Chapter 1

Epidemiology and Etiology of AML

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Abstract

AML is a grave disease with an incidence of 4 per 100,000 and year, it can present in all ages, but the median age is 70 years. One third of patients have secondary AML, i.e., AML following chemoradiotherapy or a transformation from previous myelodysplastic syndrome (MDS) or myeloproliferative neoplasia. A combination of genetic, epigenetic and environmental factors may be responsible for the development of most cases of AML. The pathogenesis of AML is characterized by serial acquisition of somatic mutations and several genes are recurrently mutated in AML. Exposures to benzene, cigarette smoking, pesticides, embalming fluids, accidental or professional ionization radiation, therapeutic radiotherapy and radioactive I-131 therapy can cause AML with or without a preceding MDS phase. Alkylating agents (e.g. melphalan, cyclophosphamide), topoisomerase-II inhibitors (e.g. etoposide, doxorubicin) and other drugs (e.g. azathioprin) are described to be associated with the development of therapy-related AML (t-AML). Furthermore, about 5% to 15% of adults and 4% to 13% of pediatric patients with MDS or AML carry germline pathogenic variants in cancer susceptibility genes. Individuals with clonal hematopoiesis (CHIP) progress to AML at a rate of about 1% per year. Higher age of onset, obesity, previous autoimmune disease and antecedent MDS or MPN are associated with a risk for developing AML.

Key words: incidence, prevalence, sex, diagnosis, survival, mutations, exposure, hereditary conditions, benzene, t-AML, secondary AML

1.1 Incidence of AML by age and year

Acute myeloid leukemia (Döhner et al. 2015) is a grave disease, resulting in 85,000 deaths and 2.6 million years of lost life globally in 2016 (Foreman et al. 2018), and these numbers are expected to rise to over 150,000 deaths and 3.8 million years of lost life in 2040. This increase is mainly caused by a growing and ageing global population. For 2020, 20,000 new cases per year are expected in USA (SEER 2020) and 3,100 in the UK (Cancer Research UK 2020).

In addition to the human loss, there is a substantial cost for treatment, care, and disability, calculated to 170,000 € per patient younger than 60 years for the first five years in Sweden, with somewhat lower costs for older patients (Hernlund et al. 2019).

AML may strike at any age, from newborn to very elderly. However, the incidence rises sharply during middle age and peaks in ages 75-85 years (Figure 1.1). The reported median age ranges from 68 years in the USA, Denmark and Switzerland (SEER 2020, Østgård et al. 2015, Schnegg-Kaufmann et al. 2018) to over 70 in Japan, France, UK and Sweden (Maynadi et al. 2011, Ohnishi et al. 2014, Roman et al. 2016, Juliusson et al. 2009).

The overall crude incidence in the Scandinavian countries 2012-16 is according to NORDCAN 2.9 per 100,000 males (M) per year and 2.6 for females (F) (NORDCAN 2020), 2.5 in Burgundy, France (M 2.8, F 2.2; Maynadi et al. 2011), 3.8 in Switzerland (M 4.1; F 3.4; Schnegg-Kaufmann et al. 2018), 4.26 in Kagawa, Japan (Ohnishi et al. 2014), 4.39 in the UK (M 4.9; F 3.9; Roman et al. 2016), and 4.31 in the United States in 2016 (M 5.4, F 3.5, according to SEER 2020). Age-adjusted incidences have significant variation due to the choice of standard population, in UK the adjusted standardized incidence 2004-2013 ranged from 2.58 through 5.06 per 100,000 and year with different standard reference populations (Roman et al. 2016).

Age-adjusted incidence rates by year in USA (SEER 2020), and by year, age and sex in the Nordic countries (NORDCAN 2020) are shown in Figure 1.2. In contrast to the slightly decreasing trend for age-adjusted incidence, the crude incidence in Sweden increased from 4.7 in 1997-2006 to 5.3 in 2007-2015; i.e., an annual increase of 1.2% (Nilsson et al. 2020).

AML in children is most common in newborns up to age 4 (Figure 1.1), and SEER data 1975-2014 indicates a rising incidence from 0.7 through 1.2 per 100,000 and year (Chen et al. 2019).

As with most hematologic malignancies, AML is more common in males than in females, which is most clearly seen in the age groups 60-90 years. However, there are AML subsets which are more

common in females, such as AML with *FLT3* internal tandem duplication (ITD) and/or *NPM1* mutation (Juliusson et al, 2020) and therapy-related AML (t-AML) (Hulegårdh et al. 2015, Nilsson et al. 2020).

1.2 Prevalence

The number of people living after a diagnosis of leukemia overall in USA is estimated to be 400,000 (SEER 2020), over 60,000 of them with AML, with a prevalence of 19 per 100,000, according to SEER (Shallis et al, 2019). The prevalence of AML patients in Scandinavia 2016 according to NORDCAN is 13.9 per 100,000 (M 13.1, F 13.9), and the age distribution of prevalent Swedish patients in 2014 is shown in Figure 1.3 (Juliusson et al. 2017), with a skewing towards younger people due to the strong effect of age on survival (Juliusson et al. 2009).

1.3 Evaluating incidence

Most AML patients are previously healthy and have *de novo* disease (Juliusson et al. 2009), but one third have previously received chemoradiotherapy for another malignant or non-malignant disease (t-AML), or have transformed from another hematologic disease (Figure 1.4), typically myelodysplastic syndrome (MDS) or myeloproliferative neoplasia (MPN) (Chapter 2). The epidemiology of AML, including incidence and outcome, is therefore dependent on diagnostic criteria, which have changed.

Biologically and clinically, there is a continuum between high risk MDS and AML with myelodysplasia-related changes, according to WHO (Swerdlow et al. 2017). These entities have genetic features in common (Lindsley et al. 2015), and whereas some genetic markers, such as *FLT3*-ITD and *NPM1*-mutations, present late in the development of AML and therefore indicate *de novo* AML (Abelson et al. 2018), others are common in both AML and MDS. Historically, the boundary between MDS and AML have been the percentage of leukemic blasts in blood and/or bone marrow. Up to 2002 patients with less than 30% blasts were diagnosed as MDS, but this borderline was subsequently lowered (Vardiman et al. 2002) so AML became defined by 20% blasts or more, with some exceptions. However, WHO states: “It is important to recognize that the threshold of 20% blasts distinguishing AML from MDS does not reflect a therapeutic mandate to treat cases with $\geq$20% blasts as acute leukemia” (Swerdlow et al. 2017, page 98). In Sweden, one fourth of the AML patients are now reported with <30% marrow blasts at diagnosis. This change of diagnostic criteria penetrated

gradually into the clinic, and no clear-cut rise in the incidence was seen in the early 2000's, but it adds to the complexity of interpreting incidence data. Furthermore, secondary AML has often been excluded from clinical trials, and was not reported to SEER before 2010 (Polednak 2014).

Another epidemiologic hazard is to distinguish if high risk MDS patients actually have fulfilled criteria for AML transformation. It is common that late-stage MDS patients deteriorate with or without increasing white blood cell counts and appearance of circulating blasts, and abstention of full diagnostics in patients not eligible for specific treatment is common and clinically relevant. The variation of median ages at diagnosis of AML in different countries with similar life expectancy of the general population might also be due to different clinical routines among the very elderly (Lazarevic et al. 2018).

Secondary AML is rare in younger patients. Since MDS is most common among older males a transformation of MDS to AML is also more common in males. In contrast, t-AML is more common in females, since chemoradiotherapy for breast cancer is a common background (Hulegårdh et al. 2015, Nilsson et al. 2020). The incidence of t-AML is dependent on the type and intensity of chemoradiotherapy given, the number of such patients treated, and their long-term survival. In the 1970's Hodgkin's lymphoma was treated with multiple alkylating agents (including nitrogen mustard) and large-field radiotherapy, leading to frequent cures of lymphoma but a high risk of therapy-related myeloid neoplasia (t-MN). With improved Hodgkin therapy this risk decreased considerably already in the 1980's. Today, successful treatments of lymphomas and advanced breast cancer that still include alkylating agents and topoisomerase II-inhibitors seem to induce an increased proportion of t-AML (Nilsson et al. 2020).

1.4 Incidence of special genetic subtypes

AML can be associated with a large number of different driver mutations, with different clinical impact. AML patients with rearrangement of *KMT2A* (previously named *MLL*) at 11q23 are younger (median age 20 years), and have poor prognosis, whereas those with core-binding factor AML [t(8;21)(q22;q22.1), *RUNX1-RUNX1T1*; and inv(16)(p13.1q22), *CBFB-MYH11*] also are young (median 45 years) (Roman et al. 2016) but have better prognosis. In contrast, those with MDS-related abnormalities [del(5q); monosomy 7, complex karyotypes, and more] are older and have poor prognosis. The concept of age-related clonal hematopoiesis (ARCH), with certain gene mutations in hematopoietic stem cells that when expanded with age may predispose to AML (Shlush 2018, Abelson et al. 2018), is an important development shedding light on AML pathophysiology.

A rare specific AML subtype is acute promyelocytic leukemia (APL) (Chapter 6), characterized by the *PML-RARA* hybrid gene, leading to AML with impaired hemostasis. Due to the high sensitivity of APL cells to the differentiating agents all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) the long-term clinical outcome is favorable, with minimal need for chemotherapy and usually no indication for stem cell transplantation. Of interest is the great variation in incidence of APL between European countries, from 0.26 per 100,000 and year in Spain and Iceland to tenfold less in other countries, many of them in eastern Europe (Dinmohamed and Visser 2019); in Sweden the crude incidence of APL is 0.2 per 100,000 and year. The median age of APL is lower than that of most other AML subsets, in Sweden 58 years (quartile range 43-69 years), but still the incidence increases with age (Figure 1.5). Despite therapeutic improvements, the early death rate remains high in older patients (Lehmann et al. 2017). It seems likely that still not all APL patients are diagnosed and reported properly.

1.5 Survival

Survival of AML patients is highly dependent upon age (Figure 1.6), genetic subtype (Döhner et al. 2015, Chapter 5), performance status (Juliusson et al. 2009), comorbidity and previous diseases (Hulegårdh et al. 2015). Survival has improved during recent decades, mostly for males in ages 50-75 years (Juliusson et al. 2019), in part due to greater use of allogeneic stem cell transplantation. Females have longer survival in most populations, both overall and with various cancer diseases, but currently the survival of AML in Sweden is independent of sex (Juliusson et al. 2019).

1.6 Etiology

Genomic instability is a hallmark of cancer. So far, the reason for this instability is largely unclear, but it is generally assumed that aberrations simply arise in a stochastic manner. The "two-hit hypothesis" of leukemogenesis implies that AML is the consequence of two or more mutations, one conferring a proliferative advantage (class I mutations) and another impairing hematopoietic differentiation (class II mutations) (Reilly et al. 2005). Type I mutations include those of *FLT3*-ITD, *KRAS* and *KIT* mutations, while fusions involving core binding factors (CBF) and mutations in *CEBPA* are type II abnormalities (Bachas et al. 2010). However, this model does not account for the wide spectrum of more recently described somatic alterations, nor do all patients carry class I and class II mutations.

The pathogenesis of AML is characterized by serial acquisition of somatic mutations and several genes are recurrently mutated (Jaiswal and Ebert 2019). Most mutations are inconsequential, and some passenger mutations may have neutral effects, while others clearly give rise to proliferative advantage, thereby increasing the risk of malignant transition (Cypris et al. 2019). Furthermore, aging is associated with a steady increase in the number of somatic mutations in nearly all tissues (Blokzij et al. 2016).

In contrast to genomic changes, epigenetic aberrations do not involve alterations in the DNA sequence. Dynamic modification of DNA and DNA binding proteins play a crucial role in the regulation of gene expression, chromatin accessibility, and nuclear architecture and it is postulated that age-related epigenetics can trigger leukemogenesis (Bocker et al. 2011, Jaiswal and Ebert 2019). Causes and risk factors for developing AML are listed in Table 1.1.

1.6.1 External physical and chemical exposures

Occupational exposures have decreased substantially in developed countries during the last decades due to an increased awareness of chemical and mutagenic hazards and new regulations reducing exposures at workplaces. Thus, occupational exposure as a role for AML etiology has decreased but may still play a role in many parts of the world.

Benzene is probably the strongest carcinogen associated with leukemogenesis (Snyder 2012). In a recent laboratory study, hydroquinone, the major metabolite of benzene in humans, increased expression of the p53 protein, increased apoptosis and induced DNA double strand breaks in human bone marrow stem cells as well as decreased stem cell differentiation and proliferation (Fircanis et al. 2014). A limited list of the toxic agents found in cigarette smoke includes benzene, formaldehyde, polonium 210, arsenic, lead, and ammonia. Interestingly, in this study yolk sac stem cells seemed to be especially sensitive to the effects of hydroquinone, which is supported by evidence that exposure to smoking during pregnancy increases the risk of leukemia during childhood (Mucci et al. 2004).

A positive association between domestic pesticide exposure and childhood leukemia is confirmed with statistically significant increased risks were observed for all types of leukemia, and specifically for exposure during pregnancy, indoor exposure, prenatal exposure to insecticides and whatever the age at diagnosis. The highest increased risks were observed for AML among children aged 2 years or less, as well as for unspecified leukemia type observed after prenatal indoor exposure. Although the literature provides moderate to low-quality of evidence, these new results further justify the need of limiting the use of household pesticides during pregnancy and childhood (Van Maele-Fabry et al. 2019).

Excess mortality from lymphohematopoietic malignancies, in particular myeloid leukemia, and brain cancer has been found in surveys of anatomists, pathologists, and funeral industry workers, all of whom may have worked with formaldehyde (Hauptmann et al. 2009).

Ionizing radiation and alkylating agents share the ability to induce DNA damage, usually through double strand breaks that may cause the mutations, deletions, or translocations required for hematopoietic stem cell transformation. A recent meta-analysis found an increased risk of leukemia among workers receiving protracted exposure to low-dose gamma radiation (Daniels et al. 2011). On the other hand, a study in radiology technologists identified an increased risk of leukemia among workers employed before 1950, when radiation exposures were higher. However, there was no convincing evidence of an increased risk of leukemia in medical radiation workers exposed to current levels of radiation (Yoshinaga et al. 1994). In a cohort of 308,297 radiation-monitored workers employed for at least 1 year by the Atomic Energy Commission, AREVA Nuclear Cycle, or the National Electricity Company in France, the Departments of Energy and Defence in the USA, and nuclear industry employers included in the National Registry for Radiation Workers in the UK showed strong evidence of positive associations between protracted low-dose radiation exposure and leukemia (Leuraud et al. 2015). Patients developing a therapy-related myeloid neoplasm (t-MN) after radioiodine treatment usually present with biological characteristics similar to those seen in patients with t-MN following other cytotoxic treatment modalities, associated with a low response rate to induction chemotherapy and poor prognosis. Karyotype was abnormal in 68% of patients, with chromosomes 7 (30%), 5 (26%), 8 (26%) and 3 (17%) being most frequently affected (Schroeder et al. 2012). t-MN after radiotherapy alone bears striking clinical and cytogenetic similarities to alkylator-associated t-MN, with frequent clonal abnormalities of chromosomes 5 and 7, relatively long latency, and poor outcomes even with intensive therapy (Nardi et al. 2012). However, some patients who develop t-MN after radiotherapy alone have recurring, balanced chromosomal translocations or normal karyotypes, and they have a better response to antileukemia treatment and longer survival. It confirms that cytogenetics, not just previous therapies, determines the course of t-MN (Kayser et al. 2011).

1.6.2 Chemotherapy agents

The development of MDS and AML following chemotherapy for a variety of malignancies (e.g., breast cancer, Hodgkin's lymphoma) is an unfortunate complication of curative treatment strategies, such as dose-intensive therapy with or without hematopoietic cell transplantation and growth factor support

(Stone et al. 1994). This identification of an increasing incidence of t-AML in an attempt to improve cure rates emphasizes the critical importance of understanding the underlying pathogenetic mechanisms for development of t-AML (Seedhouse et al. 2007). t-AML typically develops following alkylating agent-induced damage, at a median of three to five years following therapy for the primary malignancy, and is usually associated with an antecedent myelodysplastic disorder (Le Beau et al. 1986). This latency period suggests that multiple mutational events are involved in the development of the malignant phenotype (Schantz et al. 2018). However, increasing evidence points to the importance of selection pressure by chemotherapy conferring survival advantage of preexisting minimal mutated clones (such as *TP53* mutations) present already at the start of the treatment for the primary disease (Wong et al. 2015). Clonal chromosomal abnormalities have been reported in the majority of cases of t-AML. The most frequently reported abnormalities involve complete loss or interstitial deletions of the long arm of chromosomes 7 and/or 5. Other therapy-related leukemias are associated with rearrangements of the *MLL* (*KTM2A*) gene in chromosome band 11q23 (Thirman et al. 1993). AML associated with 11q23 often develops after treatment with drugs that target DNA-topoisomerase II (e.g., epipodophyllotoxins, anthracyclines) with a short latency of 12 to 18 months following treatment, and typically not associated with an antecedent MDS (Pedersen-Bjergaard et al. 1991). Typical lesions are reciprocal translocations, such as t(9;11)(p21;q23) and t(11;19)(q23;p13); other translocations that do not involve the *MLL* locus have also been described, including the t(15;17), t(8;21), and inv(16) rearrangements. The risk of t-AML varies based on the chemotherapy dosing schedule, cumulative dose received, additional cytotoxic agents, and underlying disease characteristics, but generally does not exceed 5% of patients treated with topoisomerase II inhibitors. Accelerated telomere loss may precede the development of t-MN after autologous hematopoietic cell transplantation resulting in genetic instability and thereby contributing to the leukemic transformation (Chakraborty et al. 2009). Genetic polymorphisms of a number of drug-metabolizing enzymes may alter the risk of t-AML. As an example, polymorphisms in genes that encode glutathione S-transferases (GST), which detoxify potentially mutagenic chemotherapeutic agents, may increase susceptibility to t-AML as well as MDS. In one study, relative to *de novo* AML, the GSTP1 codon 105 Val allele occurred more often among patients with t-AML with prior exposure to chemotherapy, particularly those with exposure to known GSTP1 substrates (odds ratio 4.3; 95% CI 1.4-13), and not among t-AML patients with prior exposure to radiotherapy alone (Allan et al. 2001). DNA-damaging chemotherapy carries ~1% risk of t-MN, often harboring complex karyotypes and *TP53* mutations (Gillis et al. 2017). Preexisting clonal hematopoiesis (CHIP) at the time of start of chemotherapy for a primary malignancy significantly increases the risk of developing t-MN (Takahashi et al. 2017). CHIP after chemotherapy is likely related to a competitive advantage of pre-existing (possibly multiple) clones after the stress of chemotherapy or an altered immune microenvironment, rather than a direct mutagenic effect.

Previously treated patients have increased rates of clonal hematopoiesis (CH), with enrichment of mutations in DNA Damage Response (DDR) genes (*TP53, PPM1D, CHEK2*). Exposure to radiation, platinum and topoisomerase II inhibitors have the strongest association with CH with evidence of dose-dependence and gene-treatment interactions. In patients who progressed to t-MN, the clone at CH demarcated the dominant clone at t-MN diagnosis (Bolton et al. 2019).

There is some evidence of association between AML and treatment with other drugs. In a large population with primary autoimmune diseases, azathioprine exposure was associated with a 7-fold risk for myeloid neoplasm (Ertz-Archambault et al. 2017). There are still controversies if the use of taxanes, e.g paclitaxel, increases the risk of AML as well as the use of G-CSF for SCN or low-dose of methotrexate for rheumatoid arthritis (RA) (Bhatnagar et al. 2016). High frequency of CH in cancer patients suggests that screening for CH prior to initiation of oncologic therapy may be feasible and may represent an avenue for molecularly based early detection and interception (Bolton et al. 2019).

1.6.3 Myeloid neoplasms with germline predisposition

(this paragraph is likely to be covered in Chapter 2, and might therefore be deleted in this chapter)

Germline *CEBPA* mutations are inherited in an autosomal dominant fashion and highly penetrant. The age of onset for AML with germline *CEBPA* mutations is younger than for sporadic AML, with a median of 24.5 years (range 1.75–46 years) in ten affected families (Tawana et al. 2015). AML patients with *CEBPA* mutations have a favorable clinical outcome that is limited to those with double mutations. Interestingly, individuals with germline *CEBPA* mutation–associated AML may recur with a different somatic *CEBPA* mutation, whereas in sporadic AML the *CEBPA* mutation appears stable throughout the disease course. Although the recurrence is triggered by independent clones, the patients can still achieve a durable response to therapy and favorable long-term outcome.

Myeloid neoplasms with germ line *DDX41* mutation. Similar to AML with biallelic *CEBPA* mutations, the presence of *DDX41* germline mutation predisposes acquisition of additional *DDX41* somatic mutation on the other allele. Detection of biallelic *DDX41* mutations is strongly supportive of a predisposing germline *DDX41* variant. The most common acquired somatic mutation is *DDX41* c.G1574A (p.R525H) which occurs in a highly conserved C-terminal motif affecting ATP-binding site. The p.R525H mutation has also previously been reported at the time of progression to MDS or AML. The p.R164W mutation is associated with a predisposition to lymphoproliferative neoplasms, particularly follicular lymphoma. Lewinsohn et al. (2016) reported that 3 of their 9 families with *DDX41* germline mutations had granulomatous immune disorder, raising the possibility of *DDX41* functions in

immune response and their potential link to the lymphoid malignancy in affected pedigrees. In contrast to other myeloid neoplasms with germline predisposition, patients with *DDX41* germline mutation have long latency to develop myeloid neoplasm, with a mean age at diagnosis of 62 years, more similar to that of patients with sporadic AML/MDS. *DDX41* mutations are relatively common in adult MDS/AML (2.4%), often without known family history. Salient features of *DDX41*-related myeloid malignancies include male preponderance (79%), frequent preexisting cytopenia, additional somatic *DDX41* mutation, and relatively good outcome (Sébert et al. 2019).

Myeloid neoplasms with germ line *RUNX1* mutation is reported in families with platelet disorder that was previously called familial platelet disorder with propensity to myeloid malignancies. These patients are characterized by lifelong history of mild to moderate thrombocytopenia, mild bleeding tendency, and an increased lifetime risk of developing MDS or AML. The familial platelet disorder is inherited in an autosomal dominant fashion. There is also mild platelet aggregation defect with collagen and epinephrine, similar to abnormalities caused by aspirin. Carriers of germline *RUNX1* mutations have an increased lifetime risk (35%–40%) of developing MDS or acute leukemia, with an average age at diagnosis of 33 years (range, 6–76 years). However, there is clinical heterogeneity in the degree of platelet disorder as well as the varying risks of developing MDS and AML manifested with a large range of prevalence of myeloid malignancy among affected families. In addition to myeloid neoplasm, development of T-lymphoblastic leukemia/lymphoma has also been reported in the context of familial platelet disorder with *RUNX1* mutation. AML secondary to familial platelet disorder has a high frequency of biallelic alteration in the *RUNX1* gene, indicating acquisition of additional genetic events involving the other nonmutated *RUNX1* cooperative genes during progression to AML. There is no clear association of *RUNX1* mutational status with morphologic subtype of AML. Cytogenetic analyses have reported trisomy 21, monosomy 5 and 5q deletion in AML in the context of familial platelet disorder (Gao et al. 2019).

Myeloid neoplasms with germ line *ANKRD26* mutation present with thrombocytopenia, previously called thrombocytopenia 2 and are characterized by moderate thrombocytopenia with normal platelet size, no or very mild spontaneous bleeding, and predisposition to developing myeloid neoplasm. It is inherited in an autosomal dominant manner. All individuals reported to date have an affected parent. Each child of an individual with *ANKRD26*-related thrombocytopenia has a 50% chance of inheriting the *ANKRD26* pathogenic variant. Once the *ANKRD26* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible; however, phenotypic variability (due to variable expressivity) within families is

observed. Recognition of this insidious form of inherited thrombocytopenia and its associated risk for myeloid neoplasm is important, as these cases may be inappropriately managed as idiopathic thrombocytopenia purpura and treated with steroids or splenectomy or misdiagnosed as MDS (Gao et al. 2019).

Myeloid neoplasms with germ line *ETV6* mutation is another autosomal dominant familial thrombocytopenia, previously referred to as thrombocytopenia 5. The *ETV6* gene is located on the short arm of chromosome 12. *ETV6* encodes a transcriptional repressor critical for hematopoiesis, megakaryopoiesis, and embryonic development. Germline *ETV6* mutations are typically located in the DNA binding ETS domain and result in autosomal dominant inhibition of *ETV6* function through dimerization. Individuals carrying germline *ETV6* mutations have increased risks for hematologic malignancies, including AML, MDS, chronic myelomonocytic leukemia, B-lymphoblastic leukemia, and myeloma. Data are scant on disease penetrance. Thus far, the numbers of total patients reported is too few to ascertain associated syndromic features (Kennedy and Shimamura 2019).

Myeloid neoplasms with germ line *GATA2* mutation have the broad phenotypic spectrum and may present with MonoMac syndrome or Emberger syndrome. However, germline *GATA2* mutations may also present with isolated neutropenia or bone marrow failure without syndromic features or family history. The bone marrow histology in *GATA2* deficiency is typically hypocellular and may manifest characteristic megakaryocyte dysmorphologies with micronuclei or splayed nuclei. Additional findings include monocytopenia and immunologic abnormalities. MDS with germline *GATA2* mutations is frequently associated with monosomy 7/del(7q) or trisomy 8, particularly in children and younger adults. A study of 426 cases of pediatric MDS identified germline GATA2 mutations in 37% of patients with primary MDS with monosomy 7 and in 16% of MDS cases with trisomy 8. Germline GATA2 mutations were identified in 72% of adolescents with MDS and monosomy 7 (Kennedy and Shimamura 2019).

Myeloid neoplasms associated with bone marrow failure syndromes. These entities include dyskeratosis congenita, Diamond-Blackfan anemia, Fanconi anemia, Shwachman-Diamond syndrome and severe congenital neutropenia. These conditions are often diagnosed in childhood, if classical physical findings are absent diagnosis in adulthood is often delayed due to decreased awareness among practitioners (Gao et al. 2019).

Myeloid neoplasms associated with telomere biology disorders. Telomere disorders with germline *TERC* and *TERT* mutations have an autosomal dominant inheritance pattern with variable clinical presentations. The *TERT* and *TERC* mutation carriers may present with essentially normal complete blood cell count with only subtle abnormalities, such as elevated mean corpuscular volume or thrombocytopenia, before developing bone marrow failure. Some patients may have idiopathic pulmonary fibrosis or liver fibrosis. The co-occurrence of aplastic anemia and idiopathic pulmonary fibrosis is considered quite predictive for germline telomerase gene mutation. Bone marrow biopsy may show moderately increased reticulin fibrosis, notable myeloid dysplasia, and megakaryocytic lineages characterized by predominantly small, hypolobated, dysplastic-appearing forms. The affected families may have anticipation with progressive shortening of the telomeres in passing generations and show worsening phenotype. In addition to predisposition to MDS/AML, the telomere disorders may be associated with a variety of solid tumors, including squamous cell carcinoma and stomach, lung, esophageal, and colon cancers. Patients are sensitive to toxicities from chemotherapy and radiation and warrant specially tailored transplant regimens.

JMML associated with neurofibromatosis. Neurofibromatosis type 1 (*NF1*) is a hereditary condition commonly associated with multiple café-au-lait spots on the skin. About 10% to 25% of the general population has café-au-lait spots; *NF1* is suspected when a person has 6 or more. People with *NF1* also tend to develop varying numbers of neurofibromas, meaning benign (noncancerous) tumors on the covering of the nerves. The association between hematologic malignancies and germ-line mutations of *NF1* has been established in the pediatric setting. Children with neurofibromatosis 1 have a 500-fold increased risk of developing a rare form of leukemia, known as juvenile myelomonocytic leukemia (JMML); a higher incidence of non-Hodgkin's lymphoma and acute lymphoblastic leukemia has also been reported. *NF1* is a tumor suppressor gene localized on 17q11.2. It encodes neurofibromin, a negative regulator of proto-oncogene RAS. The loss of neurofibromin promotes RAS activity leading to constitutive downstream signaling and increased uncontrolled cell growth. Hyperproliferation is a mechanism that involves every organ system leading to the predisposition for both cancerous and non-cancerous disorders. It is at the base of the so-called RAS-opathies, a group of inherited disorders that share a germ-line mutation of the RAS-MAPK pathway, to which *NF1* belongs. Given the incidence of neurofibromatosis type 1 in the population (1/3000), and that of AML, more studies are needed to establish a direct connection between the AML and Neurofibromatosis type 1.

Noonan syndrome or Noonan syndrome-like disorders. Noonan syndrome (NS) is an autosomal dominant developmental disorder characterized by short stature, facial dysmorphisms and congenital

heart defects. Six cancer types have previously been reported in the literature in patients with NS and a *PTPN11* mutation, that is, JMML, neuroblastoma, ALL, non-Hodgkin lymphoma, glioma and breast cancer. A JMML-like myeloproliferative disorder has been described in neonates with NS and the *PTPN11* mutation. The disorder often regresses spontaneously, but fatal complications may occur. Other mutations that can cause hematological malignancies are *SOS1, RAF1, KRAS, NRAS, BRAF, MAP2K1*. CBL syndrome (more formally known as "Noonan-syndrome-like disorder with or without JMML") has overlapping features to Noonan syndrome with significant variability. CBL syndrome and other RASopathy disorders, including Noonan syndrome, neurofibromatosis 1, and Costello syndrome, are important to recognize as these are associated with a cancer-predisposition. CBL syndrome carries a very high risk for JMML (Jongmans et al. 2011).

Myeloid neoplasms associated with Down syndrome. Down syndrome is caused by trisomy 21 and is associated with an approximately 10–20-fold elevated relative risk of AML and MDS compared with the general population, and in particular an increased risk for acute megakaryocytic leukemia, FAB M7 (Schand 2017). Infants with Down syndrome may experience transient abnormal myelopoiesis (TAM), where circulating peripheral blood blasts are seen and may be accompanied by hepatic dysfunction, effusions, and rash; this occurs in approximately 10% of these patients. The majority of TAM cases harbor somatic mutations in *GATA1*, resulting in altered function of this transcription factor that plays an important role in hematopoietic cell maturation, particularly in the megakaryocyte lineage. Decreased *GATA1* expression results in megakaryocyte proliferation. Indeed, up to 30% of persons with TAM will progress to AML, commonly acute megakaryocytic leukemia. The development of AML in patients with Down syndrome likely relates both to acquired somatic mutations, such as *GATA1*, and also the presence of additional copies of genes on chromosome 21 that facilitate leukemogenesis, such as the oncogenes *RUNX1*, *ERG*, and *ETS2* (Brunner and Graubert 2018).

Newly discovered hereditary predisposition syndromes include, for example, *SAMD9* and *SAMD9L* mutations which give rise to myeloid malignancies with chromosome 7 involvement in combination with neurological symptoms; in severe case, they manifest as MIRAGE syndrome (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, enteropathy). Patients with germline *SAMD9* or *SAMD9L* mutations have a propensity to develop clones that have lost or inactivated the mutant SAMD9/SAMD9L allele. The mechanisms of this adaptation can be through truncating or loss of function mutations in cis with the mutant *SAMD9* or *SAMD9L* allele, or through genetic reversion through duplication of the wild-type allele. Improvement in blood counts has been observed to accompany this somatic inactivation of the mutant *SAMD9/SAMD9L* allele. A second strategy to eliminate the mutant gene is to delete all or part of chromosome 7 carrying the

mutant *SAMD9/SAMD9L* allele. Although this is predicted to result in improved cell growth, this comes at the cost of promoting development of MDS with monosomy 7 (Tesi B et al. 2017).

1.6.4 Other inherited diseases with predisposition to AML

Klinefelter´s syndrome is characterized by an extra chromosome X in boys/men; the 47,XXY karyotype associated with hypogonadism and infertility, and an increased risk for developing breast cancer, non-Hodgkin lymphoma and lung cancer. Despite claims that Klinefelter´s syndrome (KS) (Deschler and Lübbert 2006, Keung et al. 2002) increases the risk of having ALL, MDS and AML, studies to date have not definitively established an epidemiological link. Intriguingly, almost half the cases of AML with KS occurred in the pediatric population (≤18 years old at diagnosis), and no cases were diagnosed over the age of 64, in contrast to AML in general. These observations raise the question of whether KS, like certain other constitutional abnormalities, may predispose to an earlier onset of AML.

Fanconi anemia (FA) is the most common inherited bone marrow failure disorder and is caused by germline mutations in factors involved in DNA repair. FA is characterized by physical abnormalities present in 60%–75% of affected individuals, most often presenting with short stature and skeletal abnormalities, bone marrow failure, and a propensity to develop malignancy. FA mutations are inherited generally in an autosomal recessive manner, or as an X-linked trait for pathogenic variants in *FANCB*. Causative mutations in at least 21 genes are responsible for the FA complementation groups. The estimated cumulative incidence of bone marrow failure is 50%–90% by age 40, and the cumulative incidences of MDS, AML, and solid tumor malignancies are 30%, 10%, and 30%, respectively (Godley and Shimamura 2017).

Li-Fraumeni syndrome (LFS) is a rare cancer predisposing condition caused by germline mutations in *TP53*, the gene encoding the p53 transcription factor. LFS is typified by the development of a wide spectrum of childhood and adult onset malignancies, which includes, among others, the lymphoid and myeloid leukemias, myelodysplastic syndrome and, to a lesser extent, lymphoma. The distribution of *TP53* germline mutations in LFS is similar those identified in tumours, with the majority clustered within the DNA binding domain where there are six recurrent 'hotspot' mutations involving different codons. The published literature as to whether the presence of a germline *TP53* mutation confers a poorer prognosis in patients with haematopoietic cancers is limited. Similarly, there is little information

regarding the optimal treatment approaches for primary or therapy-related disease in germline *TP53* mutation carriers. At present, it is not clear whether treatment regimens should be altered to avoid or reduce exposure to DNA damaging chemotherapeutic agents, as is done with patients who have FA or Ataxia Telangiectasia (Swaminathan et al. 2019). In addition, t-MN including MDS and AML are common in patients with LFS and portend a dismal prognosis with standard therapies and even allogenic SCT (Valdez et al. 2017).

Bloom syndrome (BS) is a rare genetic disorder characterized by short stature, increased skin sensitivity to ultraviolet rays from the sun (photosensitivity), multiple small dilated blood vessels (telangiectasia) over the nose and cheeks resembling a butterfly in shape, mild immune deficiency with increased susceptibility to infections, and most importantly, a markedly increased susceptibility to many types of cancer, especially leukemia, lymphoma and gastrointestinal tract tumors. Bloom syndrome is a prototype of a group of genetic conditions known as chromosome breakage syndromes. The genetic abnormality in Bloom syndrome causes problems with DNA repair, resulting in a high number of chromosome breaks and rearrangements. The abnormal DNA repair is responsible for the increased risk for cancer. Bloom syndrome is inherited as an autosomal recessive genetic trait. The causative gene has been mapped to chromosomal locus 15q26.1 and is responsible for encoding a protein known as BLM. A single mutation, known as *BLMAsh*, is responsible for almost all cases of Bloom syndrome among Ashkenazi Jews. Analogous to Fanconi anemia, a preferential occurrence of monosomy 7 or del(7q) was found in bone marrow cells from Bloom syndrome patients with MDS or AML.

Nijmegen breakage syndrome (NBS) is a rare genetic disease presenting at birth with microcephaly and dysmorphic facial features that become more noticeable with age, growth delay, and later-onset complications such as malignancies and infections. NBS is caused by mutations in the *NBN* gene (8q21-q24) which lead to partially functional truncated fragments of nibrin, the gene product involved in repairing DNA double strand breaks. There is no specific treatment for NBS. Subjects should be evaluated for immunodeficiency and treated as appropriate. Parents and caregivers should be counseled about the presenting signs of lymphoma and other malignancies. Radiation therapy should be avoided, if possible. Hematopoietic cell transplantation (HCT) is an option for selected patients.

Constitutional mismatch repair deficiency syndrome (CMMRD) refers to patients and families with a germline mutation in one of the DNA mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) or the *EPCAM* gene. It is the most common cause of inherited colorectal cancer. While leukemia is not a typical malignancy seen in Lynch syndrome, there is a variant of this disorder that presents with similar features to *NF1* called mismatch repair deficiency syndrome, which is caused by homozygous mutations in one of four mismatch repair genes: *MLH1, MSH2, MSH6,* or *PMS2*. Café-au-lait spots, brain tumors, colorectal cancer, osteosarcoma, and other solid tumors are some clinical characteristics. Lifetime risk for myeloid malignancies is unknown, there is a risk ~30% for developing lymphoma/ALL.

Ataxia telangiectasia (AT) is an autosomal recessive neurodegenerative disorder characterized by progressive ataxia, ocular telangiectasias, immune dysregulation, and a predisposition to lymphoreticular malignancies. Associated features include pulmonary disease, an increased incidence of malignancy, radiation sensitivity, growth retardation, and diabetes mellitus caused by insulin resistance. Patients with AT are either homozygous or compound heterozygotes for mutations in the gene ataxia telangiectasia mutated (*ATM*) located on 11q22.3 that results in truncated proteins in the majority of families with AT. The greatest risk, however, is in patients with biallelic germline mutations who are at increased risk of developing lymphoma and leukemia with observed/expected ratios of between 50 and 750. When treating leukemia in patients with AT, it is important to remember that ionizing radiation can carry exquisite toxicity in these patients owing to their impaired DNA repair pathway (Brown AL et al. 2017).

Werner's syndrome (WS) is an autosomal recessive genetic disease, which is mainly characterized by scleroderma-like skin changes, juvenile cataracts, short stature, and signs of premature aging. The mutated gene is called *WRN (RECQL2)* located at chromosome 8p12, but the risk for developing AML is still unknown (Seiter 2005).

Severe congenital neutropenia (SCN) encompasses a diverse range of disorders, including Kostmann syndrome which is generally manifest in infants with recurrent infections (Kostmann 1956). The most common form of the disease is autosomal dominant and is related to *ELA2*, which encodes for neutrophil elastase, a serine proteinase involved in neutrophilic function. Recently, several other mutations in genes including *HAX1, G6PC3, GFI1, GATA2*, and *WASP* have all been implicated in SCN.

The latest data on the long-term risk of developing a myeloid malignancy in this population is 2.3% per year after the first decade (Dale et al. 2000, Klein 2011).

Dyskeratosis congenita (DKC) is a bone marrow failure syndrome characterized by inherited mutations in the telomere maintenance pathway. DKC can be inherited in an autosomal dominant, autosomal recessive, or X-linked recessive pattern. Mutations in *TERT*, *DKC1*, *TERC*, or *TINF2* account for most cases. Typical findings among patients with DKC include the "triad" of skin hyperpigmentation, nail dystrophy, and oral leukoplakia, and these patients will typically develop bone marrow failure by 20–30 years of age. As a result of the underlying mutation, patients have markedly shortened telomeres, which contribute to bone marrow failure, as well as damage to other organs including pulmonary fibrosis and hepatic cirrhosis. Compared with the normal rate of telomere shortening in unaffected individuals of approximately 60 bp per year, individuals with telomere disorders lose telomeric DNA at approximately 120 bp per year. Transformation to AML occurs in approximately 10% of patients and is thought to occur via genomic instability related to shortened telomeres and associated DNA damage, resulting in dysplasia and an increased risk of hematopoietic malignancy (Brunner and Graubert 2018).

Schwachman-Diamond syndrome (SDS) is an autosomal recessive disorder caused by mutations in the *SBDS* gene, located on the long arm of chromosome 7 (7q11.21). The exact function of *SBDS* is unknown but involvement in RNA processing and building of ribosomes is suggested. Hematopoietic manifestations of SDS most often include isolated neutropenia, although many patients will eventually develop pancytopenia which may progress to aplastic anemia. AML or MDS occurs in up to a third of patients by 30 years of age and is thought to relate to chromosomal instability and accelerated rates of apoptosis, which may be due to the role of *SBDS* in stabilizing the mitotic spindle during mitosis. Common cytogenetic abnormalities include monosomy 7, isochromosome 7, and deletion of 20q. Mutations of the tumor suppressor gene, *TP53*, may contribute to the development of MDS and AML in SDS. Hematopoietic cell transplantation should be discussed when clear evidence of progressive myelodysplasia is present and before AML develops (Brunner and Graubert 2018).

Diamond-Blackfan anemia (DBA) is characterized by red cell aplasia and typically spares the leukocyte and platelet lineages. DBA is typically inherited in an autosomal dominant fashion and is associated with mutations in a number of ribosomal proteins. The gene encoding ribosomal protein 19 (*RPS19*), located at 19q13.2, is mutated in 25 percent of patients with DBA. Disease-causing mutations in genes

encoding the large (*RPL35A, RPL5, RPL11, RPL27*) and small (*RPS24, RPS17, RPS7, RPS10, RPS26, RPS27, RPS29*) ribosomal subunits have been described. Defects in ribosome function result in anemia early in life and patients with DBA may have characteristic skeletal anomalies, including craniofacial defects, and at times the classic triphalangeal thumb; this anemia is often steroid responsive, but many eventually require chronic transfusional support and hematopoietic cell transplantation. AML can occur in up to 20% of patients and typically occurs after 40 years of age. Although an HLA-matched sibling is the preferred donor for a patient with DBA requiring HCT, one must ensure that the donor does not also carry the same DBA defect as the patient (Brunner and Graubert 2018).

Congenital amegakaryocytic thrombocytopenia (CAMT) and **thrombocytopenia with absent radii** (TAR) syndrome are both characterized by hypoplastic thrombocytopenia. CAMT is inherited in an autosomal recessive manner via mutations in the *MPL* gene, which encodes the receptor for thrombopoietin (TPO). Patients have concomitant elevations in serum TPO levels, and thrombocytopenia from birth, which typically progresses to aplasia. CAMT is associated with an increased incidence of AML, typically in the second decade of life. While CAMT does not have phenotypic manifestations outside of thrombocytopenia, TAR syndrome is also associated with thrombocytopenia at birth, as well as characteristic absence of the radii. TAR syndrome has been associated with mutations in *RBM8A*, which is involved in messenger RNA (mRNA) splicing. The thrombocytopenia in TAR syndrome often improves over time; both acute lymphoblastic leukemia and AML have been reported among patients with this rare disorder (Brunner and Graubert 2018).

1.6.5 Clonal Hematopoiesis

Clonal hematopoiesis (CH) has a role as a predisposition factor to AML. CH can be defined as the presence of clonal leukemia-associated somatic mutations in leukocytes from apparently healthy individuals that increases the risk to transform into malignant myeloid disease and is frequently related to stem cell depletion or exhaustion in the elderly (>65 years) (Babushok et al. 2016, Valent et al. 2019). CH of indeterminate potential (CHIP), alternatively named age-related CH (ARCH) (Shlush 2018), is a clinical entity defined by the presence of a cancer-associated clonal mutation in at least 4% of nucleated blood cells of individuals without frank neoplasia. However, these somatic clones do not always lead to overt disease, and instead can remain dormant in a preleukemic state. Mutations in genes involved in epigenetic regulation (*DNMT3A*, *TET2*, *ASXL1*) account for the majority of mutation-driven CH in humans. These mutations are rare in the young but highly prevalent in the elderly, with

between 10 and 20% of those older than age 70 harboring a clone of appreciable size (Genovese et al. 2014). Two recently published retrospective studies have dealt with the question whether one can predict the onset of AML within the general population. A predictive AML 'prodrome' could be identified by molecular genetic screening and the laboratory parameter of red cell distribution width (Abelson et al. 2018, Desai et al. 2018, Shlush 2018). To reflect this, a new model has been proposed that differentiates CH into CH of indeterminate potential (CHIP) and CH of oncogenic potential (CHOP), based on the type and function of the acquired somatic variants and their subsequent risk to transform into AML (Valent et al. 2019). Thus, CHIP mutations create a background conducive to the development of malignancy, but patients harbouring these variants have only a slightly elevated risk of myeloid transformation compared to controls (Genovese et al. 2014, Steensma et al 2015, Sperling et al. 2017, Valent et al. 2019). On the other hand, CHOP mutations are associated with disease progression playing a role in differentiation and/or proliferation of neoplastic cells, and many individuals with these mutations will develop a myeloid malignancy in their lifetime after a variable latency period (Valent et al. 2019). CHOP mutations are indicative of a high risk of malignant transformation with variable outcome determined by secondary driver lesions, the prognostic impact of CHIP mutations depends on the type and number of acquired mutations, their variant allele frequency (VAF), and the dynamics of clonal evolution. For example, isolated CHIP mutations may indicate clonal stability and are associated with relatively good prognosis, whereas co-occurrence with CHOP mutations or the presence of multiple CHIP mutations is often indicative of adverse outcome (Lin et al. 2016, Bullinger et al. 2017, Rose et al. 2017, Sallman et al. 2017, Valent et al. 2019). The appropriate management of individuals with CHIP is debatable but monitoring for haematological changes to detect signs of disease progression is certainly warranted (Steensma 2018). Prospective studies will be necessary to determine whether screening for AML will one day be feasible and clinically meaningful.

1.6.6 Other risk factors for developing AML

Age. AML is more common in older people (Figure 1.1). Historically, DNA damage was thought to be the main responsible for hematopoietic stem cells (HSC) aging. However, in the last years, many new findings have defined an increasing number of biological processes that are intrinsically changing with age in HSCs. Epigenetics and chromatin architecture together with autophagy, proteostasis and metabolic changes and how they are interconnected to each other gain growing importance for understanding the intrinsic aging of stem cells (Mejia-Ramirez 2019). Mechanistic understanding of why these variants are positively selected during aging is lacking in most cases. Further complicating the picture, CH has been observed in the absence of any known driver mutation. What causes apparent

clonal expansion in these cases is unknown, but clonal expansion could be due to mutations in genes not previously queried in surveys of CH, mutations in the noncoding genome, or even genetic drift due to accelerated constriction of the stem cell pool (Jaiswal and Ebert 2019).

Obesity is a risk factor for cancer. Molecular changes during adipose tissue dysregulation can result in oxidative stress and subsequent DNA damage. This represents one of the many critical steps connecting obesity and cancer since oxidative DNA lesions can result in cancer-associated genetic instability. In addition, the by-products of the oxidative degradation of lipids (e.g., malondialdehyde, 4-hydroxynonenal, and acrolein), and gut microbiota-mediated secondary bile acid metabolites (e.g., deoxycholic acid and lithocholic acid), can function as genotoxic agents and tumor promoters. Obesity is also a risk factor for hematologic malignancy, and there is evidence that the association remains regardless of timing of obesity (Poynter et al. 2016). A recent meta-analysis of prospective studies yielding an adjusted relative risk (RR) for AML of 1.53 (95% CI, 1.26–1.85) for individuals with a BMI >30 kg/m^2 compared to individuals with a BMI <25 kg/m^2. Obesity in adulthood is a modifiable risk factor for both MDS and AML (Castillo et al. 2012).

Autoimmune diseases (ADs) are associated with an increased risk, not only of lymphoproliferative disorders, but also of myeloid malignancies. The excess risk of myelodysplastic syndromes and/or acute myeloid leukemia is observed across several AD types, including systemic lupus erythematodes, rheumatoid arthritis, inflammatory bowel disorders, multiple sclerosis, among others. There appears to be an excess risk of MN risk in AD, independent of cytotoxic exposure, as suggested by occurrence of MNs early in the treatment course and among patients with no prior therapy (Boddu and Zeidan 2019). Certain drug classes, such as thiopurines (azathioprine), alkylating agents (cyclophosphamide), and topoisomerase inhibitors (e.g. mitoxantrone), should be carefully considered due to their well-documented leukemogenic potential and preferably substituted with safer treatment alternatives. On the contrary, a population-based study from Denmark showed that AD and infections were associated with an increased AML risk only in subjects with prior hematological disease and/or cytotoxic treatment. These observations suggest that inflammation plays a minor role for the development of *de novo* AML (Østgård et al. 2018). Other epidemiological data showed that chronic immune stimulation acts as a trigger for AML/MDS development (Kristinsson et al. 2011). The underlying mechanisms may also be due to a common genetic predisposition or an effect of treatment for infections/AD. However, survival data lend support to the notion that AML in patients with ADs

appears to have characteristics and outcome more analogous to *de novo* AML than t-AML (DiNardo et al. 2013).

Previous hematologic disease (MDS, MPN). Other myeloid malignancies, mainly MDS and MPNs, carry a risk of disease evolution to secondary AML (sAML). The risk of transformation varies depending upon the underlying disease, and may be facilitated by certain exposures, including genotoxic chemotherapy. Patients with MPN have an approximately 10% risk of evolution to AML over 10 years, which varies according to the underlying disease. The risk is lowest in essential thrombocythemia and as high as 20% for myelofibrosis (Cerquozzi and Tefferi 2015). There is a clear association between therapies used in treating MPN, specifically alkylating agents and radioactive phosphorus, and AML evolution; treatment with these agents results in a three to fourfold increase in incidence of AML. Another mechanism that may contribute to clonal evolution and disease progression may be a chronic inflammatory state related to the underlying MPN (Gillis et al. 2017). Sequencing of secondary AML cases developing in the background of an MPN has identified recurrent mutations in *TET2*, *JAK2*, *IDH*, *IKZF1*, and *ASXL1*. Moreover, a number of patients with a *JAK2*-mutated MPN may develop *JAK2* wild-type AML, thought to arise either from a common pre-*JAK2* founding clone, or due to parallel expansion of a distinct hematopoietic clone (Theocharides et al. 2007). Post-MPN AML with mutated *JAK2* typically proceeds through an accelerated myelofibrosis phase, while post-MPN AML that no longer harbors a *JAK2* mutation tends to arise from chronic phase disease and may be associated with the use of cytotoxic therapies (Iurlo et al. 2019). Prior to the introduction of tyrosine kinase inhibitors (TKI) for chronic myeloid leukemia (CML), patients with CML typically progressed from chronic phase to blast phase within 5 years, at a rate of over 20% per year. Most cases of blast phase CML have a myeloid phenotype, while approximately 30% of patients have a lymphoid phenotype. Additional mutations may occur during transformation of CML, and approximately 80% of patients have additional cytogenetic abnormalities, such as duplication of the Philadelphia chromosome, and trisomies that are recurrent in *de novo* AML. Up to one third of patients with CML in myeloid blast phase harbor mutations in the tumor suppressor gene *TP53* (Hehlmann 2012). Additionally, *BCR-ABL* signaling upregulates transcription factors implicated in AML pathogenesis, e.g. *EVI1*, which may contribute to leukemic transformation. Underscoring the continued requirement for *BCR-ABL1* signaling in CML evolution, the rate of transformation to blast phase CML in the TKI era has decreased markedly to approximately 1% per year (Jain et al. 2017). Approximately one third of patients with MDS progress to secondary AML, although this varies significantly according to the underlying MDS subtype and disease characteristics, including the percentage of bone marrow blasts, presence of characteristic cytogenetic abnormalities, degree of cytopenia and fibrosis in the bone marrow.

Progression to AML is associated with acquisition of additional somatic mutations as well as epigenetic alterations within the MDS clone. Mutations in transcription factors and cytokine signaling genes, including *RUNX1*, *NRAS*, and *ETV6*, are more common at progression to sAML, compared with the frequency of these mutations at MDS diagnosis. Mutations in *RUNX1* are enriched in populations with tAML and other forms of sAML. Epigenetic modifications of the MDS genome appear to also play a significant role in AML progression, particularly through DNA methylation-mediated silencing of tumor suppressor genes (Brunner and Graubert 2018).

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Table 1.1. Causes and risk factors for developing AML

External physical and chemical exposures

- Benzene
- Cigarette smoking
- Pesticides
- Embalming fluids
- Accidental or professional radiation exposure
- Radiotherapy
- Radioiodine (I-131) therapy

Chemotherapy agents

- Alkylating agents (e.g. melphalan, cyclophosphamide)
- Topoisomerase-II inhibitors (e.g. etoposide, doxorubicin)
- Other drugs (e.g. azathioprin)

Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction

- AML with germ line *CEBPA* mutation
- Myeloid neoplasms with germ line *DDX41* mutation
- Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
- Myeloid neoplasms with germ line *RUNX1* mutation
- Myeloid neoplasms with germ line *ANKRD26* mutation
- Myeloid neoplasms with germ line *ETV6* mutation
- Myeloid neoplasms with germ line predisposition and other organ dysfunction
- Myeloid neoplasms with germ line *GATA2* mutation
- Myeloid neoplasms associated with BM failure syndromes
- Myeloid neoplasms associated with telomere biology disorders
- JMML associated with neurofibromatosis
- Noonan syndrome or Noonan syndrome-like disorders
- Myeloid neoplasms associated with Down syndrome

Other inherited diseases with predisposition to AML

- Klinefelter´s syndrome
- Fanconi anemia
- Ataxia telangiectasia (AT)
- Li-Fraumeni syndrome
- Blooms syndrome
- Niejmegen breakage syndrome
- Constitutional mismatch repair deficiency syndrome
- Werner syndrome
- Severe congenital neutropenia
- Dyskeratosis congenita
- Schwachman-Diamond syndrome
- Diamond-Blackfan anemia
- Congenital amegakaryocytic thrombocytopenia and thrombocytopenia with absent radii

Clonal Hematopoiesis

- CHIP (Clonal hematopoiesis of indeterminate potential)
- CHOP (Clonal hematopoiesis of oncogenic potential)

Other risk factors for developing AML

- Higher age
- Obesity
- Autoimmune disease
- Previous hematologic disease (MDS, MPN)

Legend to Figures

Figure 1.1. Incidence of AML (number of patients per 100,000 inhabitants and year) by age at diagnosis, sex and region (Swe, Swedish AML Registry 1997-2013; Nord, NORDCAN i.e., Nordic countries 2001-2016; SEER, US registry 2012-2016). M, males; F, females.

Figure 1.2. Top: Incidence rates per 100,000 and years 1975-2016 from SEER, age-adjusted to the 2000 US standard population (SEER 2020). Middle and Bottom: Incidence rates by age and year 1978-2016 in the Nordic countries (NORDCAN 2020). Middle: females. Bottom: males.

Figure 1.3. Prevalence in 2014 of people in Sweden diagnosed with AML 1997-2013 by age and sex.

Figure 1.4. Proportion of *de novo* and secondary subtypes of AML in Sweden by age and time period. tAML, therapy-related AML; MDSAML, AML with previous myelodysplastic syndrome; MPN, AML with previous myeloproliferative neoplasia; AHD, AML with undefined antecedent hematologic disease.

Figure 1.5. Incidence of APL in Sweden by age and sex.

Figure 1.6. Overall survival by age in Sweden. Left: total cohort excluding APL 1997-2016.

Right: *de novo* AML non-APL patients receiving intensive chemotherapy 2012-2016.