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Case Report
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Hereditary Predisposition to Acute Myeloid Leukemia in Older Adults

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Over the past 2 decades, it has become evident that a significant proportion of acute myeloid leukemia (AML) occurs on the background of predisposing germline aberrations. The diagnosis of these disorders is of clinical interest as it may imply specific management of AML patients, especially for the selection of intrafamilial hematopoietic stem cell (HSC) donors, as well as genetic counseling and/or surveillance in other family members. However, the determination of an underlying genetic predisposition remains challenging[1-3] and is not automatically part of the diagnostic work-up of AML in clinical practice, especially in elderly patients. Here we present 3 unrelated patients diagnosed with AML after the age of 60 and for whom a suggestive family history has led to the identification of a germline predisposition (Figure 1A–C). Individuals were referred to the university hospitals of Lille and Amiens-Picardie, France. Genetic analyses in patients with AML were performed on leukemic cells as part of the initial diagnostic screening. Additionally, genetic analyses on germline tissue in the described patients (skin fibroblasts in CII.3) or their relatives (sorted CD3+ lymphocytes in AII.3, skin fibroblasts in patients BII.2) were performed after genetic counseling and informed consent. The study was conducted according to the Declaration of Helsinki and was approved by the Human Research Committee of Lille and the internal review board of the Lille University Hospital Tumor Bank (certification NF 96900-2014/65453-1).

The first patient (AII.1) is a 74-year-old man with a diagnosis of AML. Screening of myeloid malignancies-associated mutations by high-throughput sequencing (HTS) found mutations in *DNMT3A* (NM_022552:c.1906G>A; p.V636M), *IDH1* (NM_005896:c.394C>T; p.R132C), *RUNX1* (NM_001754:c.611G>A; p.R204Q), and *SRSF2* (NM_003016:c.284C>T; p.P95L) (Figure 1D). The diagnosis of *RUNX1*-mutated familial platelet disorder (FPD) with propensity to AML was previously made in this family and described in reference.[4] All affected individuals shared the p.R204Q variant (considered as pathogenic according to the ClinGen Myeloid Malignancy Variant Curation Expert Panel[5]) in the DNA-binding domain of RUNX1. The *RUNX1* gene (21q22) encodes the alpha subunit of the core-binding factor, which regulates expression of genes critical for normal hematopoiesis. To date, more than 200 pedigrees with FPD have been described, and it is estimated that more than 5000 families are affected worldwide.[6] Individuals classically exhibit a mild to moderate thrombocytopenia and a predisposition to the development of hematological malignancies (HMs), especially myelodysplastic syndromes (MDSs) (~25%), AML (~60%) and T-cell acute lymphoblastic leukemia (ALL, <10%).[7] Overall, the median risk of HM is 40% before the age of 50 but the age of onset is highly variable, ranging from 5 to more than 75 years.[4,6,7] This contrasts particularly with predispositions involving other transcription factors such *GATA2* or *CEBPA*.[7] Evidence suggests that this heterogeneity (in terms of age of onset and phenotype) is supported by the acquisition of a variety of secondary genetic aberrations. This is well illustrated by the pedigree reported here in which individual AIII.1 developed T-cell ALL with acquisition of *NOTCH1*, *PHF6*, and *WT1* mutations while individual AII.3 acquired a second *RUNX1* mutation and *FLT3*-internal tandem duplication that triggered the development of AML. A second hit targeting the other *RUNX1* allele (or increase in the dosage of the germline mutation) is the most frequent lesion in FPD patients evolving to AML.[4] This alteration is assumed to be an early event in leukemic progression leading to a significant genetic instability, impairment of DNA repair pathways and the rapid acquisition of other molecular events. Interestingly, leukemic progression in the patient described here was not characterized by a second *RUNX1* aberration but was marked by a long period (>9 y) of *DNMT3A*-mutated clonal hematopoiesis (CH) with slow expansion and final acquisition of *SRSF2* and *IDH1* mutations at AML diagnosis, which may reflect a distinct pattern of leukemogenesis with a later onset of AML.

The second patient (BII.1) was diagnosed with AML at age 61 (previously reported in reference[8]). HTS revealed mutations in *BRAF* (NM_004333:c.1799 T>A; p.V600E), *TET2* (NM_001127208:c.2586dup; p.H863fs and NM_001127208:c.4087_4088delinsG; p.K1363fs), and *ZRSR2* (NM_005089:c.930del; p.I311fs) (Figure 1E). The family history was marked by a case of chronic myelomonocytic leukemia in a sister (BII.2) and a polycythemia vera (PV) in another

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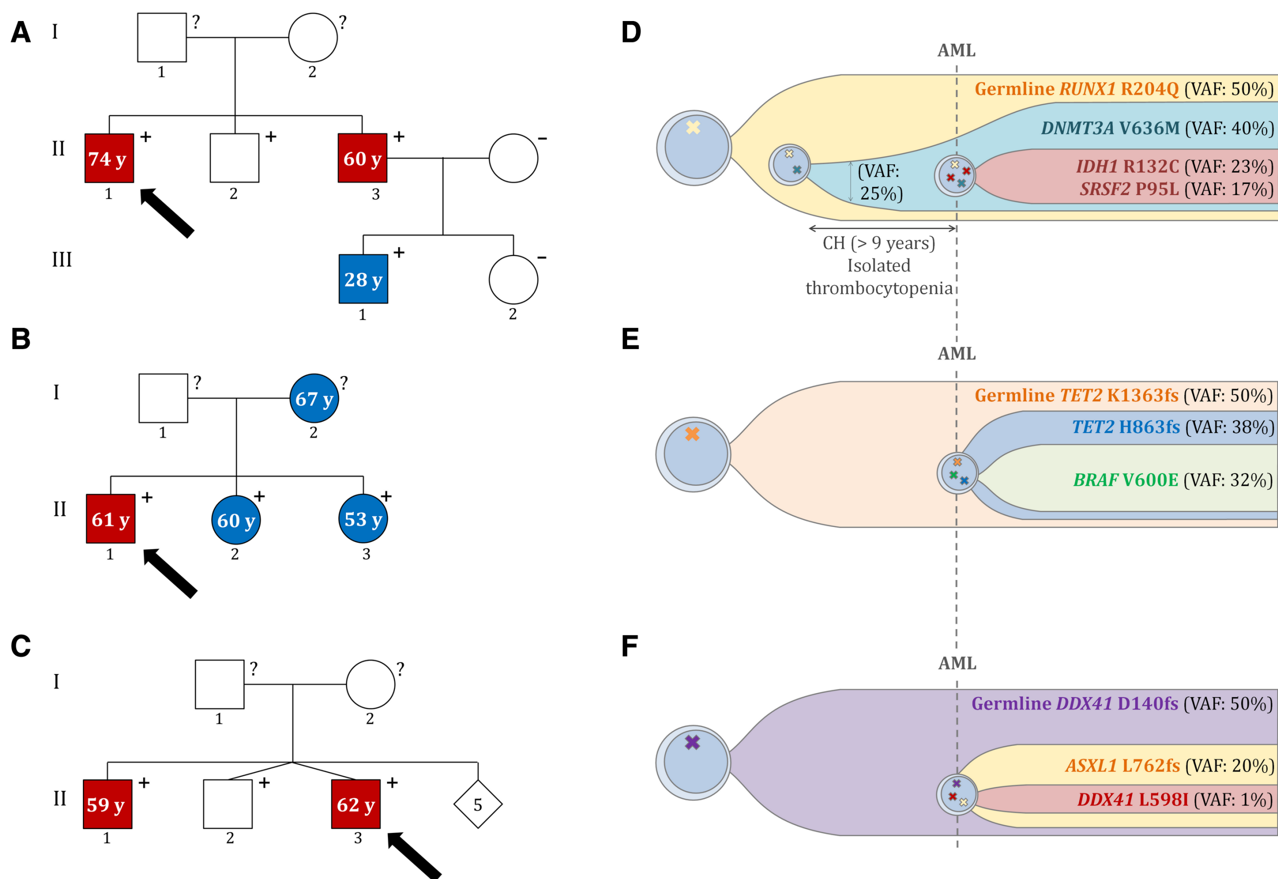

Figure 1. Patients' characteristics. The left panel depicts the pedigrees harboring germline mutations in *RUNX1* (A), *TET2* (B), and *DDX41* (C). Age at diagnosis of AML (red color) or other hematological malignancy (blue color) is indicated inside the symbols. The reported patient in each family is indicated with an arrow. The right panel (fish diagrams D–F) shows putative clonal hierarchies at diagnosis of AML in the patients. The symbols indicate individuals carrying the germline mutation ("+") or not ("–") or whose the status is unknown ("?"). AML = acute myeloid leukemia; CH = clonal hematopoiesis; VAF = variant allele frequency.

one (B.II3). The *TET2* mutation p.K1363fs was confirmed to be shared by all siblings (BII.1, BII.2, and BII.3) and the germline origin was confirmed by sequencing on a fibroblast culture. The patient underwent allogeneic HSC transplantation from an unrelated donor but relapsed 4 months later. It was decided to perform a second HSC transplantation with the same donor allowing a durable complete remission. The *TET2* gene (4q24) encodes a methylcytosine dioxygenase that promotes DNA demethylation. Although somatic *TET2* mutations have been extensively reported, little is known about individuals with germline *TET2* mutations. A first report mentioned a patient with a PV and an asymptomatic sister both carrying a germline frameshift *TET2* (p.D1858fs) mutation.[9] In another pedigree harboring a distinct germline frameshift *TET2* (p.K1500fs) mutation, affected members developed Hodgkin lymphoma and T-cell-rich B-cell lymphoma.[10] The acquisition of secondary aberrations and genetic background are likely to explain the heterogeneity in disease phenotypes. Somatic *TET2* mutations are frequently observed in myeloid and lymphoid malignancies and in CH.[11] Such mutations could be found in HSC from healthy individuals and usually persist in patients achieving complete remission. In clinical practice, this makes *TET2* mutational status difficult to assess without studying a tissue of germline origin. Thus, the prevalence of germline *TET2* mutations may be underestimated and the associated risk of developing HM difficult to estimate.

The third patient was diagnosed with AML at age 62 (CII.3). HTS identified a mutation in *ASXL1* (NM_015338:c.2285dup; p.L762fs) and *DDX41* (NM_016222:c.415_418dup; p.D140fs) (Figure 1F). Additional analyses showed that the *DDX41* mutation was present in skin fibroblasts and shared with a brother (CII.1) who had developed AML few years before leading to the diagnosis of a predisposing syndrome in this pedigree. CII.1 and CII.3 both received intensive chemotherapy and underwent HSC transplantation from *DDX41*-wild-type siblings. The *DDX41* gene (5q35) encodes a DEAD (Asp-Glu-Ala-Asp)-box RNA helicase involved in many aspects of RNA metabolism. Germline *DDX41* mutation carriers usually have normal blood counts but exhibit a risk of MDS and AML that develop at an age similar to that observed in sporadic cohorts of both disorders.[12,13] Median age at AML diagnosis is about 60 to 70 years old,[12-14] and it frequently occurs after a phase of MDS.[14] Acquired mutations at AML stage frequently involve *ASXL1*, *SRSF2*, *TP53*, and the other *DDX41* allele.[12,14] The prognosis remains to be evaluated in collaborative studies but may depend on cooperating genetic aberrations.[12,14] However, the present case raises the question of systematic testing for *DDX41* mutations in adult MDS and AML because of their prevalence and implications for the choice of familial donors for HSC transplantation. This issue remains problematic for all genetic predispositions to MDS/AML or other HM.

AML is a clonal disease characterized by the accumulation of genomic recurrent aberrations affecting key processes of hematopoiesis and cell biology. A number of genes that cause inherited AML can also be somatically mutated in sporadic cases and are routinely screened at HM diagnosis. The cases reported here show that advanced age at AML diagnosis should not preclude a genetic predisposition, especially regarding the range of acute leukemia or MDS onset in *RUNX1* or *DDX41* germline mutated carriers (Figure 2). Skin fibroblasts are the preferred source of

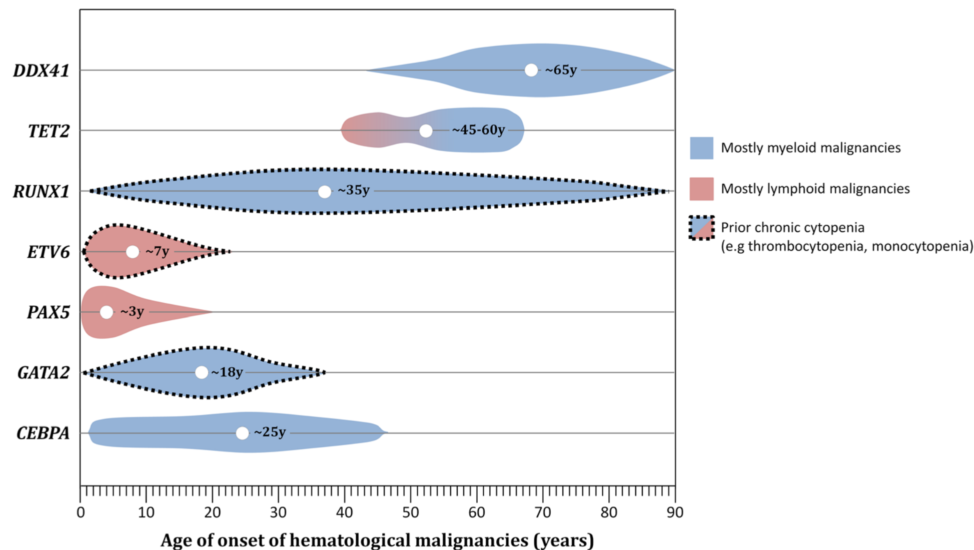

Figure 2. Age of onset of hematological malignancies in germline mutation carriers. The plots show the predominant age of acute leukemia/myelodysplastic syndrome onset. The median age at diagnosis is indicated for each gene.

germline DNA but their systematic use remains difficult in our practice. Thus, we recommend that AML/MDS patients be screened at diagnosis (on tumor sample) with a sequencing panel including known predisposition syndrome-associated genes, at least in patients who are candidates for allogeneic HSC transplantation. Overall, genetic counseling and subsequent screening of germline DNA is proposed after informed consent in those who present a personal or family history indicative of a predisposition (including chronic cytopenia) or patients for whom the diagnostic work-up has detected gene variants compatible with a germline state (ie, *CEBPA*, *DDX41*, *ETV6*, *GATA2*, *RUNX1* with allele frequency ≥40%). However, we acknowledge that these criteria may overlook germline variants in other genes (eg, *TET2* mutations) in patients lacking a suggestive family history. In our experience, 25% to 30% of individuals who develop malignancies are 60 years of age or older among germline *RUNX1*-mutated carriers. This situation is more striking for germline *DDX41*-mutated individuals, as approximately 60% of those who develop AML/MDS are over 60. Among AML patients diagnosed after the age of 60, suspected germline *DDX41* mutations may account for 5% of all cases making them, to date, the most common predisposition syndrome to HM.[12] By contrast, all other cases of AML/MDS occurring in germline *CEBPA* or *GATA2*-mutated individuals diagnosed in our center are younger than 50 years old. Finally, although the family history described here was very suggestive of a predisposition syndrome, we can expect that some apparently sporadic AML (ie, lacking family history) in elderly patients may be secondary to these disorders. In addition, we can assume that this situation is currently underdiagnosed since, depending on clinicians' practice, genetic screening is not systematic in older patients, especially when intensive therapy is not possible.

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Disclosures

The authors have no conflicts of interest to disclose.

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