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REVIEW AND PERSPECTIVES

The International Consensus Classification (ICC) of hematologic neoplasms with germline predisposition, pediatric myelodysplastic syndrome, and juvenile myelomonocytic leukemia

Martina Rudelius[1] · Olga K. Weinberg[2] · Charlotte M. Niemeyer[3,4] · Akiko Shimamura[5] · Katherine R. Calvo[6]

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Abstract

Updating the classification of hematologic neoplasia with germline predisposition, pediatric myelodysplastic syndrome (MDS), and juvenile myelomonocytic leukemia (JMML) is critical for diagnosis, therapy, research, and clinical trials. Advances in next-generation sequencing technology have led to the identification of an expanding group of genes that predispose to the development of hematolymphoid neoplasia when mutated in germline configuration and inherited. This review encompasses recent advances in the classification of myeloid and lymphoblastic neoplasia with germline predisposition summarizing important genetic and phenotypic information, relevant laboratory testing, and pathologic bone marrow features. Genes are organized into three major categories including (1) those that are not associated with constitutional disorder and include *CEBPA*, *DDX41*, and *TP53*; (2) those associated with thrombocytopenia or platelet dysfunction including *RUNX1*, *ANKRD26*, and *ETV6*; and (3) those associated with constitutional disorders affecting multiple organ systems including *GATA2*, *SAMD9,* and *SAMD9L*, inherited genetic mutations associated with classic bone marrow failure syndromes and JMML, and Down syndrome. A provisional category of germline predisposition genes is created to recognize genes with growing evidence that may be formally included in future revised classifications as substantial supporting data emerges. We also detail advances in the classification of pediatric myelodysplastic syndrome (MDS), expanding the definition of refractory cytopenia of childhood (RCC) to include early manifestation of MDS in patients with germline predisposition. Finally, updates in the classification of juvenile myelomonocytic leukemia are presented which genetically define JMML as a myeloproliferative/myelodysplastic disease harboring canonical RAS pathway mutations. Diseases with features overlapping with JMML that do not carry RAS pathway mutations are classified as JMML-like. The review is based on the International Consensus Classification (ICC) of Myeloid and Lymphoid Neoplasms as reported by Arber et al. (Blood 140(11):1200–1228, 2022).

Keywords ICC · Hematologic neoplasms · Leukemia · Refractory anemia of childhood (RCC) · Myelodysplastic syndrome (MDS) · Juvenile myelomonocytic leukemia (JMML) · Germline predisposition to myeloid malignancy · *CEBPA* · *DDX41* · *TP53* · *RUNX1* · *ANKRD26* · *ETV6* · *GATA2* · *SAMD9* · *SAMD9L*

Martina Rudelius and Olga K. Weinberg contributed equally.

✉ Katherine R. Calvo
calvok@mail.nih.gov

[1] Institute of Pathology, Ludwig-Maximilians-University of Munich, Munich, Germany

[2] Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA

[3] Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology and Oncology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[4] German Cancer Consortium (DKTK), Heidelberg, Germany

[5] Dana-Farber/Boston Children's Hospital Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA, USA

[6] Hematology Section, Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Bethesda, MD 20814, USA

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Classification of hematologic neoplasia with germline predisposition

Definition and introduction

Hematologic neoplasms commonly present in older adults as sporadic disease associated with acquired genetic alterations. Over the past decade, there is increased recognition of the role germline mutations play in hematologic neoplasia, particularly in pediatric and young/middle aged adults, and germline predisposition is now also recognized in older adults. Germline predisposition should be considered in patients with a history of multiple cancers, first- or second-degree relative(s) with hematologic neoplasms or solid tumors, immunodeficiency, thrombocytopenia or bleeding disorder preceding myeloid malignancy, or physical stigmata associated with predisposition syndromes. While many germline mutations are associated with neoplasia that develops at a young age, malignancy can occur at any age, and even in the elderly population for some genes including *DDX41* or *TERT*. Germline mutations are often associated with family history of malignancy; however, variable penetrance and expressivity can cloud recognition of the familial nature of disease. De novo germline mutations are found in the patient but not present in either parent. Hence, lack of a family history of malignancy does not exclude germline mutation. Inheritance patterns may differ depending on the gene and include autosomal dominant, autosomal recessive, or X-linked inheritance patterns.

Recognition of malignancies arising in patients with germline predisposition is critical for pathologists not only to arrive at the proper diagnosis, but for informing selection of optimal treatment and conditioning regimens, donor selection for hematopoietic stem cell transplantation (HSCT), and genetic counseling. Inadvertent use of a healthy related donor for HSCT that harbors the same germline mutation as the patient, has resulted in donor-derived MDS or acute myeloid leukemia (AML), failed engraftment, poor graft function, or other avoidable poor outcomes [2–5] underscoring the importance of identifying these patients. The ICC expands the number of recognized genes predisposing to hematologic disease adding *TP53*, *SAMD9*, and *SAMD9L* (Table 1). Additionally, new genes with growing evidence of germline predisposition to hematologic malignancy are given a provisional status. Provisional genes will be incorporated into the classification in the future as sufficient evidence in the literature emerges.

Ideally, germline testing is performed on cultured fibroblasts from skin biopsies in order to avoid contamination from hematologic cells that may harbor somatic mutations. Given the wide spread use of next-generation sequencing (NGS) panels for analysis of hematologic malignancies in bone marrow or blood, many cases are initially suspected when mutations are identified with high variant allele

Table 1 ICC of hematologic neoplasms with germline predisposition

Hematologic neoplasms with germline predisposition without a constitutional disorder affecting multiple organ systems
Myeloid neoplasms with germline *CEBPA* mutation
Myeloid or lymphoid neoplasms with germline *DDX41* mutation
Myeloid or lymphoid neoplasms with germline *TP53* mutation
Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder
Myeloid or lymphoid neoplasms with germline *RUNX1* mutation
Myeloid neoplasms with germline *ANKRD26* mutation
Myeloid or lymphoid neoplasms with germline *ETV6* mutation
Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems
Myeloid neoplasms with germline *GATA2* mutation
Myeloid neoplasms with germline *SAMD9* mutation
Myeloid neoplasms with germline *SAMD9L* mutation
Myeloid neoplasms associated with bone marrow failure syndromes
Fanconi anemia
Shwachman-Diamond syndrome
Telomere biology disorders including dyskeratosis congenita
Severe congenital neutropenia
Diamond-Blackfan anemia
Juvenile myelomonocytic leukemia associated with neurofibromatosis
Juvenile myelomonocytic leukemia associated with Noonan-syndrome-like disorder (CBL-syndrome)
Myeloid or lymphoid neoplasms associated with Down syndrome
Acute lymphoblastic leukemia with germline predisposition*
Acute lymphoblastic leukemia with germline *PAX5* mutation
Acute lymphoblastic leukemia with germline *IKZF1* mutation

*Down syndrome and germline mutations in *ETV6* or *TP53* also predispose to acute lymphoblastic leukemia

frequencies (VAF) over 40%. Confirmation of germline mutation can be inferred if the same mutation is detected in a parent or sibling, or if the mutation persists at a high VAF at serial timepoints after chemotherapy. Some pathogenic mutations are located in non-coding regions that may not be covered by whole-exome sequencing or NGS panels. If there is high suspicion of a germline mutation and testing is negative by whole-exome sequencing (WES) or germline panel, additional testing for non-coding or pathogenic synonymous mutations, or large deletions/insertions may be considered.

MDS diagnosis in the setting of germline predisposition

Many germline predisposition syndromes are associated with cytopenia(s), hypocellular marrows, and dysmorphic bone marrow findings that may overlap with dysplasia in the absence of hematologic malignancy. Evaluation of bone marrow requires experience and caution to avoid over-interpretation and premature diagnosis of MDS. In general, progression to MDS is often associated with progressive cytopenias in the setting of increased marrow cellularity, multilineage dysplasia, cytogenetic abnormalities, new genetic alterations, or increased blasts (Table 2). Presence of the following are considered MDS-defining: monosomy 7, monosomy 5, del(7q), del(5q), multi-hit *TP53* mutations (defined as 2 or more distinct *TP53* mutations each with VAF ≥ 10%, or a single *TP53* mutation with (1) 17p deletion on cytogenetics, (2) VAF of ≥ 50%, or (3) copy neutral LOH at the 17p*TP53* locus), *TP53* mutation (VAF ≥ 10%), and complex karyotype often with loss of 17p, or *SF3B1* mutation (VAF ≥ 10%) [1]. Clonal hematopoiesis and somatic mutations must be interpreted in the context of the specific germline predisposition and associated findings in the peripheral blood and marrow. For example, monoallelic *TP53* mutations with stable low VAF are common in Schwachman-Diamond syndrome; however, overt myeloid malignancy is associated with biallelic *TP53* mutations.

Table 2 Features associated with progression to myelodysplastic syndrome in patients with germline predisposition (these are guidelines and are not intended as absolute criteria; clinical judgement must be applied in each case

Two out of three of the following:

- Acquired pathogenic genetic alteration
- Monosomy 7, monosomy 5, del(7q), del(5q), multi-hit *TP53* mutations (defined as 2 or more distinct *TP53* mutations each with VAF ≥ 10%, or a single *TP53* mutation with (1) 17p deletion on cytogenetics, (2) VAF of ≥ 50%, or (3) copy neutral LOH at the 17p*TP53* locus), *TP53* mutation (VAF ≥ 10%) and complex karyotype (often with loss of 17p), or *SF3B1* mutation (VAF ≥ 10%) are considered MDS-defining**
- Cytopenia in a new lineage(s) or progressive cytopenia***, particularly in the context of increasing marrow cellularity
- Multilineage dysplasia****

Or:

- Increased blasts

oo ≥ 5% in marrow; ≥ 2% in peripheral blood

**Genetic alterations should be interpreted in the context of the specific germline condition

***In adults, cytopenias are defined as hemoglobin < 12 g/dL in females and < 13 g/dL in males, absolute neutrophil count < 1.8×10^9/L, and/or platelets < 150×10^9/L. In children, cytopenia is defined according to age-adjusted values for hemoglobin, absolute neutrophil count, and platelet count

****Baseline marrows in patients with germline mutations may show evidence of dyspoiesis; hence, care must be made not to over-interpret dysmorphology as criteria for MDS in the absence of additional supporting evidence. Patients with germline mutations in *RUNX1*, *ANKRD26*, and *ETV6* with isolated thrombocytopenia commonly show megakaryocytic atypia at baseline, and as a sole finding, this is not sufficient for a diagnosis of MDS. Dysplasia is defined as dysplastic cytologic changes in ≥ 10% of erythroid cells, ≥ 10% of granulocytic cells, and/or ≥ 10% of megakaryocytes

Hematologic neoplasms with germline predisposition without a constitutional disorder affecting multiple organ systems

Myeloid neoplasm with germline *CEBPA* mutation

CEBPA is a single-exon gene located on chromosome 19q13.1 that encodes for CCAAT/enhancer-binding protein-α, a lineage-specific basic leucine zipper (bZIP) transcription factor required to form myeloid progenitors from multipotent hematopoietic stem cells. The mRNA may be translated into either a full-length 42-kDA isoform (p42) or a truncated 30-kDa (p30) isoform, both of which can homo- or hetero-dimerize with other CEBP proteins to regulate genes involved in cell differentiation, survival, metabolism, growth, and inflammation [6]. Mutations occur in two main hotspots: N-terminal (frame-shift mutations) and C-terminal (inframe insertions/deletions). The inheritance of a germline *CEBPA* mutation predisposes to the development of AML with autosomal dominant inheritance. CEBPA-associated familial acute myeloid leukemia (AML) is defined as the presence of a heterozygous germline *CEBPA* pathogenic variant in an individual with AML and/or family in which more than one individual has AML. The germline (often protein-truncating) mutation commonly affects the N terminus, whereas the acquired mutation arises in the C-terminal bZIP region (predominantly missense or in-frame indels) [7]. Although numbers are limited, families with germline N-terminal mutations display a higher degree of penetrance (~90%) compared with the families with germline C-terminal mutations (~50%) [8, 9].

Progression to AML is frequently associated with an acquired mutation in the remaining wild-type *CEBPA* allele [8, 10]. When these patients have disease recurrence after chemotherapy, typically they do so with new clones that

have a different spectrum of acquired mutations, including new somatic *CEBPA* mutations, demonstrating that these are second leukemias and not true relapses [8]. This pattern of progression likely underlies the clinical observations that patients with AML and germline *CEBPA* mutations have a good outcome yet are prone to second leukemias that continue to be sensitive to chemotherapy, unlike true relapsed disease.

Myeloid or lymphoid neoplasms with germline *DDX41* mutation

DDX41 is composed of 17 exons and is encoded on the distal end of the long arm of chromosome 5. It belongs to the DEAD-box helicase family of genes that have been characterized in multiple cellular roles [11]. Unlike other hereditary hematologic malignancies, *DDX41* mutation is associated with late onset myeloid neoplasms typically in the 6th decade, often occurring after years of typically mild cytopenia, or macrocytosis. While germline *DDX41* mutations should be considered in patients with a personal or family history of hematologic malignancy, a family history of malignancy is often lacking [12]. Lymphoid neoplasms have also been described but are less common with germline *DDX41* mutations. DDX41-associated AML is often associated with bone marrow hypocellularity and a borderline increase in blasts with mostly normal immunophenotype and with normal karyotype. These features make the initial diagnosis of this inherited AML more challenging than other hereditary hematologic predisposition syndromes. In the few years since the initial identification of germline and somatic *DDX41* mutations in myeloid malignancies, the total number of DDX41 mutant families worldwide has risen to over 70 making it one of the most frequently mutated myeloid malignancy predisposition genes [13]. The most common phenotypes of individuals with germline *DDX41* mutations are myeloid malignancy associated with hypocellular bone marrow and erythroid dysplasia. Myeloid neoplasia is often associated with biallelic *DDX41* mutations due to acquisition of a somatic mutation in the wild type allele in combination with the germline mutation [12].

Myeloid or lymphoid neoplasms with germline *TP53* mutation

Transcription factor p53, encoded by the *TP53* gene, plays a central role in cell cycle, DNA repair, and apoptosis; and mutations in this tumor suppressor gene are associated with a variety of cancers in both adults and children [13]. Loss-of-function germline genetic variation in *TP53* results in a rare familial cancer predisposition condition, known as Li-Fraumeni syndrome (LFS), with autosomal-dominant inheritance of cancer phenotypes [14]. The most common malignancies that occur in LFS include breast cancer, sarcomas, and brain tumors, whereas primary myeloid malignancies are relatively uncommon [15]. Incidence of leukemias in LFS is ~4% [16], predominantly hypodiploid acute lymphoblastic leukemia (ALL) and therapy-related myeloid disorders including AML and MDS [17–20].

Therapy-related AML and MDS frequently occur in patients with LFS, likely related to the patients' extensive cancer history and prior myelosuppressive treatments. Cytotoxic agents like alkylating agents and topoisomerase inhibitors, as well as radiation therapy, are known to be associated with t-MDS/t-AML [21]. *TP53* alterations are present in almost all cases of ALL with low hypodiploidy and are associated with alterations of the lymphoid transcription factor IKZF2 and the tumor-suppressor gene loci *CDKN2A* and *CDKN2B*. Remarkably, more than half of *TP53* mutations in low-hypodiploid ALL in children are also present in nontumor cells, indicating that low-hypodiploid ALL is a manifestation of Li–Fraumeni syndrome.

Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder

Each of the three recognized germline predisposition genes leading to thrombocytopenia with increased risk of myeloid malignancy is associated with varying degrees of dysmegakarypoiesis at baseline in the absence of myeloid malignancy [22–25]. Germline mutations in *RUNX1*, *ANKRD26*, and *ETV6* lead to increased small hypolobated megakaryocytes with impaired maturation and diminished proplatelet formation. Dysmegakaryopoiesis should not be considered as a criterion for MDS in the absence of other findings supporting a diagnosis of MDS including progressive cytopenias involving red cells and/or neutrophils in addition to platelets, multilineage dysplasia, acquired cytogenetic/genetic alterations, or increased blasts.

Myeloid or lymphoid neoplasms with germline *RUNX1* mutation

RUNX1 (previously known as *CBFA2* or *AML1*) is located on chromosome 21q22, and encodes a subunit of core binding transcription factor that is critical for regulation of hematopoiesis including megakaryopoiesis, and proplatelet formation [26]. Autosomal dominant germline heterozygous mutations in *RUNX1* were discovered in patients with familial platelet disorder with propensity to develop acute myeloid leukemia in 1999 [27]. The syndrome is characterized by lifelong thrombocytopenia with increased risk of developing myeloid malignancies, and less frequently lymphoid malignancy. Platelet studies show normal size with impaired platelet aggregation to epinephrine and collagen,

and dense granule storage deficiency. A minority of patients may have near normal platelet counts; however, platelet function is abnormal leading to increased bleeding risk out of proportion to quantitative platelet count. The overall risk of developing myeloid malignancies is estimated at 30–40% with a median age of 34, with a wide age range of 6–72 years [28]. The most common malignancies are myeloid including MDS, AML, and chronic myelomonocytic leukemia (CMML). T-ALL is also reported less frequently, and B-ALL or other B-lineage neoplasms are rare.

The prevalence of germline *RUNX1* mutations has not been determined. The penetrance is incomplete with variable expressivity. Typical baseline bone marrow findings in RUNX1 patients with isolated thrombocytopenia include normocellular or hypocellular marrow for age with evidence of occasional atypical megakaryocytes or frank dysmegakarypoiesis (Fig. 1). The number of megakaryocytes may be normal or slightly increased with small hypolobated forms and/or forms with separated nuclear lobes (Fig. 1A–D). Morphologically, the marrow features may overlap with those seen in immune thrombocytopenic purpura (ITP). Marrows may also show a mild increase in eosinophils. As noted above, progression to MDS, AML, or CMML is associated with hypercellularity in the setting of new cytopenias, increased blasts, multilineage dysplasia, or cytogenetic/molecular abnormalities [22] (Fig. 1E–F). AML cases are typically with blasts demonstrating an immature myeloid immunophenotype; Auer rods are common.

Myeloid neoplasms with germline *ANKRD26* mutation

Germline heterozygous mutations in *ANKRD26* (chromosome 10p12.1), with an autosomal dominant inheritance pattern, were identified in multiple families with familial thrombocytopenia 2 (THC2) in 2011 [29, 30]. THC2 is characterized by moderate thrombocytopenia with normal sized platelets with reduced alpha granules, and absent or mild bleeding. There is no consistent defect seen on platelet aggregation studies. Germline mutations in *ANKRD26* are located in the 5′ untranslated region and disrupt the binding of co-repressors RUNX1 and FLI1 to the promoter resulting in increased *ANKRD26* transcription. These gain-of-function mutations lead to increased signaling in the MPL pathway impairing proplatelet formation [23]. Because these mutations are in a non-coding region, they may be missed in standard whole-exome sequencing, or in NGS panels that do not cover the 5′ UTR. The incidence of *ANKRD26* germline mutations is unknown. There is an increased risk of MDS/AML estimated to be about 24 times greater than expected in the general population with onset ranging from 35 to

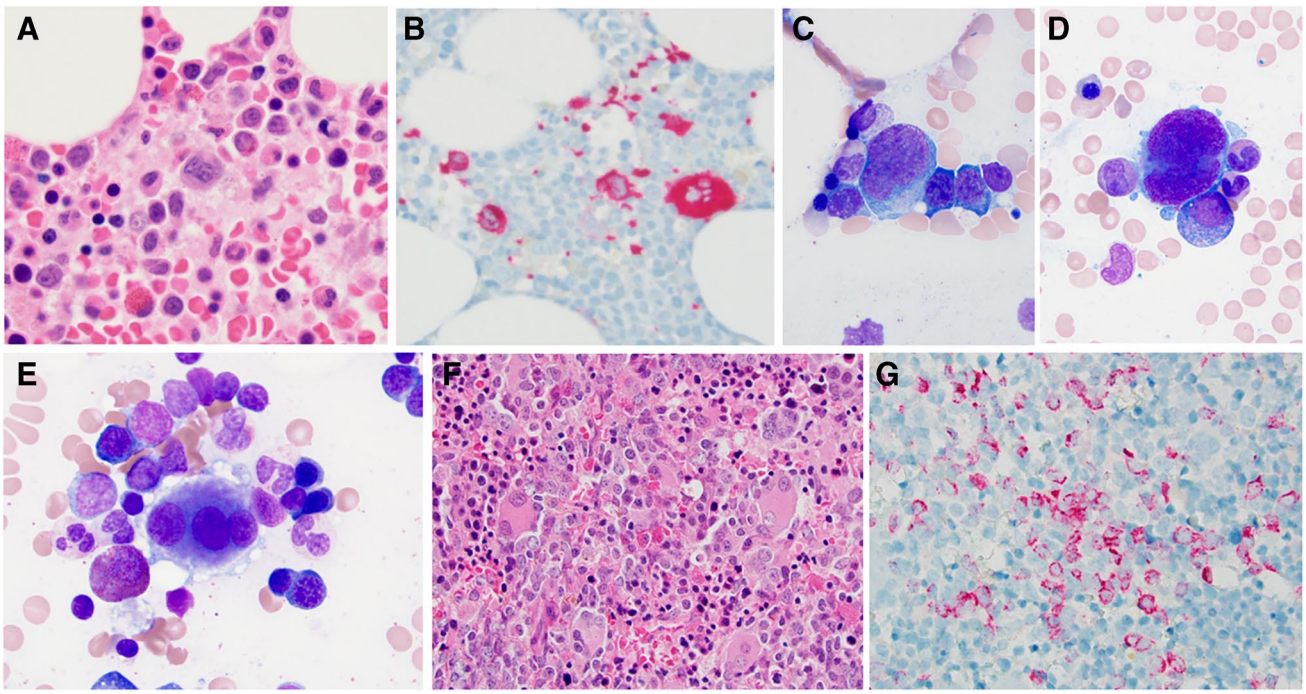

Fig. 1 RUNX1 familial platelet disorder. Megakaryocytes display morphologic features overlapping with dysplasia at baseline in the absence of myeloid malignancy characterized by a subset of small forms visible on marrow biopsy (**A**, H&E 500×), highlighted by CD61 immunohistochemistry (**B**, 500×). Small hypolobated forms can be noted on aspirate smears (**C** and **D**, modified Wright Giemsa, 1000×), and occasionally forms with separated nuclear lobes (**E**, 1000×). Progression to MDS/AML is often associated with hypercellularity (**F**, 500×), and increased blasts highlighted by CD34 immunohistochemistry (**G**, 500×)

70 years [31]. CMML, chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) have also been reported. Similar to RUNX1-FPD, dysmegakaryopoiesis is a common feature in the bone marrow at baseline in patients with stable disease and no malignancy [24]. Progression to MDS/AML is associated with additional cytopenia/cytoses, multilineage dysplasia, increased blasts, and/or cytogenetic/molecular abnormalities associated with malignancy.

Myeloid or lymphoid neoplasms with germline *ETV6* mutation

ETV6 is located on chromosome 12p13 and a member of the ETS family of transcription factors. Germline mutations in *ETV6* were identified in families with thrombocytopenia and increased hematologic neoplasms in 2015 [32, 33]. The hematologic malignancies reported include both myeloid and lymphoid and are comprised of B lymphoblastic leukemia (most common), MDS, AML, CMML, and myeloma. Non-hematologic neoplasms are also reported including colorectal carcinoma and breast cancer. The incidence of germline *ETV6* mutations is unknown. Approximately 30% of all reported carriers have been diagnosed with a hematologic malignancy. Platelet size is normal, and patients have mild to moderate thrombocytopenia, with mild to moderate bleeding tendency. The germline mutations frequently involve the ETS DNA binding domain leading to impaired nuclear localization resulting in reduced transcriptional repression by ETV6 and decreased proplatelet formation. Bone marrows often show an increase in small hypolobated immature megakaryocytes with decreased mature forms [25]. Dyserythropoiesis may be prominent.

Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems

Myeloid neoplasms with germline *GATA2* mutation

GATA2 is located on chromosome 3q21.3 and encodes a transcription factor that is a master regulator of hematopoiesis. Germline heterozygous mutations in *GATA2* were identified in 2011 associated with four separate syndromes with high incidence of myeloid malignancy called monoMAC (for monocytopenia and mycobacterium avium complex infections) [34], DCML deficiency (for deficiency of dendritic cells, monocytes, and lymphocytes) [35], Familial MDS/AML [36], and Emberger syndrome [37]. It is now recognized that all four syndromes represent the same disease with protean manifestations termed GATA2 deficiency [38, 39]. Many of the patients initially described presented with immunodeficiency and susceptibility to disseminated opportunistic infections with mycobacterium avium complex, fungi, and viruses including HPV, and disseminated warts. Other features included pulmonary alveolar proteinosis, lymphedema, and deafness. The overall prevalence of myeloid malignancy in GATA2 deficiency is estimated at 75% with the average age of onset of malignancy at 20 years, ranging from 5 months to 78 years [38, 39]. The most common myeloid malignancies are MDS, AML, and CMML. Many patients have a family history of myeloid malignancy with an autosomal dominant inheritance pattern; however, de novo germline mutations are also common. In 2016, it was discovered that germline *GATA2* mutations are present in up to 7% of pediatric MDS patients overall, and up to 75% of adolescents with MDS and monosomy 7 [40]. *GATA2* germline mutations are also reported in patients presenting with congenital neutropenia, bone marrow failure, and aplastic anemia [41, 42]. The development of immunodeficiency or marrow failure may precede myeloid malignancy, or the patient may present with myeloid malignancy without evidence of preceding immunodeficiency [36, 43]. Other malignancies including B or T lymphoblastic leukemia, EBV- and HPV-associated tumors, and solid tumors have also been reported [38, 44, 45].

Bone marrow evaluation often shows a hypocellular marrow with a spectrum of dysplastic changes ranging from minimal to severe [46]. The cellularity in some marrows may be so low as to overlap with severe aplastic anemia; however, the peripheral blood counts are usually higher in GATA2 deficiency than in severe aplastic anemia. Flow cytometric analysis of the marrow may be helpful in identifying disproportionate loss of monocytes, B-cells, B-cell precursors, NK-cell, and dendritic cells in GATA2 deficiency [47]. Pediatric and adolescent marrows often meet criteria for refractory anemia of childhood (RCC). MDS in GATA2 deficiency is most commonly hypocellular with multilineage dysplasia with or without increased blasts (Fig. 2A–I). Nearly, all marrows have evidence of megakaryocytic dysplasia with over half having megakaryocytes with separated nuclear lobes and/or micromegakaryocytes (Fig. 2A–F). AML may be associated with either hypocellular or hypercellular marrows, with immature myeloid, monocytic, or myelomonocytic immunophenotype of the blasts.

Penetrance is incomplete with variable expressivity. Donor-derived MDS/AML has been reported with inadvertent use of a healthy mutation positive related donor for hematopoietic stem cell transplant [3].

Myeloid neoplasms with germline *SAMD9* or *SAMD9L* mutation

In 2016, germline mutations in *SAMD9* were reported in MIRAGE syndrome manifesting with myelodysplasia with monosomy 7, infection, growth restriction, adrenal hypoplasia, genital phenotypes, and enteropathy [48]. A

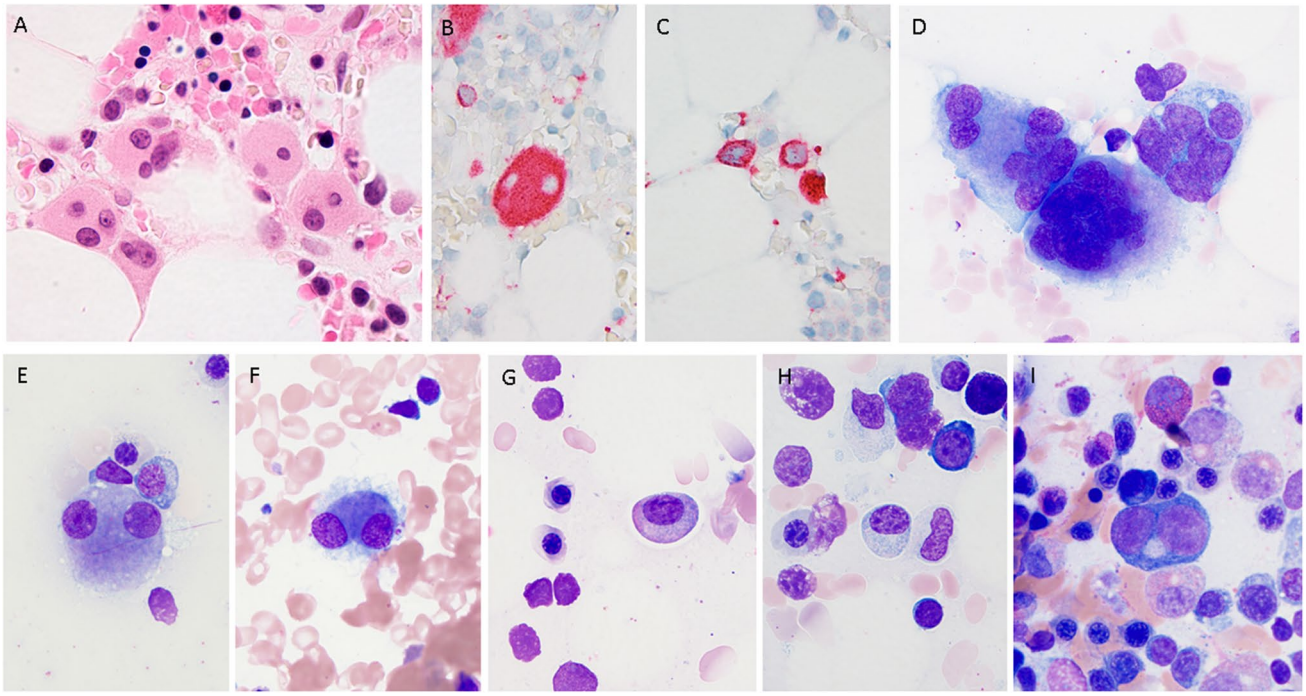

Fig. 2 MDS with germline *GATA2* mutation. Abnormal megakaryocytes with separated nuclear lobes are commonly seen on core biopsy (**A**, H&E, 500×), and highlighted by immunohistochemistry with CD61 (**B**, 500×) which also may reveal micromegakaryocytes (**C**, 500×). Dysplastic megakaryocytes of varying sizes are commonly seen on aspirate smears (**D**–**F**, Wright-Giemsa, 1000×). Multilineage dysplasia may be evident with hyposegmented (**G**) and hypogranular myeloid precursors (**H**), and erythroid dysplasia indicated by binucleation (**I**), nuclear budding, or megaloblastic changes (not shown). Blasts may or may not be increased

separate group reported germline mutations in a related gene, *SAMD9L*, associated ataxia-pancytopenia syndrome with high incidence of bone marrow failure and MDS with monosomy 7 [49]. Since then, *SAMD9/SAMD9L* mutations have been found to be among the most frequent germline mutations in pediatric MDS in addition to GATA2 [50], and often not associated with syndromic features of MIRAGE or ataxia-pancytopenia [51]. The prevalence of *SAMD9/SAMD9L* mutations in patients with suspected inherited bone marrow failure syndrome not due to Fanconi anemia is as high as 18% [42]. *SAMD9L* germline mutations have also been reported in association with pediatric autoinflammatory disease [52], and rarely with B lymphoblastic leukemia [53]. The penetrance of the mutations is incomplete, and there are various clinical and pathologic outcomes [54]. Bone marrow evaluation often shows hypocellular marrow with or without evidence of dysplastic changes [55]. Patients can progress to overt MDS or AML with monosomy 7 [55]. However, transient monosomy 7 with complete hematologic remission has also occurred [54]. *SAMD9/SAMD9L* mutations are gain-of-function mutations that enhance the antiproliferative effects of the wild type genes leading to cytopenias and growth restriction. Both genes are located on chromosome 7, and the frequent emergence of monosomy 7 is thought to occur as a maladaptive outcome reversing the effects of the mutation [48, 50]. Other adaptive outcomes include somatic genetic rescue via uniparental disomy of 7q or somatic loss of function mutation at a second site on *SAMD9/SAMD9L* that abrogates the effect of the germline mutation [50]. Loss of the mutated allele due to UPD or monosomy 7 may confound genetic diagnosis.

Myeloid neoplasms associated with bone marrow failure syndromes

The inherited marrow failure syndromes are a heterogeneous group of diseases characterized by failure in the production of one or more blood lineage with varying clinical manifestations. Different genes are involved in diverse cellular functions underlying these disorders. Most of the inherited marrow failure syndromes are associated with a predisposition to develop MDS and AML. The highest risk of MDS/AML occurs in Fanconi anemia (FA) and severe congenital neutropenia (SCN) whereas dyskeratosis congenita (DC), Shwachman-Diamond syndrome (SDS), and Diamond-Blackfan anemia (DBA) generally have lower risks.

Fanconi anemia Fanconi anemia is a heterogeneous disorder with widely variable presentation including congenital anomalies, bone marrow failure, and non-hematologic symptoms [56]. Congenital anomalies may include thumb and radial ray abnormalities, kidney and urinary tract malformations, short stature, and café au-lait spots. Patients may present at any age including adulthood, though typical age of presentation is between 5 and 10 years. Fanconi anemia is often associated with increased fetal hemoglobin and macrocytosis. Germline mutations may involve any of 23 genes and are mostly autosomal recessive and some rare X-linked recessive or autosomal dominant subtypes. The cumulative incidence of bone marrow failure varies from 18 to 83% depending on the risk groups [57]. The cumulative incidence of AML at age 40 years is estimated at 15–20%, and the cumulative incidence of MDS at age 50 years is 40% [58]. The relative risk of AML is increased 700-fold in comparison with the general population and that of MDS is increased 6000-fold [59]. AML is particularly more frequent in *FANCD1/BRCA2* group, with a cumulative incidence of 80% at age 10 years. Patients with Fanconi anemia may also present with T-ALL, particularly in the FANCD1/BRCA2 subtype. Patients with Fanconi anemia are at risk for solid tumors, particularly squamous cell carcinomas of the head, neck, GI tract, vulva, and hepatic tumors. In a family study of Fanconi anemia, heterozygous mutations in *FANCA* or *FANCC* were not associated with increased cancer risk; due to small numbers, other Fanconi anemia genotypes could not be assessed. Microscopic examination of a bone marrow biopsy shows hypoplasia and hypocellularity. Hypocellularity is often out of proportion of cytopenias. In some cases, erythroid hyperplasia and dysplasia are also present.

Severe congenital neutropenia Severe congenital neutropenia (SCN) includes a heterogeneous group of genetic disorders that manifest early in infancy with the occurrence of usually severe, once often lethal infections, in which absolute neutrophil count (ANC) is below 0.5×10^9/L, leading to life-threatening bacterial infections [60]. Autosomal dominant mutations in *ELANE*, the gene-encoding neutrophil elastase, are the most frequently observed genetic defects in SCN patients. Importantly, SCN patients have a high risk of developing MDS or AML, with a median incidence of 21%, 15 years after initiation of GCSF treatment [61, 62]. The majority of SCN patients with leukemic progression show the appearance of hematopoietic clones with somatic mutations in *CSF3R*, resulting in a truncated form of CSF3R with defective internalization and aberrant signaling properties [63]. These clones may persist for months or even years without progression to malignancy. At baseline, the marrow for ELANE-mutant SCN classically shows early myeloid maturation arrest at the promyelocyte stage with normocellularity [60].

Shwachman-Diamond syndrome Shwachman-Diamond syndrome (SDS) is caused by pathogenic biallelic or homozygous variants in the gene-encoding Shwachman Bodian-Diamond syndrome protein and is characterized by pancreatic insufficiency and neutropenia [64]. SDS patients typically present with neutropenia as their initial hematologic finding, but cytopenias may present in any lineage either singly or in combination [65, 66]. Cytopenias may be mild or absent; however, patients remain at risk for myeloid malignancies even if cytopenias were previously asymptomatic [67]. Clonal cytogenic abnormalities involving i(7q) and del(20q) are reported but are not associated with progression to malignancy in patients with SDS [66, 68]. The risk of worsening cytopenia(s), clonal myeloid evolution, or AML is estimated at 20% by age 18 [69]. The Severe Chronic Neutropenia International Registry reported a 1% per year progression rate to MDS/AML in patients with SDS, with a cumulative risk of MDS/AML reaching 36% by 30 years of age [70]. Small stable clones with heterozygous *TP53* mutations are common in patients with SDS; however, biallelic *TP53* mutations were observed in myeloid malignancies and may be present prior to the development of overt malignancy [71]. At baseline, the marrow is typically hypocellular even if blood counts are normal. Myeloid dysplasia such as nuclear hyposegmentation and hypogranularity are common, and mild megakaryocytic dysplasia may be present in a small subset of cells. Erythroid dysplasia is typically absent at baseline [67].

Dyskeratosis congenita and telomere biology disorders Dyskeratosis congenita (DC) and telomere biology disorders (TBD) are a spectrum of disorders caused by pathogenic germline variants in telomere biology genes. Although classically associated with mucocutaneous triad of dysplastic nails, reticular skin pigmentation, and oral leukoplakia, the majority of patients lack these findings. TBD is characterized by a high risk of hematologic and solid malignancies, bone marrow failure, and other medical problems [72–75]. In addition to X-linked pathogenic variants in dyskerin, encoded by *DKC1*, DC is also caused by heterozygous pathogenic variants in components of the shelterin telomere protection complex, including TERT, TERC, TINF2, ACD, and POT1, in the DNA helicase and the telomere biology protein, RTEL1, a component of the telomerase holoenzyme complex, NAF1, and the telomere capping protein STN1. NCI cohort of 197 DC patients found a cumulative incidence of cancer of 2% by age 50 years for leukemia and 11% by age 50 years for solid cancers [76]. Patients with autosomal dominant mutations

in *TERT* or *TERC* may display variable penetrance and present in adulthood with pulmonary fibrosis, hepatic cirrhosis, and early graying of the hair [77]. Bone marrow is typically hypocellular with diminished hematopoietic progenitors [77].

Diamond-Blackfan anemia Diamond-Blackfan anemia (DBA) is an inherited pure red blood cell aplasia typically caused by pathogenic autosomal dominant variants in ribosomal proteins. X-linked mutations in *GATA1* also cause a DBA phenotype. DBA is often associated with congenital anomalies, particularly abnormalities of the thumbs facial features, kidneys, heart, and short stature. DBA is usually diagnosed by the presence of severe, often macrocytic, anemia in infancy or early childhood, but patients may present in adulthood [78]. Patients are at increased risk of cancer; the two most prevalent solid tumors are colorectal cancer and osteogenic sarcoma [79]. There is also some increased risk of myeloid malignancy [80]. The bone marrow shows a characteristic of erythroblastopenia with normal lymphoid, granulocytic, and megakaryocytic lineages and is usually normocellular or slightly hypocellular [81].

Juvenile myelomonocytic leukemia associated with neurofibromatosis, Noonan syndrome, or Noonan-syndrome-like disorders (refer to JMML section below)

Myeloid neoplasms associated with Down syndrome

Children with germline trisomy 21 and Down syndrome are predisposed to developing transient myeloproliferation and AML which is addressed in the acute myeloid leukemia classification [82]. These patients also have increased incidence of B lymphoblastic leukemia [83].

Acute lymphoblastic leukemia with germline predisposition

Germline mutations in several genes have been associated with predisposition to B lymphoblastic leukemia including *PAX5* and *IKZF1*, as well as genes associated with immune dysregulation such as ataxia telangiectasia, Nijmegen breakage syndrome, or inborn errors of immunity (IEI) [84–86]. Down syndrome and germline mutations in *TP53* and *ETV6* predispose to both B-ALL and myeloid neoplasm [32, 33, 87].

Acute lymphoblastic leukemia with germline PAX5 mutation

PAX5 is located on chromosome 9p13 and encodes a transcription factor that is important in regulation of B-cell development. Inherited mutations in *PAX5* were found in families with increased incidence of B-ALL in 2013 [84, 88]. The inheritance pattern is autosomal dominant with variable penetrance relative to the development of B-ALL. Emergence of B-ALL in this setting is associated with chromosomal loss of 9p containing the wild type copy of *PAX5* and retention of the mutated copy in the leukemic cells. The immunophenotype and morphology of the blasts overlap with that of sporadic B-ALL.

Acute lymphoblastic leukemia with germline IKZF1 mutation

IKZF1 encodes IKAROS which is a transcription factor that is critical for B-cell development. Several families have been reported with germline mutations in *IKZF1* that were associated with impaired B-cell maturation, common variable immunodeficiency with B-cell lymphopenia, and increased incidence of B-ALL [85, 89].

Additional conditions with germline predisposition to hematologic malignancy and provisional entities

Other rare germline mutations predispose to the development of hematologic malignancies and include Bloom's syndrome (*BLM*), constitutional mismatch repair deficiency (*MLH1*, *MSH2*, *MSH6, EPCAM*, *PMS2*), *DNMT3A*, *ERCC6L2, MBD4*, and xeroderma pigmentosum (*XPC*) [90, 91]. Limited cases of hematologic malignancy have been reported with germline mutations in *CSF3R*, *MECOM*, *SRP72*, and *TET2*.

Classification of refractory cytopenia of childhood and pediatric myelodysplasia

Background/introduction The ICC classifies pediatric myelodysplastic syndrome (MDS) separately from adult MDS. The separation recognizes the unique biology of MDS in children and adolescents, which differs significantly from MDS in older individuals with respect to genetic landscape and treatment approaches. Pediatric MDS lacks recurrent mutations in genes of epigenetic regulation or RNA splicing known to expand clonal hematopoiesis in adults; instead, somatic aberrations in *SETBP1*, *ASXL1*, *RUNX1*, and the RAS/MAPK pathway mutations define the genomic landscape [51, 92, 93].

Recently, novel germline mutations in genes including *GATA2*, *SAMD9*, or *SAMD9L* have been identified which predispose to MDS at a young age. In the absence of excess of blasts, the histopathology of these cases often displays the characteristic pattern defined as refractory cytopenia of childhood (RCC) [94]. It is important to recognize that the histomorphology of RCC is independent of the presence of markers of clonality such as chromosomal abnormalities or somatic oncogenic mutations, and may also be observed in some cases of inherited bone marrow failure disorders such as Fanconi anemia. The ICC updates the diagnostic criteria of RCC (Table 3) and recognizes that this entity categorizes cases that might progress to MDS with excess blasts and develop clonal rescue hematopoiesis or severe bone marrow failure. This concept of evolution meets the challenges of bone marrow plasticity in young individuals with the increasing recognition of adaptive and maladaptive rescue mechanisms. Furthermore, it allows risk-adapted treatment strategies and paves the way for future research.

Therapy options and prognosis of myeloid neoplasms differ substantially according to age. In contrast to MDS in older adults, therapeutic strategies for children and adolescents with MDS are generally curative [95]. Particularly for MDS with underlying germline predisposition, early hematopoietic stem cell transplantation rather than intensive AML-therapy is standard of care. Therefore, the distinction between MDS and de novo AML is crucial in pediatric myeloid neoplasia, and the ICC retained the definition of pediatric MDS-EB defined as MDS with 5–19% blasts instead of replacing MDS with 10–19% by MDS/AML like in adults.

Table 3 ICC diagnostic criteria for refractory cytopenia of childhood (RCC)

1. Persistent cytopenia

Number of cytopenias (1-3). Cytopenia is defined according to age-adjusted values for hemoglobin, absolute neutrophil count, and platelets.

2. Manifestation of dysplasia

Dysplastic changes in at least two lineages or in ≥ 10% in one lineage

Typical dysplastic features of RCC (not all are required)

Specimen	Cellularity	Erythropoiesis	Granulopoiesis	Megakaryopoiesis *
Bone marrow aspirate		-nuclear budding -multinuclearity -megaloblastoid changes	-Pseudo-Pelger-Huët cells -hypo- or agranularity	- separated nuclear lobes -round monolobated nucleus -micromegakaryocytes
Bone marrow Biopsy	-patchy pattern in otherwise hypocellular marrow or - rarely diffuse pattern in normo- or hypercellular marrow**	-patchy (few multi- or unifocal cluster) -left-shift -increased mitosis	-marked decrease	-marked decrease or aplasia -round monolobated nucleus - separated nuclear lobes -micromegakaryocytes

*immunohistochemistry for megakaryocyte markers is required on the biopsy

** normo- or hypocellular RCC requires significant dysplasia in megakaryocytes (≥10%)

3. Other required criteria

Blast percentage in peripheral blood <2% and bone marrow <5%

No prior cytotoxic chemotherapy or radiation therapy

No fibrosis

Refractory cytopenia of childhood (RCC)

Definition RCC is characterized by persistent cytopenia and dysplastic changes in at least two hematopoietic lineages or in ≥ 10% of cells in one lineage (Table 3). The histomorphologic pattern is RCC defining, and about 80% of cases present with a hypoplastic bone marrow. There is no blast excess with < 5% of blasts in bone marrow and < 2% blasts in peripheral blood. While some cases of RCC are bona fide MDS, others may lack evidence of clonality.

Clinical features Patients present with symptoms of pancytopenia like bleeding, malaise and infection, or may be asymptomatic [96, 97]. Lymphadenopathy, secondary to local or systemic infection, is occasionally observed, but hepatosplenomegaly is generally not a clinical feature of RCC. In patients with a germline disorder, abnormalities in other organ systems may be due to the underlying predisposition. In contrast to adult MDS, isolated anemia is rare in low-grade MDS in children, while age-specific macrocytosis of red blood cells is noted in most RCC patients. Thrombocytopenia is most frequent, and severe neutropenia is present in up to 25% of cases [96, 97].

Morphologic features Peripheral blood smears show macrocytosis and anisopoikilocytosis. Often thrombocytopenia is present with anisocytosis and few giant thrombocytes. Neutrophils display dysplastic changes such as pseudo-Pelger-Huët cells, hypogranularity, and giant bands, however, in cases with severe neutropenia dysplasia can be missed. There is no increase in blasts.

In bone marrow aspirate smears, erythropoiesis is characterized by megaloblastoid changes, nuclear budding, or multinuclearity. Granulopoiesis shows nuclear-cytoplasmic maturation defects with hypogranularity of the cytoplasm and pseudo-Pelger-Huët cells. Megakaryopoiesis can be aplastic, and if present, is characterized by small round or separated nuclei. Micromegakaryocytes are noted in some cases and are supportive of the diagnosis RCC.

The majority of patients present with a hypocellular bone marrow [98, 99]; therefore, high quality representative bone marrow biopsies are essential for diagnosis. A hallmark of RCC is a patchy distribution of hematopoiesis (Fig. 3A, E), which can be missed in bone marrow aspirates. Marrow architecture is disturbed with predominance of erythropoiesis and significantly reduced granulopoiesis and megakaryopoiesis. Erythroid islands are enlarged with dysplastic features and impaired maturation (Fig. 3D). Granulopoiesis is severely reduced and left-shifted. Megakaryocytes can be absent and micromegakaryocytes are rarely detected. There is no increase of myeloblasts (blast count < 5%). Hyper- or normocellular RCC is characterized by similar morphologic changes; however, megakaryocytic dysplasia requires significant dysplastic features in ≥ 10% of megakaryocytes. (Table 3).

Immunohistochemistry of megakaryocytic antigens such as CD61 or CD41 are mandatory to identify micromegakaryocytes (Fig. 3F), which can be crucial in the differential diagnosis of severe aplastic anemia. CD34 immunhistochemistry is helpful to quantify myeloblasts; however, exclusion of an increased number of hematogones with staining of TdT and CD79a or PAX5 is important.

Cytogenetics and Molecular Genetics Most patients with RCC have a normal karyotype in hematopoietic cells. Monosomy 7 is the most common cytogenetic aberration present in about 20% of RCC patients [98, 100]. GATA2 deficiency and SAMD9/SAMD9L germline disease account for approximately half of these monosomy 7 cases [50, 101]. Trisomy 8 is the second most common chromosomal abnormality, and random chromosomal changes and complex karyotypes are noted occasionally [98].

Somatic mutations in genes of epigenetic regulation or RNA splicing are rare, instead mutations in *SETBP1*, *ASXL1*, *RUNX1*, and the RAS/MAPK pathway mutations are the most common somatic aberrations [51, 92, 93]. Approximately 20% of RCC cases have an underlying germline predisposition like GATA2 deficiency, SAMD9/SAMD9L syndrome, Fanconi anemia, or RUNX1 deficiency [50, 101].

Differential diagnosis The diagnosis of hypoplastic RCC is challenging, and it is important to integrate the clinical course, cytogenetics, molecular genetics, and morphology to make the correct diagnosis. A variety of reactive bone marrow changes due to infection, metabolic disorders (e.g., deficiency of vitamin B12), rheumatologic disease, paroxysmal nocturnal hemaglobinuria, and autoimmune lymphoproliferative disorders can present with features resembling RCC. For the differential diagnosis of aplastic anemia, it is important to carefully assess dysplastic changes of all three hematologic lineages. In this context, the detection of micromegakaryocytes is specifically helpful to render the diagnosis of RCC.

Myelodysplastic syndrome (NOS)

Cases of pediatric MDS without excess blasts that do not present with the histomorphological pattern of RCC are classified as MDS not otherwise specified (MDS-NOS) (Table 4). This category will also include cases with monosomy 7 and del(7q) in the absence of cytopenia and/or dysplasia. Rarely, adult-type MDS, e.g., neoplasia with *SF3B1* mutations or del(5q), are noted in pediatrics; these cases can be classified according to the MDS classification for adults.

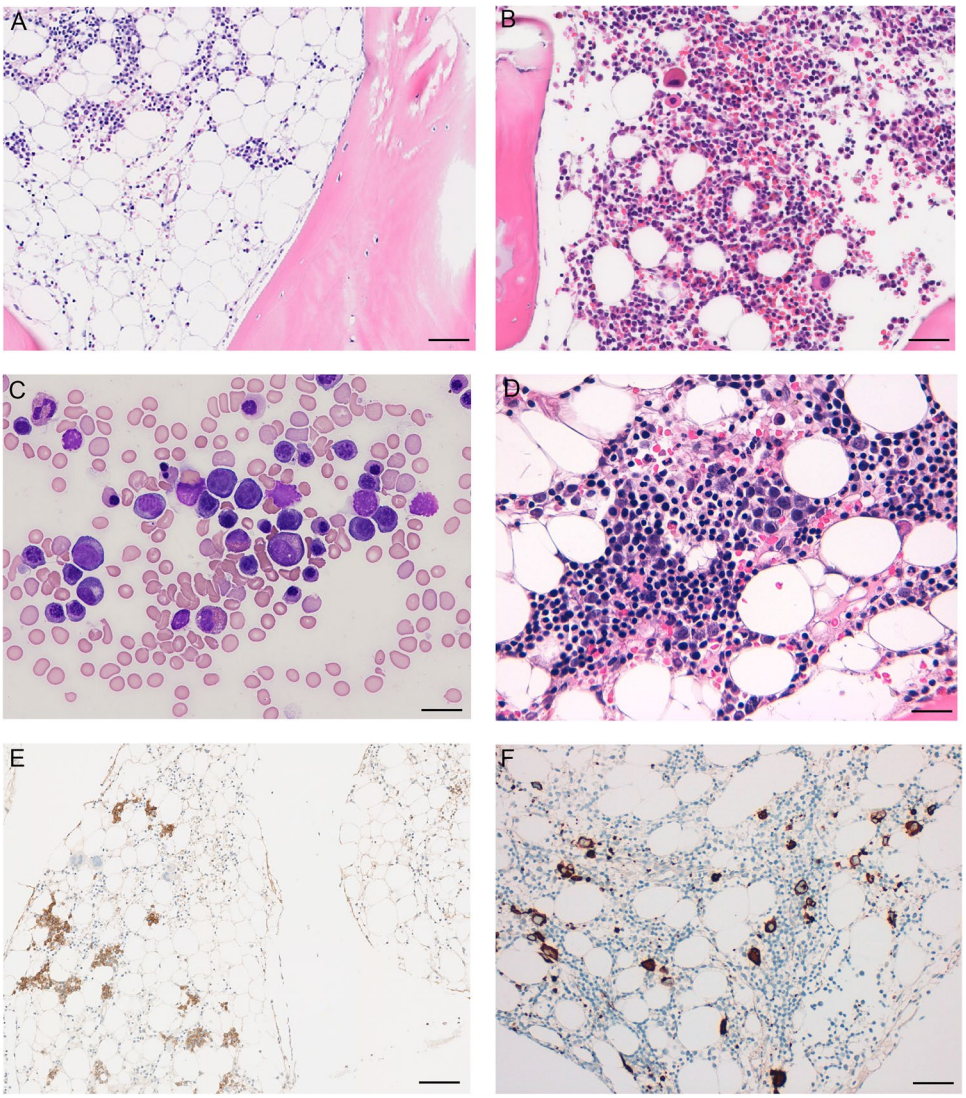

Fig. 3 Refractory cytopenia of childhood. H&E staining of hypocellular RCC (**A**) and normocellular RCC (**B**) with patchy distribution of the erythropoiesis. E-cadherin (**E**) highlights the patchy distribution of erythropoiesis. Bone marrow aspirate smear (**C**) and bone marrow core biopsy (**D**) with dysplastic changes of the erythropoiesis (nuclear budding and maturation defect). Hypolobulated megakaryopoiesis with few micromegakaryocytes are shown by CD61 immunohistochemistry (**F**). Scale bars: **A**, **B**, **E**, **F** 100 µm; **C** 10 µm; D 50 µm

Table 4 Refractory cytopenia of childhood and pediatric myelodysplastic syndromes

	Dysplastic lineages	Cytopenia	Blasts	Cytogenetics	Mutations
Refractory cytopenia of Childhood (RCC)	≥ 1*	≥ 1	< 5% BM < 2% PB	Any**	Any
MDS, NOS	0–3	0–3***	< 5% BM < 2% PB	Any** or MDS defining if no dysplasia or cytopenia	Any
MDS with excess blasts (MDS-EB)	0–3	0–3	5–19% BM 2–19% PB, or Auer rods	Any**	Any, except *NPM1*, biallelic *CEPBA* or multihit *TP53*

*See Table 1

**Except AML-defining cytogenetics which are listed in the AML section

***Includes cases with no cytopenia if an MDS-defining cytogenetic abnormality is present

MDS with excess blasts

Pediatric MDS with excess blasts is defined as MDS with 5–19% blasts in the bone marrow or 2–19% blasts in the peripheral blood (Fig. 4). Like in adults, genetic lesions or clinical course rather than a fixed threshold of blast percentage best define MDS and AML in pediatrics. In addition, disease with AML-defining cytogenetics, NPM1, or bi-allelic CEBPA mutations is considered AML at any age and irrespective of blast percentage. Therapy options and prognosis of myeloid neoplasms differ, however, substantially according to age. Most pediatric patients with MDS-EB are offered allogeneic hematopoietic stem cell transplantation without preceding AML-induction chemotherapy [95]; thus, the distinction between de novo AML and MDS is crucial to enhance cure rates for young individuals with myeloid neoplasia.

Classification of juvenile myelomonocytic leukemia

The ICC separates juvenile myelomonocytic leukemia (JMML) from adult MDS/MPN as the biology and molecular profiles are distinct. JMML is now a genetically defined disease with the requirement of canonical RAS-pathway mutations in *NRAS*, *KRAS*, *PTPN11*, *NF1*, *CBL*, or rarely *RRAS* for diagnosis. Neoplasms in children resembling JMML without RAS-pathway mutations are classified as JMML-like.

Juvenile myelomonocytic leukemia

JMML is a unique disorder of early childhood with distinct clinical and hematologic features; the ICC revised the diagnostic criteria (Table 5). Splenomegaly is the most consistent clinical symptom, but may be absent in 3% of patients at diagnosis [102, 103]. Hepatomegaly, lymphadenopathy, enlarged tonsils, interstitial lung disease, and gut infiltrates are also common. About a quarter of patients have pleomorphic leukemic skin lesions. In addition, non-specific skin lesions like juvenile xanthogranuloma may be present.

Table 5 Diagnostic criteria for juvenile myelomonocytic leukemia

I. Clinical and hematologic features (the first two features are present in most cases; the last two are required)
- PB monocyte count $\geq 1 \times 10^9$/L[#]
- Splenomegaly[§]
- Blast percentage in PB and BM < 20%
- Absence of *BCR::ABL1*

II. Genetic studies (1 finding required)
- ••Somatic mutation in *PTPN11** or *KRAS** or *NRAS** or *RRAS**
- ••Germline *NF1* mutation and loss of heterozygosity of *NF1* or clinical diagnosis of neurofibromatosis type 1
- ••Germline *CBL* mutation and loss of heterozygosity of *CBL*†

[#]This monocyte threshold is not reached in approximately 7% of cases

[§]Splenomegaly is absent in 3% of cases at presentation

[*]Germline mutations (indicating Noonan syndrome) need to be excluded

[†]Occasional cases with heterozygous splice site mutations

While 1–2 café au lait spots are often noted in patients with CBL syndrome [104, 105], the clinical diagnosis of NF1 in infants with JMML requires ≥ 6 lesions of > 5 mm in size.

Leukocytosis is usually present, and the median-reported white blood count (WBC) in larger patient series varies from 25 to 30×10^9/L, but occasionally, the WBC is within the normal range [102, 103]. There is monocytosis, often with dysplastic forms, and a monocyte count > 1×10^9/L. Of note, 7% of cases have a lower monocyte count at time of diagnosis (Table 5) [102, 106]. Presence of myeloid and often erythroid precursors is a consistent feature of JMML. Blasts usually account for fewer than 5% of WBC, and always less than 20% (Table 5). Thrombocytopenia is often present with the exception of cases of NF1-associated JMML, who mostly have platelet counts within the normal range [102]. Anemia is not a leading sign; macrocytosis or persistent microcytosis of red cells may be present. The bone marrow (BM) is hypercellular with granulocytic predominance (Fig. 5); the monocytic compartment is generally less prominent than in peripheral blood. The most consistent finding

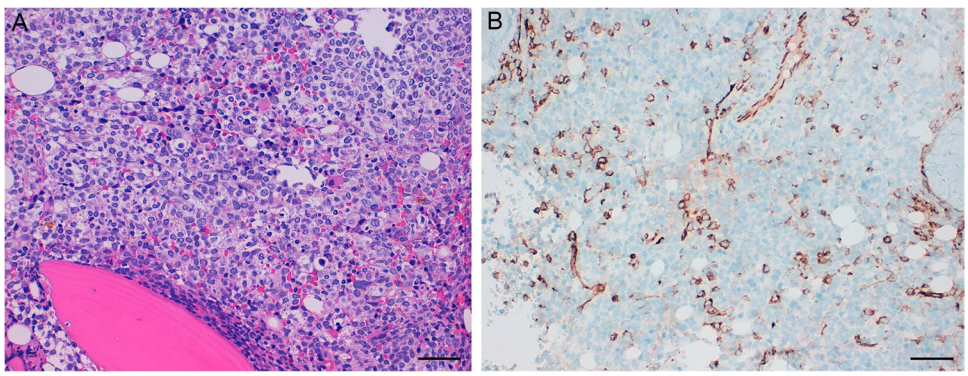

Fig. 4 Myelodysplastic syndrome with excess blasts. H&E of bone marrow biopsy shows hyperplastic hematopoiesis with disrupted architecture, maturation defect of granulopoiesis and monolobulated megakaryocytes (**A**). Myeloblasts are highlighted by CD34 immunohistochemistry (**B**). Scale bars: **A**, **B** 50 µm

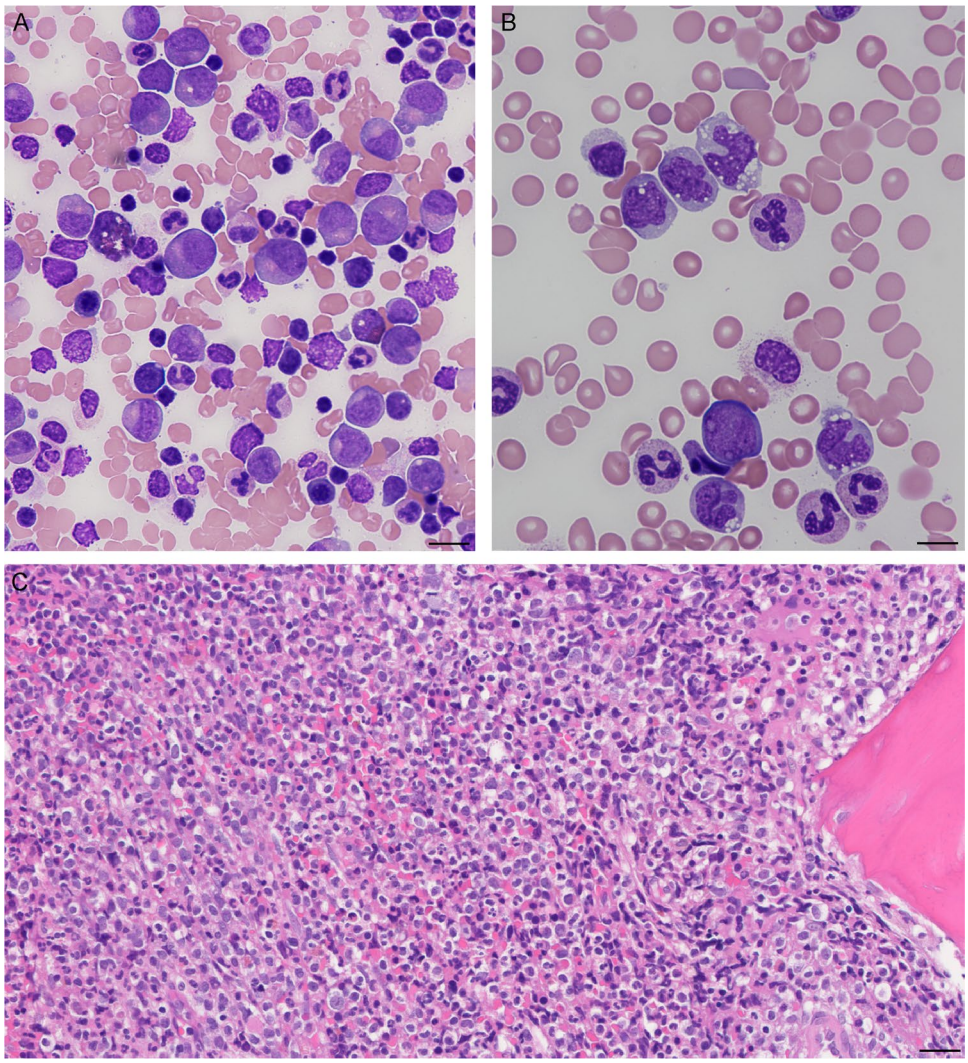

Fig. 5 Juvenile myelomonocytic leukemia. Bone marrow aspirate smear (**A**) with increase in granulocytes and monocytes. In blood smears (**B**), dysplastic monocytes with cytoplasmic vacuoles are visible. H&E of bone marrow core biopsy (**C**) shows granulocytic hyperplasia with reduced megakaryopoiesis. Scale bars: **A**, **B** 10 µm; **C** 50 µm

in BM specimens is the reduced number of megakaryocytes [102]. The blast percentage must be less than 20% (Table 5).

Constitutive activation of the RAS signal transduction pathway has long been recognized as hallmark of JMML. In fact, recent studies demonstrate RAS pathway mutations in the *PTPN11*, *NRAS*, *KRAS*, *NF1*, *CBL*, and rarely *RRAS* genes present in leukemic cells of more than 95% of JMML patients [107, 108]. These RAS pathway mutations define genetically and clinically distinct subtypes. Three of these subtypes, *PTPN11*-, *NRAS*-, and *KRAS*-mutated JMML, are characterized by heterozygous somatic gain-of-function mutations in children without constitutional abnormalities, whereas two subtypes, JMML in neurofibromatosis type 1 and JMML in most children with CBL syndrome, are defined by germline Ras disease and acquired biallelic inactivation of the respective genes in hematopoietic cells. Germline *CBL* patients often experience spontaneous resolution of disease, [107, 109, 110] while JMML driven by *PTPN11* or *NF1* is generally rapidly progressive requiring HSCT [108, 111–113]. *KRAS*- and *NRAS*- mutated JMML with a normal karyotype share overlapping features with a rare disorder called RAS-associated autoimmune leukoproliferative disorder, which may represent different phenotypes of the same disorder [114]. The ICC integrated these molecular data and sharpened the diagnostic criteria by requiring the presence of one of these canonical RAS pathway mutations for diagnosis of JMML (Table 5).

JMML-like neoplasms

Some rare cases of childhood neoplasia are phenotypically identical to JMML but lack a driver RAS pathway mutation. The ICC refers to these disorders as JMML-like neoplasms (Table 6). This category includes cases with rearrangements like *ALK* [115, 116], *ROS1* [116], *FIP1L1::RARA* [117, 118], or *CCDC88C*::*FLT3*1 [119, 120]. Of note, clinical and biological features of cases with *FIP1L1::RARA* fusion genes are distinct from those observed in acute promyelomonocytic leukemia (APL). While patients with JMML-like

Table 6 Juvenile myelomonocytic leukemia (JMML), JMML-like neoplasms and Noonan syndrome-associated myeloproliferative disorder

	PB/BM blasts	Mutation	Secondary mutations	Karyotype
JMML	< 20% PB < 20% BM	*PTPN11*, *NRAS*, *KRAS*, *RRAS*, *NF1**, *CBL***	Any	Any (monosomy 7 in 25%)
JMML-like neoplasms	< 20% PB < 20% BM	Absence of RAS-pathway mutation	Any	Any
Noonan syndrome–associated myeloproliferative disorder	< 20% PB < 20% BM	*PTPN11****, *NRAS****, *KRAS**** *RIT1****	None	Normal[#]

[*] Germline mutation with additional aberration resulting in biallelic inactivation of the *NF1* gene

[**] Germline mutation with additional aberration resulting in biallelic inactivation of the *CBL* gene; some cases with heterozygous germ line mutation only

[***] Germline mutation, patients generally display syndromic features of Noonan syndrome

[#] In rare instances monosomy 7 can develop[122, 123]

neoplasms can benefit from targeted therapy, HSCT appears the only curative option. Disease with AML-defining genetic lesions like *KMT2A* or myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions are excluded from JMML-like neoplasms.

Noonan syndrome–associated myeloproliferative disorder

Children with Noonan syndrome and germline mutations in *PTPN11*, *KRAS*, *NRAS*, or *RIT1* can develop a myeloproliferative disorder during the first year of life [121]. While this disorder can in its severe form be indistinguishable from JMML by clinical and hematological parameters, acquired somatic mutations are conspicuously absent, and the disorder generally has a self-limiting course. In very rare instances, monosomy 7 has been described [122, 123].

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Author contribution All authors contributed to the gathering of supporting data for the ICC and this manuscript. MR, OKW, AS, CMN, and KRC wrote the manuscript. MR and KRC made the figures. All authors edited the manuscript and contributed to the tables. The first two authors contributed equally.

Declarations

Compliance with all ethical standards was undertaken for this work. No research involving human participants and/or animals was performed for this work. No informed consent was required.

Conflict of interest The authors declare no competing interests.

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