (*NUP98*) located on chromosome 11p15 is commonly involved in cryptic translocations in AML. NUP98 is so named because it is a component of the nuclear pore. More recently, a critical role for NUP98 in the regulation of gene transcription in the hemaopoietic system has been described. NUP98 interacts with histone modifying Set1A/COMPASS complex, Trithorax/MLL1 complexes, and the males absent on the first (MOF)-containing nonspecific lethal (NSL) complex mediating gene transcription across various genetic loci, including HOX clusters in hematopoietic stem/progenitor cells [63–65]. Recurrent fusions involving NUP98 have been identified in approximately 4–9% of pediatric AML patients [32, 66–69]. While the most common fusion partner is the histone methyltransferase gene, *NSD1*, over 30 different

fusion partners have been identified to date and the incidence of various fusions is dependent on age at presentation, with *NUP98-KMT5A* fusions more prevalent in children < 3 years of age, and other NUP98 fusions being most common in children with decreasing frequency with increasing age [32] (Fig. 1). *NUP98* rearranged AML is characterized by high expression of HOX cluster genes, likely secondary to the recruitment of histone modifying complexes by the NUP98 *N*-terminal portion of the fusion protein as well as activity of the *C*-terminal portion of the partner protein [69–73]. Clinically, *NUP98* rearrangements are associated with normal karyotype AML, with most occurring in the myelomonocytic (M4/M5) FAB subtypes of AML, with the exception of *NUP98-KDM5A* fusions which are enriched in acute megakaryoblastic leukemia (AMKL)(FAB M7), occurring in approximately 10% of such cases [66, 68, 69, 74]. The presence of a *NUP98-KDM5A* fusion in AMKL is associated with a poor prognosis with an event-free survival of 25% ± 15% [74]. NUP98 fusions are also prevalent and associated with a poor outcoming in acute erythroleukemia (FAB M6), with 20% of children with this very rare AML subset having a NUP98 fusion, most commonly *NUP98-KDM5A* [75]. In non-M6/M7 AML, the *NUP98* fusions, in particular *NUP98-NSD1*, frequently co-occur with *FLT3*-ITD and *WT1* mutations (see discussion of these mutations below) [32, 66, 68, 69]. While a number of clinical studies found an association between *NUP98* rearrangement and decreased survival [66, 68, 69], an extensive integrated genome associations study on a large pediatric AML cohort found that the in isolation *NUP98* rearrangements were not independently prognostic, but the combination of *NUP98-NSD1* fusion and concomitant *FLT3*-ITD mutation was strongly associated with a poor outcome [32].

A number of strategies potentially targeting the oncogenic program enforced by *NUP98* fusions have been explored in pre-clinical models. For example, one study found that the NUP98-fusions directly interact with KMT2A to drive HOX cluster gene expression and inactivation of KMT2A reduced HOX gene expression and had anti-leukemic activity [76]. Thus, strategies targeting the KMT2A complex such as agents inhibiting the menin-KMT2A interaction could be of therapeutic benefit. Additionally, disulfiram also had therapeutic efficacy against cell lines expressing *NUP98-PHF23* and *NUP98-KDM5A* fusions by disrupting interaction between the fusions and H3K4 trimethyl, leading to downregulation of HOX cluster genes [77].

3.2 KAT6A fusions

While in pediatric AML, *KMT2A* is the most frequently rearranged epigenetic regulator gene, other epigenetic regulators are recurrently involved as well. As discussed above, NUP98 fusions have a strong epigenetic component through interaction with a number of histone modifying complexes. Another relatively well described rearrangement involving epigenetic regulators is fusions of the lysine acetyltransferase, *KAT6A* (previously Monocytic leukemia zinc finger protein, *MOZ*, or *MYST3*) which can be fused to the histone acetyltransferases CREB binding protein (*CREBBP*, *or CBP*) through t(8;16)(p11;p13) or E1A binding protein (*EP300*) from t(8;22)(p11;q13). In its wild-type state, KAT6A is known to play a critical role in hematopoietic stem cell maintenance, when deleted in the murine hematopoietic system leads to decreased expression of stem cell genes such as Hoxa9, cMpl, and cKit with embryonic lethality due to lack of erythrocyte production and characterized by severe depletion of hematopoietic stem and progenitor cells [78]. It is also a co-activator of a number of transcription factors that are critical to the maintenance of normal hematopoiesis including RUNX1, RUNX2, and PU.1 (reviewed in [79]). *KAT6A* fusions clinically occur in mainly in monocytic AML. They occur in less than 1% of all pediatric AML cases and are characterized by overexpression of *HOXA9*, *MEIS1*, *FLT3* genes, similar but not completely overlapping with the gene expression signature of *KMT2A* rearranged leukemia [80]. In adult AML, *KAT6A* fusions are associated with poor outcomes, and in children appears to be associated with a poor outcome, but the data are limited by the small number of affected patients [32]. Interestingly, a number of reports of spontaneously resolving congenital AML with *KAT6A-CREBBP* fusions have been reported [81, 82].

3.3 MNX1 rearrangement

Another overall rare but recurrent translocation in pediatric AML is t(7;12)(q36;p13), involving the *ETV6* gene on chromosome 12 and the homeobox gene, *MNX1* (motor neuron and pancreas homeobox 1, also known as Homeobox HB9, *HLX9*) on chromosome 7. While overall, found in only ~ 1% of all pediatric AML cases, is found in 4-30% of AML in children less than 2 years old [32, 83–85]. It is still not entirely clear what the molecular driver of leukemia is with this translocation, as the *ETV6-MNX1* fusion transcript is only detected in approximately half of cases harboring this translocation, yet *MNX1* is highly expressed in all such cases suggesting the ectopic expression of this homeobox gene may be the leukemogenic driver [83].

Clinically, the t(7;12)(q36;p13) translocation is common in infants, but not in congenital AML cases. Unlike other infant leukemias which are commonly of the myelomonocytic (FAB M4/5) or megakaryoblastic (FAB M7) morphology, t(7;12) AML is most commonly of the M0/M1 morphology [83–85]. Most reports have found t(7;12) associated with a poor outcome, but one study found that patients with t(7;12) AML are highly salvageable with HSCT, thus advocate for reserving HSCT for relapsed disease [85].

3.4 CBFA2T3-GLIS2

Another oncogenic fusion predominantly occurring in AMKL is *CBFA2T3-GLIS2*, caused by a cryptic inversion of chromosome 16 (inv(16)(p13.3q24.3)) [86]. CBFA2T3 is in the same complex as CBFA2T1, the protein encoded by the gene, *RUNX1T1*. CBFA2T3 plays a role in hematopoietic stem cell quiescence, self-renewal, differentiation, and is critical to megakaryocyte-erythrocyte progenitor development [86–88]. The fusion partner, GLIS2, is a zinc finger transcription factor related to the Hedgehog pathway transcriptional response GLI proteins. GLIS2 is predominantly expressed in the kidney and is thought that though its fusion to CBFA2T1 results in ectopic activity in the hematopoietic system [89, 90]. In this cryptic inversion, the first 11 exons of CBFA2T3 fuses to the last 4 exons of GLIS2 [86]. In this fusion, GLIS2 maintains its DNA binding zinc finger domains and CBFA2T3 loses its zinc finger domain that interacts with the transcriptional repressors like nuclear receptor of co-repressors (NCOR) and histone deacetylases, yet retains the ability to interact with wild-type CBFA2T3 complexes. The net result is an imbalance of transcription factors critical to the regulation of normal hematopoiesis. Specifically, the hematopoietic transcription factor, *GATA1*, which regulates megakaryocytic differentiation is downregulated while the stem cell maintenance gene, ETS-related gene (*ERG*) is significantly upregulated. This results in loss of the ability to activate a megakaryocytic differentiation gene expression program and increased expression of genes that drive a stem cell like phenotype like *KIT* [89, 90].

The *CBFA2T1-GLIS2* fusion is clinically distinct. While *CBFA2T1-GLIS2* fusion are not completely exclusive to AMKL, they are highly enriched in this disease subset, found in 20–30% of pediatric AMKL cases (specifically, AMKL without associated Down syndrome (DS)) [74, 86, 91]. There is a strong association with age, as this fusion has not been reported in adult AMKL, and in children is almost exclusively found in those under the age of 4 years [32, 74, 86, 92–94] (Fig. 1). The presence of this fusion is strongly associated with a poor response to therapy, high rates of relapse, and dismal survival [74, 86, 92, 93].

Given the poor prognosis with standard therapies, targeted approaches to *CBFA2T1-GLIS2* fusion positive AML are being explored. The demonstration that disruption of the interaction between the chimeric protein and CBFA2T1 complexes was anti-leukemic, suggesting a potential for a targeted approach [90]. Additionally, aberrant overexpression of Hedgehog-related genes has been demonstrated in *CBFA2T3-GLIS2* fusion AMKL. In a pre-clinical study, antagonism of GLI, the downstream effectors of the Hedgehog pathway, showed therapeutic activity in AMKL cell lines and patient samples with *CBFA2T3-GLIS2* [95].

3.5 Other genomic alterations in AMKL

In addition to *NUP98-KDM5A* and *CBFA2T3-GLIS2* fusions in non-Down syndrome AMKL, another 15–20% will harbor *KMT2A* rearrangements, around 15% will have fusions involving various HOX genes, and approximately 10% will have the t(1;22)(p13;q13) resulting in *RBM15-MKL1* fusion. The prognostic impact of these fusions in AMKL vary, from a relatively favorable prognosis for those with HOX rearrangements, intermediate outcomes for those with *RBM15-MKL1* fusions, and poor prognosis with *KMT2A* rearrangements and *NUP98-KDM5A* fusions as discussed above. In contrast, patients with truncating mutations of *GATA1* had excellent outcomes [74], similar to the favorable prognosis of patients with DS who develop AMKL after a preceding transient abnormal myelopoiesis driven by *GATA1* mutations during infancy [96–99].

3.6 DEK-NUP214

AML with t(6;9)(p22;q34) resulting in expression of the fusion gene *DEK-NUP214* is a relatively uncommon subset of pediatric AML with potential biologic and clinical implications. NUP214, like NUP98 discussed above, is a nucleoporin protein critical to the nucleocytoplasmic transport of a number of proteins and mature RNA. NUP214 interacts with nuclear export receptor, chromosomal maintenance 1(CRM1 or exportin 1(XPO1)) which exports proteins from the nucleus to the cytoplasm, and nuclear RNA export factor 1 (NXF1). In DEK-NUP214 fusions, the C-terminal of NUP214 is fused to DEK. DEK is an epigenetic regulator, which inhibit transcription through inhibition of histone acetyltransferases. The fusion is thought to lead to inhibition of CRM1 mediated nuclear transport with accumulation of proteins in the nucleus. It is also possible that mistargeted histone deacetylase activities of DEK lead to aberrant repression of lineage committing and differentiating gene expression programs in rearranged hematopoietic stem/progenitor cells and consistently, HOX gene overexpression in CD34+ hematopoietic cells expressing *DEK-NUP214* has been reported [100] (reviewed in [101]).

Clinically, less than 2% of children with AML with have fusions of *DEK-NUP214* [102, 103]. *DEK-NUP214* rearranged AML is associated with an older age of onset compared to non-*DEK-NUP214* rearranged pediatric AML (median age 11.4–12.6 years), M2 FAB classification, and higher blasts percent in the peripheral blood and bone marrow at presentation [102, 103]. *DEK-NUP214* rearrangement is highly associated with concomitant *FLT3* mutations, including up to 67% of *DEK-NUP214* rearranged harboring *FLT3*-ITD mutations and another 6% with *FLT3* kinase domain mutations (see discussion of *FLT3* mutations below) [102, 103]. The presence of a *DEK-NUP214* fusion is significantly and independently associated with lower rate of complete

remission, higher rates of relapse and worse overall survival. Patients with *DEK-NUP214* fusions do seem to benefit from HSCT in first CR, thus should be considered for affected patients [102, 103].

3.7 MECOM 3q26.2

An intergenic splicing event from *MDS1* and *EVI1* gene at 3q26.2 results in the *MDS1* and *EVI1* complex locus (*MECOM*). Inversions or translocations involving MECOM are rare events in pediatric AML, found in fewer than 1% of all patients. The most common structural rearrangement involving MECOM is inv(3)(q21;q26.2) or t(3;3)(q21;q26.2). Formerly, this was thought to result in fusion with the gene *RPN1*; however, more recent studies have shown that in fact this leads to the positioning of a distal GATA2 enhancer upstream of *EVI1* leading to its overexpression which drives leukemia development [104]. These lesions are associated with poor outcome in adult AML and are recognized as a distinct entity in the current WHO classification of myeloid malignancies [4]. Other rare MECOM fusion partners have been described in AML including *CDK6* (t(3;7)(q26.2;q21)), *TCRB* (t(3;7)(q26.2;q34)), *ETV6* (t(3;12)(q26.2;p13)), and *RUNX1* (t(3;21)(q26.2;q22)).

3.8 Recurrent molecular lesions in pediatric AML

While structural chromosomal changes can be detected in many patients with AML, sequencing efforts have identified many genetic mutations with biologic, clinical, and prognostic implications in AML (Table 2). Additionally, a number of these lesions represent potential targets for therapeutic intervention.

3.9 *FLT3* mutations

FMS-like tyrosine kinase 3 (*FLT3*) encoding the receptor tyrosine kinase, FLT3 (CD135) is one of the most commonly mutated genes in both adult and childhood AML [32, 47, 105–110]. In normal hematopoiesis, *FLT3* is expressed in stem/progenitor cells and plays a critical role in stem cell proliferation, survival, and differentiation [111–114]. Upon binding of its ligand, FLT3-ligand (FL), FLT3 dimerizes, activating its tyrosine kinase domain, leading to autophosphorylation and phosphorylation of downstream signaling pathways including PI3K/Akt, MAPK/ERK, and STAT5 [111, 115].

In AML, the most common type of mutation in FLT3 are internal tandem duplication (ITD) mutations, most often in the juxtamembrane domain (JMD), but can rarely occur in the first tyrosine kinase domain (TKD1). Also recurrent in AML are *FLT3* point mutations, typically occurring in the second tyrosine kinase domain (TKD2), with amino acid D835 most frequently targeted, but can occasionally occur in TKD1 as well [32, 47, 105, 108, 109, 115, 116]. Both types of mutations lead to constitutive activation of FLT3 even in the absence of FL binding; however, the prognostic and therapeutic implications of these two separate types of mutations differ. It has long been reported that *FLT3*-ITD mutations increase in frequency with age [47, 105, 108, 109, 115, 117]. However, when balanced for cytogenetic subset, the frequency of *FLT3*-ITD mutations is actually comparable in childhood AML compared to adult AML [32]. *FLT3*-TKD mutations are actually more prevalent in childhood AML relative to adult AML, including pediatric-specific *FLT3* mutations. These novel mutations consist of point mutations and small insertions/deletions of not only the TKD, but the JMD and transmembrane domains [32, 116].

Clinically, *FLT3* mutations are associated with normal karyotype, high presenting white blood cell count (WBC), and can be found across a spectrum of French-American-British (FAB) morphologic subsets including 20–35% of APL cases. Interestingly, whereas *FLT3*-ITD lesions, if present in the dominant clone as evidenced by a high allelic ratio, are consistently associated with a significantly poor outcome [105, 108–110, 115, 117], most of the published literature has shown that in both adult and pediatric studies, most *FLT3*-TKD mutations do not have an independent impact on prognosis. As such, AML with high allelic ratio *FLT3*-ITD lesions are generally categorized as high risk. With data supporting a survival advantage with allogeneic transplant in first CR for such patients [118, 119], best available donor HSCT in first CR is generally recommended for *FLT3*-ITD harboring AML patients. However, the pediatric-specific TKD mutations do seem to be associated with poor prognosis; thus, identification of these mutations at diagnosis could inform risk stratification [32, 116]. Notably, while *FLT3*-ITD mutations generally in AML are associated with increased risk of relapse and poor survival, this risk is modulated by co-occurring genetic lesions, as described in subsequent sections.

Importantly, not only are activating *FLT3* lesions prognostic, they are also potentially targetable by small molecules tyrosine kinase inhibitors (TKIs) [105–107, 120, 121]. Several FLT3 inhibitors of varying potency and specificity have been developed and tested for the treatment of *FLT3* mutant AML. A number of multi-kinase targeting first-generation FLT3 TKIs have been investigated in clinical trials (sorafenib, lestarutinib, midostaurin, ponatinib, sunitinib, others) as have a number of next-generation FLT3 TKIs with greater potency and specificity for FLT3 (crenolanib, quizartinib, and gilteritinib) (recently reviewed in [107, 120]). While most of the current robust clinical data includes only adult patients, pediatric clinical trials of FLT3 inhibitors have increased in recent years propelled by promising data from adult populations.

Table 2 Select recurrent molecular lesions in childhood AML

Genetic lesion	Incidence in pediatric AML	Outcome	Potential for targeted therapy	Common co-occurring lesions
FLT3-ITD mutations	15–20%	High allelic ratio *FLT3*-ITD mutation associated with poor outcome; *FLT3*-ITD plus *NPM1* mutations favorable; *FLT3*-ITD plus *WT1* or *NUP98-NSD1* unfavorable	FLT3-targeting TKIs, eg, sorafenib, quizartinib, midostaurin, gilteritinib, crenolanib	*NPM1* and *WT1* mutations, *PML-RARA*, *NUP98-NSD1*, *DEK-NUP214* fusions
Other *FLT3* mutations	10–15%	Possibly poor outcome	Midostaurin, gilteritinib, crenolanib	
NPM1 mutations	~10%	Favorable	DOT1L inhibitors, Menin-KMT2A interaction inhibitors	*FLT3*-ITD
CEBPA mutations	5–10%	Favorable		
RAS pathway mutations; *NRAS, KRAS, PTPN11, CBL, NF1*	40–50%	Neutral	MEK inhibitors PI3K inhibitors	*KMT2Ar*, core binding factor AML
KIT mutations	10–15%; 20–25% of CBF AML	Possibly worse outcome for CBF patients with *KIT* mutations	Dasatinib	
WT1 mutations	15%	15% Neutral but combination of *FLT3*-ITD and *WT1* mutation associated with poor prognosis	May inhibit TET2 function, therefore hypomethylating agents hypothetically could be effective	*FLT3*-ITD, PML-RARA
IDH1/2 mutations	IDH1 exceedingly rare, IDH2 2–3%	Unknown	Mutant IDH1 inhibitor, ivosidenib; Mutant IDH2 inhibitor, enasidenib	
TET2 mutations	6%	Unknown	Hypomethylating agents	
EZH2	~5%	Maybe associated with worse outcome in CBF AML		t(8;21)
ASXL1, ASXL2	~5% overall AML, ~30% t(8;21) AML	Maybe associated with worse outcome in CBF AML		t(8;21)
Cohesin complex members; *STAG2*, *RAD21*, *SMC3*, *SMC1A*, etc.	~20% t(8;21) AML	Maybe associated with worse outcome in CBF AML		t(8;21)

Recently, a large randomized adult AML trial demonstrated that the addition of midostaurin to standard chemotherapy resulted in a significantly increased event-free and overall survival in adults with *FLT3* mutations, both *FLT*-ITD mutations regardless of allelic ratio and TKD mutations [122]. Based on these data, midostaurin is now FDA-approved for adults with *FLT3*-mutant AML [123, 124]. More recently, the potent and specific FLT3 inhibitor with activity against both ITD mutations and TKD mutations, gilterintinib, has shown excellent efficacy in relapsed/refractory adult populations [125–127].

In children, clinical experience with FLT3 inhibitors is growing (reviewed extensively in [107]). For example, sorafenib, a first-generation FLT3 inhibitor that also has anti-KIT, PEDGFR, VEGFR, and Raf activity, was tested in single agent phase 1 trials by St. Jude Children's Research Hospital (SJCRH) and the Children's Oncology Group (COG) with both small studies demonstrating acceptable tolerability and some complete responses in very heavily pre-treated cohorts [128, 129]. Sorafenib was also explored in combination with standard chemotherapy for newly diagnosed high allelic ratio *FLT3*-ITD positive AML patients non-randomly in COG trial AAML1031(NCT01371981). That study is now closed to accrual, but results are not yet available. Pediatric studies of midostaurin, lestaurtinib, quizartinib, and crenolanib have also been conducted, with most of those with results reported showing some signal of efficacy (complete and partial responses) and reasonable toxicity profiles [107] providing hope that the addition of FLT3 inhibitors to standard chemotherapy will ultimately improve the outcomes of this poor prognosis subset of patients.

A variety of cell-intrinsic and extrinsic mechanisms of resistance can arise with sustained FLT3 inhibitor treatment. One major mode of resistance to FLT3 inhibitors with specificity for *FLT3*-ITD mutations (sorafenib and quizartinib) is the acquisition of resistance-conferring TKD mutations [121]. A number of the multi-kinase targeting and next-generation

FLT3 inhibitors (midostaurin, crenolanib, and gilteritinib) have activity against most of the commonly occurring TKD mutations and therefore may be preferable agents moving forward [122, 130, 131]. Particularly, given that TKD mutations are more prevalent among pediatric AML patients and these pediatric-specific TKD mutations appear to have exquisite sensitivity to FLT3-targeting TKIs in *in vitro* studies, the TKD mutation targeting TKIs will likely be best for pediatric AML *FLT3* mutated patients [32, 116].

3.10 *NPM1* mutations

Another recurrently mutated gene in adult and pediatric AML with prognostic implications is the gene nucleophosmin 1 (*NPM1*). Nucleophosmin is a chaperone protein which under normal conditions shuttles rapidly between the nucleus and cytoplasm, with predominant localization to the nucleolus. NPM1 has many functions including roles in ribosome biogenesis, cell cycle regulation, and DNA damage response. However, in AML, mutations arise in the C-terminus of NPM1 that lead to its aberrant localization to the cytoplasm *via* exportin-1 (previously known as CRM1, encolded by the gene, *XPO1*). Most mutations are in-frame insertions that cause loss of one or two critical C-terminal nucleolar localization signals and creation of a novel nuclear export signal, with a net results of aberrant cytoplasmic localization (thus the often used designation, NPMc+ AML) [132–134]. Recent work has shown that the aberrant localization of mutant NPM1 directly leads to sustained activation of oncogenic HOXA and HOXB cluster genes and *MEIS1* which drive leukemogenesis [135].

Mutations of *NPM1* constitute one of the most frequent genetic alterations in adult AML, occurring in nearly 27–35% of adults with AML, peaking in frequency in AML patients in their late 30s to early 60s [5, 47, 134]. In childhood, AML *NPM1* mutations are less common but increase in frequency with increasing age, with very rare mutations in infant AML, and mutations in ~10% of children, and ~20% of adolescents [5, 32, 117, 136]. Mutated *NPM1* in AML is associated with increased WBC and platelet count at presentation, normal karyotype, and blasts that are CD34 negative [133, 137]. Approximately 25% of AML patients with mutated *NPM1* will have trilineage dysplasia on bone marrow morphology, which is not associated with a poor outcome [133]. Over most adult and pediatric studies, the presence of an *NPM1* mutation is associated with a favorable outcome, and thus, patients are generally treated with chemotherapy alone and not offered HSCT in first CR [137]. Given its distinct morphologic, clinical, and prognostic implications, *NPM1* mutant AML is a provisional entity in the WHO classification of myeloid malignancies [4].

In both adult and pediatric AML, *NPM1* mutations commonly co-occur with *FLT3*-ITD mutations. Mouse modeling studies have shown that these mutations collaborate to drive the development of myeloid leukemia [138]. Whereas in adult data and some older pediatric data, the combination of *NPM1* and *FLT3*-ITD mutations confers and intermediate prognosis [47, 117, 136], recent pediatric data from several consortia trials found that patients harboring both mutations actually had a favorable prognosis; though the number of double mutant patients in some of the trials was small and the impact of HSCT in first CR was not fully explored, these data suggest perhaps the presence of an *NPM1* mutation outweighs the negative impact of a *FLT3*-ITD mutation [32].

As *NPM1* mutations are leukemia imitating lesions, targeted approaches could substantially improve cure rates. Given the sustained activity of HOX cluster genes and *MEIS1* in *NPM1* mutant AML, and chromatin structure regulates HOX gene expression, chromatin modulating therapy with DOT1L inhibitors and inhibitors of the MLL1-Menin interaction have been explored and have shown promising results in pre-clinical investigations [139]. Interestingly, a small clinical trial in adults with *NPM1*-mtuant AML showed dactinomycin as a promising agent, likely working because *NPM1*-mutant cells are more vulnerable to the dactinomycin-inducing a nucleolar stress response [140]. Arsenic and ATRA also appear to exert therapeutic effect in *NPM1*-mutant AML, including *via* degradation of the mutant NPM1 protein [141]. Further, given the critical role of cytoplasmic localization in mediating the oncogenic expression of HOX cluster genes, inhibition of exportin-1 which leads to re-localization of mutant *NPM1* to the nucleus has also shown efficacy in pre-clinical models [135]. Ultimately, the incorporation of these agents if proven effective in clinical trials could replace some of the intensive elements of standard therapy, further improving outcomes of this relatively common disease entity.

3.11 CEBPA mutations

Mutations of the gene CCAAT-enhancer binding protein alpha *(C/EBPA)* are also recurrent in AML. CEBPA is a transcription factor critical in myeloid lineage determination, particularly granulocytic and monocytic differentiation [142]. These mutations are more common in older children and adolescents compared to infant and young children and are present in 5–10% of adult AML with a peak incidence in individuals in their 20s to 30s [5, 32, 142, 143]. The mutations of *C/EBPA* in myeloid malignancies are inactivating mutations, thought to contribute to myeloid leukemogenesis by blocking granulocytic differentiation. Two major types of mutations of *C/EBPA* have been described, out-of-frame truncating insertions/deletions of the N-terminal portion of the gene and in-frame deletions/insertion in the C-terminal, b-Zip region which disrupt the homo- and hetero-dimerization leucin zipper domain of the protein [142, 143]. In childhood AML, most *C/EBPA* mutated patients (~80%) will have both an N-terminal

truncating mutation and an in-frame bZip (referred to in the literature as either double mutant or bi-allelic). In one large pediatric study, 95% of patients with an N-terminal mutation also had a bZip mutation, and 88% of patients with a bZip mutation had an N-terminal mutation [143]. Conversely, in adults only approximately half of *C/EBPA* mutant patients are double mutants, and in adult populations [47, 142].

Clinically, *C/EBPA* mutations are associated with normal karyotype, FAB M1 or M2 morphology and are associated with a favorable outcome and CEBPA mutant AML is a provisional entity in the WHO classification of myeloid malignancies [4, 5, 32, 142, 143]. Interestingly, in adult studies, only bi-allelic CEBPA mutations appear to be independently associated with outcome, whereas in pediatric AML, single and double mutants are both associated with excellent outcomes [47, 142, 143]. Therefore, it is generally recommended that pediatric AML patients with single or double mutant CEBPA be treated with chemotherapy alone without HSCT in first CR [143].

The prognostic impact of co-occurring mutations is not entirely clear. In adults, concomitant *FLT3*-ITD mutations in some studies are associated with a worse prognosis, whereas in others, it did not influence the outcome of those with *C/EBPA* mutations [142]. In pediatric AML, the number of patients with this combination of mutations is too small to accurately quantify the impact on prognosis [143]. *C/EBPA* mutations are essentially mutually exclusive of the CBF fusions [47, 142, 143], likely due to the fact that loss of CBF function leads to reduced expression of C/EBPA; thus, these two types of lesions would have functional redundancy.

Of note, it is estimated that 5–10% of children with double mutant *C/EBPA* AML harbor germline *C/EBPA* mutations (one constitutional, usually germline N-terminal truncating mutation with somatic acquired bZip mutation in the wild-type allele) [144, 145]. Therefore, some suggest screening for germline AML-predisposing *C/EBPA* mutations in children with this subset of disease to inform screening of family members [145].

3.12 *WT1* mutations

Another transcription factor commonly mutated in AML is the zinc finger transcription factor gene, *WT1*. WT1 protein is expressed in uroepithelium and CD34+ hematopoietic stem progenitors and plays a role in the regulation of the growth and normal development. WT1 can cause gene activation or repression depending on the isoform expressed, the relative level of expression, and the tissue it is being expressed in. Loss of function mutations of *WT1* were first reported in cases of Wilms tumor and occur in neuroblastoma. *WT1* is known to be overexpressed in many leukemias; thus, its increased expression appears to be associated with leukemogenesis. With these somewhat paradoxical findings, WT1 has been considered both a tumor suppressor and an oncogene [146]. Inactivating mutations of *WT1* are found in approximately 10% of adult AML and 15% of pediatric AML patients, and are slightly more common in children ages 3–14 years [32]. Mutations in *WT1* predominantly occur in the zinc finger DNA binding domains, mostly in exon 7 with rare lesions in exon 8 and 9, [47, 147, 148], but pediatric-specific mutations in earlier exons have recently been described [32]. Interestingly, multiple *WT1* mutations are often present in the same patient [147, 148]. How WT1 contributes to leukemogenesis is not fully known. WT1 has been shown to interact with proteins such as p53 and T cell factor (TCF) transcription factors and Wnt pathway targets and alterations of these interactions with *WT1* mutation may facilitate the development of leukemia [146, 149]. More recently, it has been reported that WT1 directly interacts with the epigenetic regulator proteins [150], TET2 and TET3 which are enzymes responsible for adding a hydroxy group onto methylated DNA cytosines. Hydroxymethylation leads to passive loss of DNA cytosine methylation with DNA replication and likely contributes directly to regulation of gene expression. Loss of function *TET2* mutations and mutations of *IDH* genes that inhibit TET protein function are recurrent in AML (discussed below) and in adult AML anti-correlated with *WT1* mutations [47]. Loss of WT1 function due to decreased expression or loss of function mutations was associated with decreased hydroxymethylation, suggesting mutations may contribute to leukemogesis *via* inhibition of TET function [150].

WT1 mutations are associated with normal karyotype and concomitant presence of a *FLT3*-ITD mutations [32, 47, 147, 148]. Patients with *WT1* mutations have a worse event-free survival (EFS) and overall survival (OS) with a trend towards those with bi-allelic mutations faring worse than those with a single mutations [147]. Though, when combined with *FLT3* status and cytogenetics, *WT1* status had no clear independent prognostic impact [147, 148]. However, the presence of both a *FLT3*-ITD mutation and *WT1* mutation(s) is consistently associated with a dismal prognosis [32, 147, 148].

3.13 RAS and other signaling pathway mutations

The Ras/MAPK pathway is one of, if not the most commonly mutated pathway across a spectrum of pediatric hematologic malignancies. Ras activating mutations are the genetic hallmark of juvenile myelomonocytic leukemia (JMML) [151], but also commonly occur in subsets of lymphoid and other myeloid malignancies. Ras-pathway mutations are particularly common in near haploid B-ALL, B-ALL in patient with Down syndrome, and high hyperdiploid B-ALL and are found in approximately 15% of children with T-ALL [43, 152–155]. In childhood AML, mutations of the Ras pathway are common, including activating *NRAS* and *KRAS* mutations, and less commonly mutations of *PTPN11* and *NF1* which lead to

constitutive activation of the RAS pathway. These mutations are particularly common in children < 3 year of age, then decrease in frequency with increasing age [32]. The common occurrence in the youngest children with AML is due to the high co-occurrence of Ras pathway mutations in *KMT2A*r AML. Approximately one-third of pediatric *KMT2A*r AML have a concomitant and Ras pathway mutation, with *NRAS* mutations being most common [32]. *FLT3* mutations also commonly co-occur in *KMT2A*r AML, suggesting cooperation between *KMT2A*r and lesions of activated signaling pathways [32, 67].

Mutations of activated signaling pathways are also the most frequent co-occurring lesions in CBF AML, found in 80% of patients with inv(16) and 65% of patients with t(8;21) [156, 157]. The most frequently mutated gene is *KIT* which occurs in approximately 40% of both CBF AML subtypes. Ras activating mutations are also common in CBF AMLs found in 54% of inv(16) and 26% of t(8;21) cases, with a higher incidence of *NRAS* mutations compared to *KRAS*. *FLT3* mutations are also common, found in 25% of CBF AML. Under the hypothesis that AML results from a combination of mutations leading to increased proliferation and impaired differentiation, it is not surprising that signaling pathway mutations occur commonly with the impaired differentiation caused by the CBF AML fusion proteins. One study using combined adult and pediatric data from two clinical trials showed that patients with t(8;21) and tyrosine kinase pathway mutations were at higher risk of relapse, with even higher relapse rates among those that also had mutations in a cohesin or chromatin modifier gene (discussed more below) [156]. Patients with t(8;21) that lacked tyrosine kinase pathway mutations only had a 16.3% cumulative relapse incidence at 5 years. Pediatric-specific studies assessing the prognostic significance of KIT mutations have had mixed results [33, 34, 158, 159]. However, a recent analysis of pediatric CBF AML patients treated on the COG AAML0531 trial demonstrated a higher risk of relapse in patients with *KIT* mutations, though this risk was abrogated with the addition of gemtuzumab ozogamicin, a CD33-targeted antibody-drug conjugate [34].

Like *FLT3* described above, many of these additional activating signaling lesions represent potential therapeutic targets. Given the high rates of Ras pathway mutations in pediatric hematologic malignancies, effective targeting of activated Ras could have a wide-reaching impact. Unfortunately, attempts to target Ras have largely fallen short, and Ras was for some time deemed "undruggable." However, small molecules directly targeting Ras have recently shown promising pre-clinical activity [160, 161]. Downstream targets have proven less challenging to inhibit, and therefore, most recent efforts have targeted MAPK and PI3K signaling pathways directly downstream of Ras. Clinical trials testing the safety and efficacy of MEK and PI3K are ongoing in relapsed/refractory pediatric hematologic malignancy cohorts.

The potent inhibitor of the ABL1 tyrosine kinase, dasatinib, currently FDA approved for the treatment of CML and Ph + B-ALL which harbor *BCR-ABL1* fusion, also potently inhibits KIT, including the mutant form most commonly occurring in CBF AML [162]. Given the frequency of activating *KIT* mutations in CBF AML, dasatinib in combination with standard chemotherapy is being explored (NCT02013648, NCT00850382, NCT 02113319).

3.14 Mutations of epigenetic regulators

Epigenetic dysregulation is increasingly recognized as a hallmark of cancer, including AML. This is often driven by genetic lesions involving epigenetic regulators, including *KMT2A* rearrangements. Additionally, recurrent mutations in a number of additional epigenetic regulators have been identified. The *de novo* DNA methyltransferase *DNMT3A* is mutated in approximately 20% of adult AML and has been associated with a poor prognosis [163]. Loss of function mutations in *TET2*, which hydroxylates methylated DNA cytosines leading to passive loss of DNA methylation with cell replication, occur in approximately 10–15% of adult AML cases [47, 164]. Additionally, *IDH1* and *IDH2* mutations are present in another 20% of adult AML and these neo-morphic gain of function mutations contribute to the development of leukemia by inhibition of the TET proteins, through decrease production of the critical TET2 co-factor alpha-2-ketoglutarate in favor of overproduction of the oncometabolite 2-hydroxyglutarate which may itself inhibit TET2 function [165]. While these regulators of DNA methylation are commonplace in adult AML, they are quite rare in pediatric AML. Loss of function *TET2* mutations are present in approximately 6% of pediatric AML cases, *IDH2* mutations in 2–3% and *DNMT3A* and *IDH1* mutations almost never occurring in pediatric cases [166].

These striking differences in mutational spectrum of DNA methylation regulators between adult and pediatric cases points towards different mechanisms of leukemogenesis in adults compared to children. Interestingly, it has been recently demonstrated that mutations of *DNMT3A* are the most frequently driving mutation in clonal hematopoiesis (CH), with *TET2* mutation second most common in most studies. Clonal hematopoiesis is an aging related disorder in which there is an expansion of blood cells derived from a single hematopoietic stem cell, usually driven by genetic mutations that likely confer specific selective fitness to a stem cell [167]. Individuals with CH are at increased risk to develop hematologic malignancies compared to individuals without CH. This suggests that mutations of *DNMT3A* and *TET2* and other mutated epigenetic regulators driving CH in older individuals may lead to the selective expansion of a mutant HSC which is then primed for acquisition of subsequent mutations that drive transformation into frank leukemia. As CH is a phenomenon of aging,

this process is not a prominent driver of disease in pediatric hematologic malignancies. While relatively rare in pediatric disease, if mutations of these DNA methylation regulators are identified, targeted interventions such as hypomethylating agents and IDH inhibitors could be considered [165, 168].

A host of additional epigenetic regulators are also commonly mutated in AML [169]. Common in AML are mutations affecting proteins that are members of or interact with the polycomb repressive complex 2 (PRC2), which critically regulates gene expression in hematopoiesis, including regulation of HOX genes through methylation of lysine 27 on the tail of histone 3 (H3K27). The mutations in AML impacting PRC2 function include loss of function mutations of *EZH2*, the enzymatic component of PRC2, *ASXL1*, which regulates PRC2 function through direct interaction, and *KDM6A*, an H3K27 demethylase [169]. In childhood AML, the frequency of *EZH2* and *ASXL1* mutations are similar to adult AML, found in ~5% [32, 47]. Interestingly, mutations of *EZH2* and *ASXL1* are enriched in t(8;21) CBF AML, and mutations of the *ASXL1* paralog, *ASXL2* are common in t(8;21) AML, yet rare in other subsets. Overall, 42% of patients with t(8;21) have mutations *ASXL1*, *ASXL2*, *EZH2*, and *KMD6A*. This is distinct from even inv(16) CBF AML, where the same genes are mutated in only 6% combined [156, 157]. Additionally, the cohesin complex, a ring like multi-protein complex involved in sister chromatid cohesion during mitosis and the regulation of gene transcription through regulation of higher order chromatin structure, is recurrently targeted by loss of function mutations, including mutations of *RAD21*, *SMC1A*, *SMC3*, and *STAG2*. While relatively rare in pediatric AML overall, cohesin complex mutations are somewhat enriched specifically in t(8;21) AML, yet are strikingly absent in inv(16) AML [156, 157]. This mutational pattern strongly suggest altered chromatin structure and accessibility likely collaborates specifically with the RUNX1-CBFA2T1 fusion protein in t(8;21) to drive leukemogenesis. In CBF, the prognostic impact of chromatin and cohesin complex mutations is not fully elucidated, but one study using combined adult and pediatric data from two clinical trials showed that patients with t(8;21) and tyrosine kinase pathway mutations were at higher risk of relapse, with even higher relapse rates among those that also had mutations in a cohesin or chromatin modifier gene [156]. Overall, more data is necessary to determine the prognostic impact of epigenetic modifier mutations in all subsets of pediatric AML, but these investigations will be challenging given the inherently small sample sizes.

3.15 Other rare genetic lesions in pediatric AML

With next-generation sequencing interrogation of large cohorts of pediatric and adult AML patient sample, a number of very rare lesions have been identified, some seemingly specific to pediatric disease [32, 47, 67]. While some genes are recurrently mutated in both adult and pediatric AML, the frequency of mutations differs in children compared to adults and some mutations of genes such as *KRAS*, *NRAS*, *MYC*, *WT1*, *CBL*, and *GATA2* are only found in pediatric AML [32]. Conversely, while some lesions are relatively common in adult AML, they are exceedingly rare in pediatric disease, such as the poor prognosis mutations of *TP53* and *RUNX1* genes [47]. Additionally, a number of rare fusions have recently been identified in pediatric AML, most of which are also incredibly rare in adult disease and some have not been described outside pediatric populations [32, 67]. These rare fusions include non-*KMT2A MLLT10* fusion, fusions of ETS family transcription factors including *FUS*, *ERG*, and novel *ETV6* fusions, as well as rare fusions involving *NPM1* [32, 67]. Additionally, a number of focal gene deletions have been described in pediatric cases, including *MBNL1*, *ELF1*, and *ZEB2* [32]. The rarity of these events in pediatric AML makes prognostication challenging. Some of the lesions occur recurrently in adult AML and clinical and prognostic data exist (for example *TP53* and *RUNX1* mutations and *FUS/ERG* and *MLLT10* fusions [170, 171]). For some lesions, it may be reasonable to extrapolate adult data as the underlying biology is likely similar; however, outcomes of the same genetic lesion may vary by age. Additionally, for the many rare, pediatric-specific lesions, no data is currently available regarding impact on response to therapy and outcome. Perhaps combing data from multiple large pediatric oncology consortia will ultimately fully define the significance of pediatric-specific lesions on prognosis.

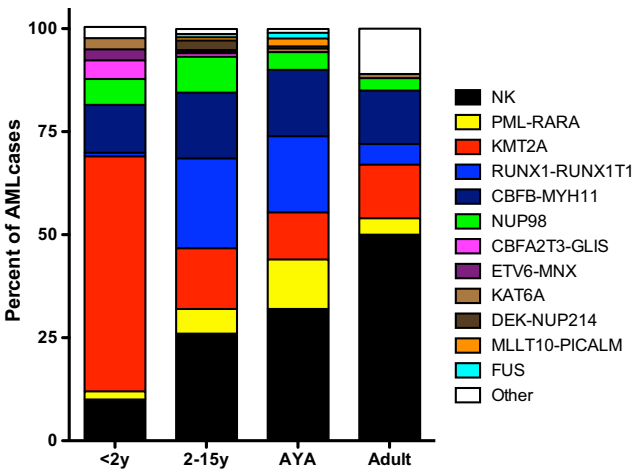

Fig. 1 Leukemic fusions in acute myeloid leukemia by age. The approximate frequency of recurrent fusions in AML in infants (defined as patients < 2 years of age), young children (2–14 years), adolescents and young adults, (AYA; 15–39 years), and adults (≥ 40 years). NK, normal karyotype. (compiled data from Creutzig et al. [5] and Bolouri et al. [32])

4 Conclusions

The mapping of the pediatric AML genome is nearing completion. These large-scale sequencing efforts have advanced the field in many ways including refined risk stratification and the identification of targeted approaches for specific genetic lesions (e.g., TKIs for *FLT3* mutant AML). Further, the identification that the genetic drivers of AML are vastly different in infants, children, adolescents, and adults could offer insight into both the regulation of normal hematopoiesis at varying ages, and the age-dependent development of leukemia (Fig. 1).

Moving forward, newly identified lesions will undoubtedly provide additional biologic insight into the genesis of leukemia. Importantly, defining if these newly identified lesions are true cancer dependencies will be pivotal in the quest to identify novel targeted approaches to therapy. While the value of developing targeted treatments for specific individual genetic lesions is clear, for many, it may prove most impactful to instead work towards developing therapies aimed at pathways upon which several genetic lesions converge (e.g., aberrant HOX gene expression). Additionally, how to incorporate the growing list of genetic lesions into a complex risk stratification algorithm is not clear given inherent uncertainty regarding the prognostic impact of rare lesions. Despite the challenges that remain, with the ultimate goal of improved risk stratified therapy and targeted approaches to treatment, the recently expanded view of the genomic landscape of pediatric AML is significant stride forward.

Authorship contributions SEC and RER reviewed the literature and wrote the paper.

Funding information This work was supported by K08CA201611 from the National Cancer Institute (RR).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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