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Familial predisposition of myeloid malignancies: Biological and clinical significances of recurrent germline mutations

Myeloid neoplasms with germ line *RUNX1* mutation

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Abstract Familial platelet disorder with propensity to myeloid malignancies (FPD/AML) is an autosomal dominant disorder characterized by quantitative and/or qualitative platelet defects with a tendency to develop a variety of hematological malignancies. Heterozygous germ line mutations in the *RUNX1* gene are responsible genetic events for FPD/AML. Notably, about half of individuals in the family with germ line mutations in *RUNX1* develop overt hematological malignancies. The latency is also relatively long as an average age at diagnosis is more than 30 years. Similar to what is observed in sporadic hematological malignancies, acquired additional genetic events cooperate with inherited *RUNX1* mutations to progress the overt malignant phase. Reflecting recent increased awareness of hematological malignancies with germ line mutations, FPD/AML was added in the revised WHO 2016 classification. In this review, we provide an update on FPD/AML with recent clinical and experimental findings.

Keywords RUNX1 · FPD/AML · FPD/MM · Germ line mutation

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Introduction

RUNX1 is a well-known critical transcription factor for embryogenesis and definitive hematopoiesis [1–5]. Somatic mutation in the *RUNX1* gene is one of the most frequent mutations identified in the patients with a variety of myeloid malignancies, such as myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), and acute myeloid leukemia (AML) [6, 7]. In most of cases, those *RUNX1* mutations are considered as "subclonal mutation" [8]. On the other hand, germ line mutations in *RUNX1* gene cause familial platelet disorder with a propensity to myeloid malignancy (FPD/AML), an autosomal dominant disorder which typically presents with quantitative/qualitative platelet defect with a tendency to develop primarily myeloid malignancies, such as MDS and AML [9]. In this case, heterozygous inherited *RUNX1* mutations play a fundamental role in the pathogenesis of FPD/AML. However, these inherited *RUNX1* mutations are not enough to develop the leukemic stage. Additional "subclonal" mutations are required to develop myeloid malignancies.

Since a certain number of cases have begun to be recognized as germ line mutation-driven myeloid diseases, "myeloid neoplasms with germ line predisposition" has recently been added as a discrete section of the WHO 2016 classification ("WHO blue book") [10]. FPD/AML is described in this section and its awareness by clinicians is increasing. In this perspective, we describe an overview of FPD/AML pathogenesis and its recent findings.

Role of RUNX1 in hematopoiesis and hematological malignancies

The t(8;21) is frequently identified in patients with AML [11]. *RUNX1* was originally cloned from the sample

obtained from an AML patient with t(8;21) [1]. The *RUNX1* gene was located at the breakpoint on chromosome 21 [1]. The critical roles of RUNX1 in a variety of physiological processes have been uncovered primarily using transgenic mice. *Runx1* deficiency is embryonically lethal because of hemorrhage in the central nervous system and a lack of definitive hematopoiesis [2]. Conditional deletion of *Runx1* gene in adult mice causes aberrant megakaryocytopoiesis, thrombocytopenia, lymphocytopenia, and expansion of hematopoietic stem cells (HSCs)/myeloid progenitors [4, 5]. Recently, it has been shown that *Runx1* deficiency causes a defect of ribosomal biogenesis (RiBi) [12].

Given that RUNX1 plays pivotal roles in the regulation of physiological hematopoiesis, the dysregulation of RUNX1 leads to defective hematopoiesis. Indeed, *RUNX1* mutations have frequently been identified in patients with MDS and AML [6, 7]. Furthermore, a higher frequency of *RUNX1* mutations (30–50%) has been reported in therapy-related and radiation-associated MDS and AML [13–15]. In general, *RUNX1* mutations are considered to result in the loss of RUNX1 functions. On the other hand, recent several reports indicate that wild-type RUNX1 is also important for growth and survival of leukemia cells [16].

Familial platelet disorder (FPD) with propensity to myeloid malignancies

In 1978, Luddy et al. reported a family in which 3 siblings, present with a lifelong history of a bleeding disorder and thrombocytopenia, died from a myeloproliferative disease [17]. After this report, a number of pedigrees have been reported and clinical evidences have been accumulated [18–20]. More than 30 pedigrees of FPD/AML have been reported to data. Typical clinical features of FPD/AML are modest thrombocytopenia, aspirin-like qualitative platelet abnormality, and a propensity to develop hematological malignancies [9]. However, thrombocytopenia is not necessary for the diagnosis of FPD/AML, as some patients do not present with quantitative and qualitative platelet defects [21]. Approximately 20–60% of the individuals in the families develop hematological neoplasms during their life time [22]. The latency until the transformation is relatively long. It has been reported that an average age at diagnosis is 33 years (up to 76 years) [23]. This trend remains unchanged in recent reports (Fig. 1).

Identification of *RUNX1* mutations as a causative genetic event in FPD/AML

In 1996, using the samples from the pedigree described by Dowton et al., the link between FPD/AML and genes

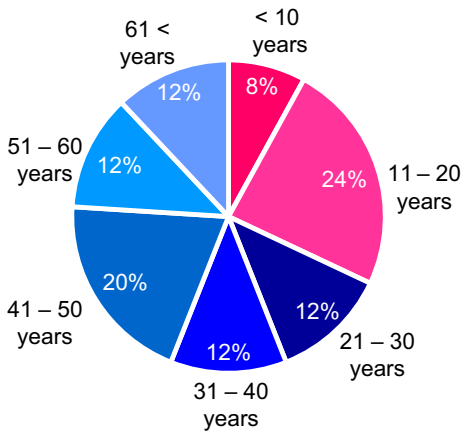

Fig. 1 Onset of hematological malignancies in FPD/AML patients. 25 affected individuals of FPD/AML from recently reported studies (in 2014–2016) [37, 43, 45, 48, 56]. The average age at diagnosis of hematological malignancies (MDS, AML, and ALL) is 34.16 years (6–72 years)

on human chromosome 21q22.1-22.2 has been reported [24]. In 1999, Song et al. identified heterozygous germ line *RUNX1* mutations as the causal abnormality in FPD/AML [9]. *RUNX1* genes encode a DNA-binding subunit that contains highly conserved Runt-homology domain (RHD) for sequence-specific DNA binding. The *RUNX1* mutations identified in the individuals of FPD/AML pedigrees are generally located in the RHD, leading to disruption of DNA binding ability. Although the incidence is less common, the mutations in the C-terminal region have been reported [25]. In this case, the mutation generates a frameshift and premature chain termination, resulting in the lack of transactivation domain [25]. Intragenic deletions, which are not identified by traditional sequence analysis, have also been reported in a few families [9, 26, 27]. In FPD/AML, most of *RUNX1* mutations cause haploinsufficiency [9], while some mutations are considered to function in a dominant negative manner [28, 29]. It is suggested that the mutations which have dominant negative effects are associated with a high frequency of leukemia progression compared to the mutations which act via haploinsufficiency [28].

Mechanism of thrombocytopenia

The molecular mechanisms of how *RUNX1* haploinsufficiency causes abnormalities of megakaryopoiesis and platelets remain to be elucidated. Recently, it has been shown that wild-type RUNX1 negatively regulates the expression of non-muscle myosin IIB heavy chain 10 (MYH10), resulting in the megakaryocyte maturation [30]. Thus, haploinsufficiency of *RUNX1* might constitutively

activate MYH10 expression and affect megakaryocyte polyploidization [30]. RUNX1 also directly regulates the expression of myosin light chain 9 (MYL9) in megakaryocytes. Thus, downregulation of MYL9 due to *RUNX1* haploinsufficiency could affect abnormal platelet production and function [31]. Platelet storage pool deficiency and low levels of MPL receptor expression have also been reported [25, 32].

Additional genetic events for mutant clone expansion and leukemia progression

Heterozygous germ line mutation in the *RUNX1* gene is obviously a cause of FPD/AML [9]. However, only about half of the individuals with germ line mutations in the families develop hematological neoplasms in their life with long latency. This clinical evidence clearly indicates that additional genetic events are required for disease transformation (Fig. 2).

CBL mutations have been found in various myeloid malignancies, such as MDS, AML, and chronic myelomonocytic leukemia (CMML) [33–35]. *CBL* mutations have also been identified in the patients with FPD/AML. Shiba et al. reported that *CBL* mutation and 11q-acquired uniparental disomy (11q-aUPD) cooperate with *RUNX1* mutation to develop CMML [36].

Recently, Yoshimi et al. have shown that somatic mutations in *CDC25C* gene are found in more than half of the patients with FPD/AML in Japan [37]. Mutant CDC25C disrupts the G2/M checkpoint and promotes cell cycle progression. *CDC25C* mutation is considered as an early genetic event that generates pre-leukemic clones. This might allow acquiring subsequent genetic events, resulting in overt leukemia progression [37]. In some FPD/AML patients who lack *CDC25C* mutation, Sakurai et al. identified *TET2* mutation or abnormal chromosome 21 (trisomy 21) with chromosomal deletion encompassing *RUNX1* locus [27]. Since both genetic events are involved in clonal expansion of HSCs and progenitors (HSPCs) [38–41], *TET2* mutation or trisomy 21 could cooperate with *RUNX1* haploinsufficiency to generate pre-leukemic clones. Those patients further acquired additional mutations, such as mutations in *RB1*, *ZRSR2*, and *BCOR*, and eventually developed overt MDS [27].

On the other hand, a high frequency of *RUNX1* biallelic mutations in the patients with FPD/AML has been reported from a French group [42, 43]. Besides *RUNX1* biallelic mutations, a variety of mutations were identified at the AML stage, such as mutations in *FLT3*, *KRAS*, *CBL*, *TP53*, *SRSF2*, *SF3B1*, *TET2*, and *DNMT3A* [43]. However, *CDC25C* mutations were not identified in this study [43]. *CDC25C* mutations were also not detected in the two affected patients with FPD/AML from the Ireland group [44] and 13 individuals of FPD/AML families from the United States [45]. The difference of ethnic origin of FPD/AML patients is suggested. After the acquisition of secondary genetic events, affected individuals of FPD/AML develop myeloid malignancies in many cases. However, some affected individuals also develop lymphoid neoplasms [20, 46–48].

Accumulating evidences have indicated that there are age-related hematopoietic clones which have somatic mutations associated with hematological malignancies, namely clonal hematopoiesis of indeterminate potential (CHIP) [49–51]. Several hematological malignancy-related mutations (such as *DNMT3A*, *TET2*, and *ASXL1*) were identified in around 10–20% of healthy individuals >65–70 years of age, while the detectable mutations were very rare in a younger cohort <40 years of age. On the other hand, a recent analysis of familial MDS/AML revealed that clonal hematopoiesis was detected in 67% of asymptomatic *RUNX1* mutant carriers <50 years of age [45]. Further study with a larger cohort will be required to determine whether detecting clonally skewed clones could predict a risk for leukemic transformation.

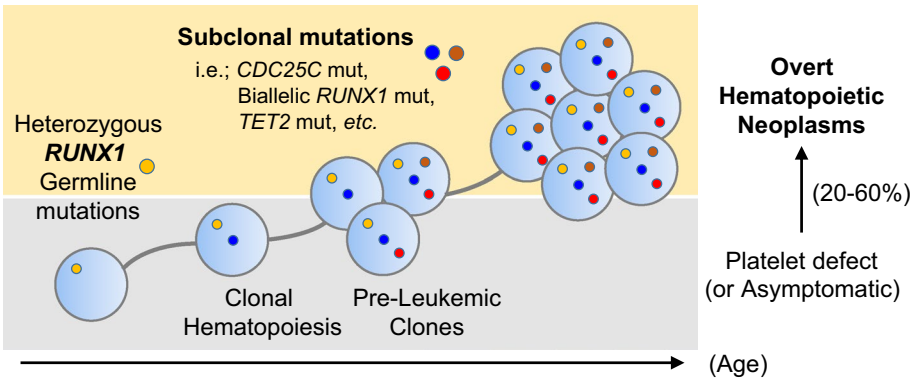

Fig. 2 Disease progression in FPD/AML. Acquired additional genetic events are required to develop the overt hematological malignancies

Recent advance on FPD/AML research using human patient-derived iPS cells

Although studies using transgenic mice have revealed many critical roles of RUNX1 in hematopoiesis, there is a clear difference between mice and humans. For instance, haploinsufficiency of *RUNX1* causes thrombocytopenia in the individuals of FPD/AML families. On the other hand, *Runx1* haploinsufficiency does not generate observable phenotypes in the megakaryocytes and platelets [29, 52], while *Runx1* homozygous deletion results in thrombocytopenia in mice [4, 5]. Considering the difference of the *RUNX1* gene dosage effect on phenotypes between humans and mice, there is no animal model that faithfully recapitulates clinically relevant pathogenesis of human FPD/AML. To overcome this problem, studies using human cells were conducted. Sakurai et al. successfully established induced pluripotent stem cells (iPSCs) from three pedigrees of FPD/AML (FPD-iPSCs) [53]. FPD-iPSCs presented with the defect of megakaryocyte differentiation. This defective phenotype was rescued by overexpression of wild-type RUNX1 in FPD-iPSCs. Connelly et al. and Iizuka et al. also established FPD-iPSCs from the patients in FPD/AML families and found defective megakaryocytic differentiation in FPD-iPSCs [54, 55]. Importantly, this megakaryocyte phenotype was able to be rescued by gene-targeting correction of *RUNX1* mutation [54, 55]. Patient-derived iPSCs would be a useful tool to dissect the pathogenesis of FPD/AML and the process of leukemic transformation in human hematopoietic cells [53]. Gene correction of *RUNX1* mutations might also hold the promise of establishing a new therapeutic strategy for FPD/AML patients [54, 55].

Clinical management for FPD/AML

Considering the cases of FPD/AML, adult-onset hematological malignancies are not always sporadic. Thus, clinicians are always required to be aware of germ line mutations and take a detailed family history regarding malignancies, bleeding tendency, and platelet abnormality (Fig. 3). Recent nationwide survey indicated that it is difficult to distinguish FPD/AML from non-FPD/AML based on clinical information alone [56]. Thus, genetic testing for *RUNX1* mutations is strongly recommended when the patients are suspected to be FPD/AML [56]. Since peripheral blood samples from patients with hematological malignancies usually contain disease clones, the mutations identified using those samples may reflect acquired mutations rather than germ line mutations even if *RUNX1* mutations are identified [23]. Thus, in this setting, alternative tissue samples, such as skin biopsy for fibroblasts, are recommended for the extraction of germ line DNA [23].

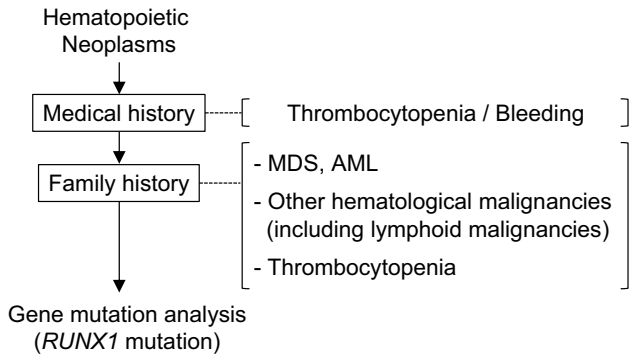

Fig. 3 Proposed clinical flowchart. Awareness of germ line mutations and a detailed family history are required to avoid overlooking the patients with FPD/AML

Currently, the guidelines of clinical management for patients and their families with familial MDS/AL predisposition syndromes are proposed [23]. At diagnosis of FPD/AML, complete blood count (CBC), bone marrow biopsy and aspiration with cytogenetic analysis, and HLA typing of both the patients and their siblings are recommended. During follow-up, annual testing of CBC and clinical examination (every 6 months), bone marrow biopsy (when any worrying changes in CBC are observed), and consultation with hematology prior to any invasive procedures are recommended [23]. When a patient is identified as an affected individual of FPD/AML and needs to undergo allogeneic stem cell transplantation, a sibling donor, who also has *RUNX1* mutations, should not be chosen. Indeed, it has been reported that the use of donors who carry the same germ line mutations results in poor outcome [20, 57]. In such a case, the use of HLA-matched unrelated donors should be considered [23].

Concluding remarks

FPD/AML is a rare autosomal dominant inherited disorder, which is derived from germ line *RUNX1* mutations. However, the awareness of FPD/AML is increasing. The incidence might still be underestimated due to its diversity of disease onset and clinical features. Similar to the cases of sporadic MDS or AML, acquisition of additional mutations and clone selection are critical steps for disease progression in FPD/AML. Prominent clonal hematopoiesis is also observed in FPD/AML. Further elucidation for clonal expansion and disease progression in FPD/AML will provide a better understanding of FPD/AML pathogenesis and may lead to the establishment of better management and therapeutic strategies for not only FPD/AML patients but also many other individuals of CHIP or hematopoietic malignancies.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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