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# Inherited and Acquired Bone Marrow Failure Syndromes: In the Era of Deep Gene Sequencing

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## Editorial

Bone marrow failure syndromes (BMFS) are a cluster of inherited or acquired disorders characterized by peripheral cytopenia due to a decrease in hematopoietic progenitors or dysregulated hematopoiesis. Inherited bone marrow failure syndromes are mainly found in pediatric group, encompassing Diamond Blackfan anemia (DBA), Fanconi anemia (FA), congenital sideroblastic anemia (CSA), congenital neutropenia (CN), congenital dyserythropoiestic anemia (CDA), Shwachman Diamond syndrome (SDS), and dyskeratosis congenita (DC) [1], In contrast, acquired bone marrow syndromes are more commonly seen in adults and mainly include acquired aplastic anemia (AA), acquired megakaryocytic thrombocytopenia (AMT), paroxysmal nocturnal hemoglobinuria (PNH), and myelodysplastic syndromes (MDS).

The prevalence and incidence of inherited BMFS are unclear in inherited BMFS [2]. The incidence of acquired BMFS depends upon the disease category, age and geographic distribution. It is found to be higher in patients with AA in Asia (0.6-1 per 100,000 a year) than those in the USA and Europe (0.2 per 100,000 a year) [3]. The prevalence of MDS increases with age from 15 to 50 per 100,000 in patients aged 60-69 and 70-79 years old, respectively [4]. Despite a heterogeneous genetic background, both inherited and acquired types of BMFS have a high risk for leukemic transformation [5-7].

The pathogenesis of BMFS is complex and could be attributed to various kinds of genetic factors. Recent adoption of next generation gene sequencing led to the discovery of novel molecular markers in BMFS. More than 80 gene mutations in several biological pathways that are attributed to BMFS have been identified, including those involved in DNA repair, telomere biology, ribosome development, and genomic stability [8,9]. The key mutations associated with BMFS are summarized in Table 1.

In addition, patients harboring germ line mutations in *RUNX1, ETV6, GATA2, ANKRD26, SRP72, CEBPA* and *DDX41* genes have been found to have a higher susceptibility to develop MDS and acute myeloid leukemia (AML) [5,10]. Six of the seven genes (*CERPA, DDX41, RUNX1, ANKRD26, ETV6* and *GATA2*) are listed under "myeloid neoplasms with germ line predisposition," a new category of precursor myeloid disorders listed in the 2016 revision of WHO classification of Tumors of Haematopoietic and Lymphoid Tissues[10].

Recent data shows a group of mutations found in AA patients are more related to immunomodulation rather than those frequently seen in MDS or myeloid neoplasms [11], suggesting the important role of immune dysregulation in development of AA. Therefore, understanding the genetic and molecular background of BMFS helps in making an accurate diagnosis, prediction of disease prognosis, and providing the appropriate management.

In addition to genetic aberrations, alterations in the bone marrow micro environmental play a pivotal role in acquired bone marrow failure. Factors ultimately contributing to ineffective hematopoiesis include abnormal inflammatory cytokine release, altered innate immune signaling, and acquired immunologic dysregulation [12,13].

Accurate diagnosis and sub-classification of inherited and acquired BMFS can be challenging because of overlapping features with mimickers, especially in the presence of morphologic dysplasia and incomplete clinical and laboratory investigation.

For example, bone marrow failure resulting from collagen vascular diseases or autoimmune disorders can have morphologic dysplasia and can be misinterpreted as MDS resulting in inappropriate treatment [15,16]. Of note, dysplasia is not exclusive to MDS, but can be seen in the bone marrow secondary to exposure to chemotherapy, toxins, infection (e.g. HIV), antibiotic use (e.g. isoniazid), and nutritional imbalances (e.g. vitamin B12, folate, copper deficiencies, or zinc overdose) [14].

Moreover, it is not uncommon to have overlapping morphologic features between AA, PNH or hypoplastic MDS. Clinically, these three entities share some similarities except for overt hemolytic/thrombolic PNH [15]. Of importance, a subset of AA or PNH patients could eventually evolve to MDS after acquisition of additional genetic mutations or aberrations [15].

As far as the treatment of BMFS is concerned, lenalidomide is becoming a popular treatment regimen used in low grade MDS with del (5q), and now also DBA to rescue erythropoiesis and eliminate abnormal cytogenetic clones [17].

Hematopoietic stem cell transplantation is the ultimate therapeutic strategy in the majority of patients with BMFS carrying on a high risk for leukemic transformation or found to be refractory to initial treatment [7,18,19].

In the era of deep gene sequencing, more genetic abnormalities will be discovered and used for targeted therapy in inherited or acquired BMFS. Given the similar morphologic bone marrow findings among the subtypes of BMFS and their mimickers, accurate diagnosis of BMFS by integrating family history, present clinical presentations, laboratory and histological findings with cytogenetic and molecular profile is important for appropriate therapy and prognosis.

| Bone Marrow Failure Syndromes | Key Gene Mutation or Alteration | Highest frequency | % Transformation to MDS or AML |
|---|---|---|---|
| **Iniherited** | | | |
| Diamond Blackfan anemia (DBA) | *RPS19 [ZL1], RPL15, RPL35a, RPS26, RPS24, RPS17, RPS7, PRD10* [33] | RPS19 (25%) | NA |
| Shwachman Diamond syndrome (SDS) | *DBDs* [33] *[ZL2]* | DBDs (>90%) | MDS or AML at young age [33] |
| Fanconi anemia (FA) | *FANC-A, -B, -C, -D1/BRCA2, -D2, -E, -F, -G/[ZL3], CC9, -I, -J/BRACH1/CRIP1, -L, -M, -N/PALB2, -O*, and *–P* [34]. 20% associated with CEPBA mutation [21] | FANC-A (60%) | 40% to MDS, 10% to AML [22] |
| Congenital sideroblastic anemia (CSA) | *ALAS2, SLC25A38, ABCB7, GLRX5, PUS1, YARS2, SLC19A2 [35]: HSPA9 [24]* and *NDUFB11* [25] | NA | NA |
| Congenital dyserythropoietic anemia (CDA) | CDA type I: *CDAN1*, *C15ORF31*<br>CDA type II: *SEC23B*<br>CDA type III familial: *KIF23*<br>Variants beyond type I-II: *GATA-1, KLF1* [26] | NA | NA |
| Congenital neutropenia, severe | *ELA-2/ELANE, GF11, HAX-1, WAS, G6PC3, CSF3R* Associated with AML when also *KIT, RAS*, or *RUNX1* gene is mutated, or chromosome 7 abnormality [27] | *ELA-2* (75%) | 30% to AML [20] [ZL4] |
| Dyskeratosis congenita | *DKC1,TINF2,TERC,TERT,NOP10/NOLA3,NHP2/NOLA2,TCAB1/WDR79/WRP53* | DKC1 (30%) | 30% to MDS and 10% to AML 9 [22] |
| **Acquired** | | | |
| Acquired aplastic anemia (AA) | *ASXL1,DNMT3A,PIGA**, BCOR/BCOR1* [28] | BCOR/BCOR-1 or DNMT3A (9-12%) | 20-25% to *MDS* or *AML* [29] |
| Acquired megakaryocytic thrombocytopenia (AT) | NA | NA | NA |
| Paroxysmal nocturnal hemoglobinuria (PNH) | PIGA gene***TET2,SUZ12,U2AF1* and *JAK2* [30] | *PIGA* (>60%) | NA |
| Myelodysplastic syndromes (MDS) | *SF3B1,SRSF2,ZRSR2,U2AF1,U2AF2,TET2,DNMT3A,IDH1/2,ASXL1,EZH,TP53,RUNX1,JAK2,KRAS,NRAS,CBL,NF1,TAG2,CTCF,SMC1A,RAD21* [31,32] | TET2-20% | 50-75% to AML |

**Table 1:** Key genes involved in inherited and acquired BMFS.

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