HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2018 May 07.

Published in final edited form as:

Pediatr Blood Cancer. 2017 December ; 64(12): . doi:10.1002/pbc.26714.

Monosomy 7/del (7q) in inherited bone marrow failure syndromes: A systematic review

Alex Pezeshki[1], **Shreya Podder**[2], **Ralph Kamel**[2], and **Seth J. Corey**[2,iD]

[1]Wayne State University School of Medicine, Detroit, Michigan

[2]Division of Pediatric Hematology, Oncology, and Stem Cell Transplantation, Children's Hospital of Richmond and Massey Cancer Center, Virginia Commonwealth University School of Medicine, Richmond, Virginia

Abstract

Inherited bone marrow failure syndromes (IBMFS) are rare cancer predisposition syndromes with an especially high risk of transformation to myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML). We performed a retrospective systematic review of reported MDS/AML arising in the eight most common IBMFS to determine the frequency and outcome of chromosome 7 abnormalities. We identified 738 MDS/AML cases of 4,293 individuals. Monosomy 7 or del (7q) occurred in ~17%. Greater understanding of the roles played by sequential acquisition of genetic and cytogenetic changes will provide insights into myeloid leukemogenesis and improve the surveillance and hopefully outcomes for individuals with IBMFS.

Keywords

acute myeloid leukemia; bone marrow failure syndromes; monosomy 7

1 | INTRODUCTION

Inherited bone marrow failure syndromes (IBMFS) are a heterogeneous set of rare genetic disorders that are characterized by inadequate blood cell production. The recognition of IBMFS is dependent upon the patient's characteristic clinical, physical, and hematologic findings and confirmed by genetic testing.[1] The accurate diagnoses of these disorders can be challenging due to a wide spectrum of clinical expression and overlap. The natural course of the IBMFS frequently involves progression to myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML) through clonal evolution. In some cases, MDS/AML may even be the first presenting signs of a patient with IBMFS.[2]

Correspondence Seth J. Corey, Division of Pediatric Hematology, Oncology, and Stem Cell Transplantation, VCU Massey Cancer Center, Box 980037, 401 College Street, Richmond, VA 23298. seth.corey@vcuhealth.org.
Seth J. Corey http://orcid.org/0000-0002-6704-4142

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

The complete loss of chromosome 7 (−7) or its long arm (del(7q)) is one of the more common cytogenetic abnormalities in pediatric and adult myeloid malignancies. −7/del (7q) occurs as either a simple or complex cytogenetic abnormality. Furthermore, analysis of MDS/AML patient outcomes suggests that −7/del (7q) carries a poorer prognosis compared to other cytogenetic abnormalities.[3,4] The goal of this systematic review was to determine the incidence and outcome of −7/del (7q) among patients with the most common of the rare IBMFS. Assessment of the frequency of 7/del (7q) with specific IBMFS may provide insight into their transformation to secondary MDS/AML and improve surveillance and outcomes through earlier detection and intervention for individuals with IBMFS.

2 | METHODS

This retrospective systematic review of literature is reported in accordance with the guidelines set forth by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org). We included patients of all ages, but carefully noted the age of diagnosis as reported. The eight most common IBMFS examined were: Fanconi anemia, Shwachman–Diamond syndrome, GATA2 deficiency, dyskeratosis congenita, Diamond–Blackfan anemia, familial platelet disorder, congenital amegakaryocytic thrombocytopenia, and severe congenital neutropenia.

We performed a search on PubMed/MEDLINE from January 1957 to September 2016 by using combined disease-specific terms (underlying bone marrow failure syndrome) and outcome-specific terms using the following algorithm: ([Fanconi anemia] OR [Shwachman–Diamond syndrome] OR [GATA2] OR [GATA2] OR [dyskeratosis congenita] OR [Diamond–Blackfan anemia] OR [familial platelet disorder]OR [congenital amegakaryocytic thrombocytopenia] OR [severe congenital neutropenia]) AND ([MDS] OR [AML] OR [monosomy 7] OR del(7q)). No restrictions concerning language of the article, age, or sex of the patients were imposed. However, we analyzed only English language publications. For sake of completeness, a second search was performed using both a Google Scholar Search and an additional PubMed/MEDLINE search with the following algorithm: ([Fanconi anemia] OR [Shwachman–Diamond syndrome] OR [GATA2] OR [dyskeratosis congenita] OR [Diamond–Blackfan anemia] OR [familial platelet disorder] OR [congenital amegakaryocytic thrombocytopenia] OR [severe congenital neutropenia]) AND ([cancer] OR [leukemia] OR [neoplasia]). Full copies of the relevant papers were obtained. All results were imported into an EndNote™ library, and duplicates were removed by examining titles, authors, and date of publication. Duplication of participants was avoided by comparing dates of published studies and patient-reported data (e.g., date of diagnosis, underlying disease, outcome, cytogenetic abnormalities). Because the diagnostic criteria of MDS and AML changed during this study period, the diagnosis of MDS or AML may have varied depending on the classification scheme (i.e., the French–American–British versus World Health Organization) used at the time of publication. In some articles, MDS and AML were combined as a single entity. In addition, some patients may have been accounted for twice if they developed MDS, then AML. While almost all the reviewed patients were published after 1990 (Supplementary Tables S1–S8), diagnostic criteria and classification of the IBMFS have become better defined and more accurate through genetic analysis. While a recent report from the Canadian IBMFS registry revealed that genetic analysis changed the

diagnosis from one IBMFS to another recognized IBMFS in 9%,[1] we relied on the diagnoses as reported by the authors.

3 | RESULTS

We identified 2,142 articles retrieved by our initial search. After eliminating titles and abstracts that were laboratory research only or did not report any cases of MDS/AML, 189 English language articles were retained for full text review. The following articles are limited to the underlying bone marrow failure syndrome of Fanconi anemia (n = 34), Shwachman–Diamond (n = 37), GATA2 deficiency (n = 14), dyskeratosis congenita (n = 9), Diamond–Blackfan anemia (n = 7), familial platelet disorder (n = 8), congenital amegakaryocytic thrombocytopenia (n = 48), and severe congenital neutropenia (n = 31). Patients with IBMFS were identified from the United States, Canada, Japan, Israel, Korea, Australia, Iran, Egypt, Malaysia, India, Pakistan, and European countries. The eight IBMFS are presented in the following order of the most number of patients surveyed.

3.1 | Severe congenital neutropenia

A total of 934 patients with severe congenital neutropenia were reported in 31 articles. Their age of diagnosis ranged from birth to 13 years of age; 11 and 8% progressed to MDS and AML (Tables 1 and 2), respectively; 17% of MDS cases and 11% of AML cases involved chromosome 7 abnormalities. Abnormalities in chromosome 21 also appear associated with cases that developed to MDS and AML. Death occurred in 17% of severe congenital neutropenia patients with MDS and 68% with AML (Tables 3 and 4). The most reported cause of death was infection and sepsis.

3.2 | Fanconi anemia

A total of 932 patients with Fanconi anemia were identified in 34 articles. Their age at diagnosis ranged from 21 months to 42 years; 21% of patients with Fanconi anemia developed MDS (Table 1), while 14% developed AML (Table 2). Approximately 13% of MDS cases involved chromosome 7 abnormalities. Specifically, 11% involved isolated loss of chromosome 7. The next most frequent abnormality involved chromosome 3 (6%). Approximately 16% of AML cases involved chromosome 7; the next most frequently involved was chromosome 1 (13%). Our review also found that 2.5% of all reported Fanconi anemia cases harbored monosomy 7 without the development of MDS or AML. Death occurred in 66% of Fanconi anemia patients with MDS and 53% with AML (Table 3, 4). Causes of death were infections and septic shock, complications of bone marrow transplant including infection, graft-versus-host disease and multiple organ failure, failure of remission and disease progression, hemorrhage, secondary solid malignancies, renal failure and Sweet syndrome, and hepatic peliosis secondary to long-standing androgen treatment.

3.3 | Diamond–Blackfan anemia

A total of 766 patients were identified as Diamond–Blackfan anemia in seven articles; 0.5% and 0.4% of patients with Diamond–Blackfan anemia went on to develop MDS and AML (Tables 1 and 2), respectively. No chromosome abnormalities, including monosomy 7, were reported. Death occurred in 33% of Diamond–Blackfan anemia patients with MDS and

100% with AML (Tables 3 and 4). The reported causes of death were progressive/metastatic disease in the setting of hematologic and solid tumors and sepsis. In some cases, the cause of death was unknown.

3.4 | Dyskeratosis congenita

A total of 618 patients were identified with dyskeratosis congenita as their underlying bone marrow failure syndrome in nine articles. Their age of diagnosis ranged from 3 to 61 years of age; 3%of patients developed MDS, and 12% of these patients exhibited isolated monosomy 7 (Table 1). Only one case of dyskeratosis congenita transforming to AML was reported (Table 2). No cytogenetic abnormalities besides chromosome 7 were indicated. No deaths were reported among the dyskeratosis congenita patients.

3.5 | Shwachman–Diamond syndrome

A total of 581 patients were identified as having Shwachman–Diamond syndrome in 37 articles. The age of diagnosis ranged from birth to 37 years of age; 11 and 12% of Shwachman–Diamond syndrome patients developed MDS or AML, respectively (Tables 1 and 2); 25% of MDS cases involved chromosome 7, with the next most common being complex karyotype not involving chromosome 7 at 3%; 15% of AML cases involved chromosome 7. Interestingly, 76% of SDS with isochromosome 7q cases did not evolve into MDS/AML (data not shown). Death occurred in 48% of Shwachman–Diamond syndrome patients with MDS and 50% with AML (Tables 3 and 4).

3.6 | Congenital amegakaryocytic thrombocytopenia

A total of 171 patients exhibited congenital megakaryocytic thrombocytopenia as their underlying bone marrow failure syndrome. Their age of diagnosis ranged from birth to 4 years of age. Based on the data from 48 articles, only one and two cases of MDS (Table 1) and AML (Table 2) were reported, respectively. No cytogenetic abnormalities involving chromosome 7 were reported. Small number of patients was reported, with only two who developed AML and both died. Causes of death included hemorrhagic complications and bone marrow transplant-related deaths.

3.7 | GATA2 deficiency

A total of 226 patients possessed GATA2 deficiency in 14 articles. Their age of diagnosis ranged from 4 to 76 years of age; 53.5% of patients with GATA2 deficiency developed MDS while 16% developed AML; 20% of MDS and 39% of AML cases involved chromosome 7. Death occurred in 20% of GATA2 deficiency patients with MDS and 68% with AML (Tables 3 and 4). Wlodarski et al. studied a cohort of 508 children diagnosed with either primary MDS or MDS secondary to chemotherapy, radiation therapy, or to acquired aplastic anemia[5]; 7% of patients with primary MDS were found to have a *GATA2* mutation, in contrast with children with secondary MDS none of whom harbored *GATA2* mutations. Monosomy 7 was identified in 70% of these patients with *GATA2* mutations.

3.8 | Familial platelet disorder

A total of 65 patients with familial platelet disorder were identified in eight articles. Age of diagnosis of familial platelet disorder ranged from birth to 30 years old; 95% of these cases exhibited a *RUNX1* mutation (data not shown); 23 and 13% of familial platelet disorder cases developed MDS (Table 1) or AML (Table 2), respectively. Chromosome 7 abnormalities were once again most recurrent; 20 and 5.3% of MDS and AML cases exhibited chromosome 7 abnormalities, respectively. Death occurred in 30% of familial platelet disorder patients with MDS and 82% with AML (Tables 3 and 4).

4 | DISCUSSION

Chromosome 7 abnormalities were the most common recurrent cytogenetic abnormalities found in individuals with IBMFS that transformed to MDS/AML. −7/del (7q) occurred in17%of cases that evolved to MDS or AML. The next most recurrent cytogenetic abnormality involved chromosome 3 and chromosome 1. In IBMFS that evolved to AML, survival outcome was less than 50%, indicating that this form of secondary AML is lethal. These outcomes may be underreported, as survival outcome data for IBMFS were collected from studies that had variable lengths of follow-up.

We hypothesized that greater insights into the biology of MDS may be gained by determining the association between −7/del (7q) and the IBMFS. We systematically reviewed published reports on the frequency of progression of the eight most common IBMFS to MDS/AML and the frequency of −7/del (7q). While the IBMFS have been long recognized clinically, an emerging concept is that they comprise genetically defined pathways fundamental to cellular physiology.[6] The IBMFS are also recognized as MDS/AML predisposition syndromes.[7] In distinction to adult MDS that harbor multiple mutations with complex clonal architecture,[8] almost all the IBMFS result from single germline mutations. The identities and roles of secondary somatic mutations and cytogenetic alterations in IBMFS remain poorly understood. Of the 4,293 IBMFS patients reported, 436 cases of MDS and 302 cases of AML were identified. Monosomy 7 or del (7q) was found in ~17% of reported IBMFS patients with MDS or AML.

The classification and prognostic scoring of MDS is biased toward adult MDS genetics and natural history as the average age of onset is 70 years.[9] Cytogenetic abnormalities contribute to enhanced classification schemes, including those applied to pediatric populations,[10,11] as well as to provide prognosis. Since the initial association of chromosome 7 abnormalities with myeloid malignancies by Freireich in 1964,[12] −7/del (7q) has been recognized to confer a poorer prognosis.[13–16]

Isolated monosomy 7 may reflect its own unique disease process in adult MDS patients.[17] The loss of heterozygosity for a tumor suppressor gene increases the chance of inactivation of remaining allele and diminishes the cancer-protective function. There is growing evidence that show that haploinsufficiency of a tumor suppressor gene can accelerate tumorigenesis. For example, it has been shown that the partial loss of function in ribosomal protein *RPS14* found on 5q produces analogous functional defect in processing pre-RNA as seen in Diamond–Blackfan syndrome linking the pathophysiology of this particular bone marrow

failure syndrome to MDS.[18] Another study showed that haploinsufficiency of a transcriptional regulator found on long arm chromosome 20, ASXL1, was associated with myelofibrosis phenotype.[19] It is possible that possible that monosomy 7/del(7q) works in a similar mechanism. Studies have identified commonly deleted segments on chromosome 7 long arm and recent comprehensive genomic analysis strongly implicate haploinsufficient role of 7q22 deletion in leukemogenesis. Recently, Wong et al. have created mice with heterozygous germ line deletion in chromosome 7q22 resulting in the mice having features of MDS seen in humans.[20]

The regulation of telomere length may also be associated with the pathogenesis of −7/del (7q). Telomeres are repetitive, noncoding sequences of DNA at the ends of the chromosomes that shorten with each progressive eukaryotic cell division. Cell cycle arrest, senescence, and apoptosis can occur when telomere attrition limit has been achieved. It has been shown that telomere attrition along with somatic mutation precede monosomy 7 and the accumulation of short telomeres gives rise to aneuploidy, which may lead to the progression of MDS/AML in patients with severe aplastic anemia.[21] On the other hand, it has also been argued that the regulation of telomere length occurs because of oncogenic mutations already existing in MDS patients.[22]

Our third aim was to evaluate the survival outcomes of patients who developed MDS/AML. Patients with Fanconi anemia had the worst survival outcome. The majority of patients with Fanconi anemia who developed MDS or AML were deceased. This result may be affected by the difference in follow-up time in each study. Looking through the MDS/AML case series for bone marrow failure patients, we found that majority of those who had poor survival outcomes were associated with chromosome 7 abnormalities. This is consistent with the view that −7/del(7q) carries poor prognosis in patients with secondary MDS/AML.[23]

No statistical analysis or meta-analysis could be done due to high frequency of case reports. There were also missing data for each variable and the retrospective design implicated biases. In addition, we have collected data from case reports that are not ideal source of epidemiologic data, but are often necessary when looking at rare disease. Aside from the inherent publication, selection and reporting bias within the articles examined, our study exhibits ascertainment bias in excluding articles that involved primary MDS/AML with chromosome 7 involvement.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

S.J.C. is supported by funding from NIH R01HL128173, Department of Defense Bone Marrow Failure Idea Development Award BM140102, Leukemia and Lymphoma Society Translational Award, Shwachman–Diamond Syndrome Foundation, and the CURE Childhood Cancer Foundation. This article is dedicated to Bob Arceci; may his memory be a blessing.

Funding Information

Grant sponsor: NIH; Grant number: R01HL128173 Grant sponsor: Department of Defense Bone Marrow Failure Idea Development Award; Grant number: BM140102; Grant sponsor: Leukemia and Lymphoma Society Translational Award Grant sponsor: Shwachman–Diamond Syndrome Foundation; Grant sponsor: CURE Childhood Cancer Foundation.

Abbreviations

AML	acute myeloid leukemia
IBMFS	inherited bone marrow failure syndromes
MDS	myelodysplastic syndrome

References

1. Ghemlas I, Li H, Zlateska B, et al. Improving diagnostic precision, care and syndrome definitions using comprehensive next-generation sequencing for the inherited bone marrow failure syndromes. J Med Genet. 2015; 52(9):575–584. [PubMed: 26136524]
2. Alabbas F, Weitzman S, Grant R, et al. Underlying undiagnosed inherited marrow failure syndromes among children with cancer. Pediatr Blood Cancer. 2017; 64(2):302–305. [PubMed: 27577695]
3. Breems DA, Van Putten WL, De Greef GE, et al. Monosomal karyotype in acute myeloid leukemia: a better indicator of poor prognosis than a complex karyotype. J Clin Oncol. 2008; 26(29):4791–4797. [PubMed: 18695255]
4. von Neuhoff C, Reinhardt D, Sander A, et al. Prognostic impact of specific chromosomal aberrations in a large group of pediatric patients with acute myeloid leukemia treated uniformly according to trial AML-BFM 98. J Clin Oncol. 2010; 28(16):2682–2689. [PubMed: 20439630]
5. Wlodarski MW, Hirabayashi S, Pastor V, et al. Prevalence, clinical characteristics and prognosis of GATA2-related myelodysplastic syndromes (MDS) in children and adolescents. Blood. 2016; 127(11):1387–1397. [PubMed: 26702063]
6. Bodine D, Berliner N. Introduction to the review series on “bone marrow failure”. Blood. 2014; 124(18):2755. [PubMed: 25237202]
7. Glaubach T, Robinson LJ, Corey SJ. Pediatric myelodysplastic syndromes: they do exist! J Pediatr Hematol Oncol. 2014; 36(1):1–7. [PubMed: 24345881]
8. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013; 122(22):3616–3627. quiz 3699. [PubMed: 24030381]
9. Corey SJ, Minden MD, Barber DL, et al. Myelodysplastic syndromes: the complexity of stem-cell diseases. Nat Rev Cancer. 2007; 7(2):118–129. [PubMed: 17251918]
10. Luna-Fineman S, Shannon KM, Atwater SK, et al. Myelodysplastic and myeloproliferative disorders of childhood: a study of 167 patients. Blood. 1999; 93(2):459–466. [PubMed: 9885207]
11. Mandel K, Dror Y, Poon A, et al. A practical, comprehensive classification for pediatric myelodysplastic syndromes: the CCC system. J Pediatr Hematol Oncol. 2002; 24(5):343–352. [PubMed: 12142781]
12. Freireich EJ, Whang J, Tiko J. Refractory anemia, granulocytic hyperplasia of bone marrow and a missing chromosome in marrow cells: a new clinical syndrome? Clin Res. 1964; 12:284.
13. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012; 120(12):2454–2465. [PubMed: 22740453]
14. Haase D, Germing U, Schanz J, et al. New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. Blood. 2007; 110(13):4385–4395. [PubMed: 17726160]
15. van Gelder M, de Wreede LC, Schetelig J, et al. Monosomal karyotype predicts poor survival after allogeneic stem cell transplantation in chromosome 7 abnormal myelodysplastic syndrome and secondary acute myeloid leukemia. Leukemia. 2013; 27(4):879–888. [PubMed: 23164802]

16. Deeg HJ, Scott BL, Fang M, et al. Five-group cytogenetic risk classification, monosomal karyotype, and outcome after hematopoietic cell transplantation for MDS or acute leukemia evolving from MDS. Blood. 2012; 120(7):1398–1408. [PubMed: 22767498]
17. Dimitriou M, Woll PS, Mortera-Blanco T, et al. Perturbed hematopoietic stem and progenitor cell hierarchy in myelodysplastic syndromes patients with monosomy 7 as the sole cytogenetic abnormality. Oncotarget. 2016; 7:72685–72698. [PubMed: 27683035]
18. Ebert BL, Pretz J, Bosco J, et al. Identification of RPS14 as a 5qsyndrome gene by RNA interference screen. Nature. 2008; 451(7176):335–339. [PubMed: 18202658]
19. Stein BL, Williams DM, O'Keefe C, et al. Disruption of the ASXL1 gene is frequent in primary, post-essential thrombocytosis and post-polycythemia vera myelofibrosis, but not essential thrombocytosis or polycythemia vera: analysis of molecular genetics and clinical phenotypes. Haematologica. 2011; 96(10):1462–1469. [PubMed: 21712540]
20. Wong JC, Weinfurtner KM, Alzamora Mdel P, et al. Functional evidence implicating chromosome 7q22 haploinsufficiency in myelodysplastic syndrome pathogenesis. Elife. 2015; 4:e07839.
21. Dumitriu B, Feng X, Townsley DM, et al. Telomere attrition and candidate gene mutations preceding monosomy 7 in aplastic anemia. Blood. 2015; 125(4):706–709. [PubMed: 25406353]
22. Hwang SM, Kim SY, Kim JA, et al. Short telomere length and its correlation with gene mutations in myelodysplastic syndrome. J Hematol Oncol. 2016; 9(1):62. [PubMed: 27465399]
23. Orozco JJ, Appelbaum FR. Unfavorable, complex, and monosomal karyotypes: the most challenging forms of acute myeloid leukemia. Oncology. 2012; 26(8):706–712. [PubMed: 22957403]

TABLE 1

Patients inherited bone marrow failure syndromes and their progression to MDS with consideration of cytogenetic abnormalities

Inherited bone marrow failure syndrome	Total number of diagnosed patients	Age of diagnosis	Total MDS development (% of total number of diagnosed)	MDS with −7 (% of MDS development)	MDS with complex karyotype 7 (% of MDS development)	MDS with other cytogenetic abnormalities
Fanconi anemia	932	21 months–42 years	199 (21.3)	21 (10.6)	5 (2.5)	44 total: 12 (3q+), 10 (1q+), 6 (others), 1(−5), 1 (dup1), 3(11q−), 1 (20q−), 1(9p+), 2 (+8), 1(+21), 6(complex)
Shwachman–Diamond syndrome	581	Birth–37 years	61 (10.5)	10 (16.4)	5 (8.2)	3 total: 1 (del 20q), 2 (complex)
GATA2 deficiency	226	4–76 years	121 (53.5 %)	14 (11.6)	10 (8.3)	16 total: 9 (+8), 1 (del 3), 1 (+1, der (1;7) (q10; p10), +8), 1 (−6, +r), 1 (+8, +mar), 1 (−Y), 1 (del (6)(p23)), 1 (der(22)t(1;22)(q12;p13)/der(15)t(1;15)(q12;p13))
Dyskeratosis congenita	618	3–61 years	17 (2.8)	2 (11.8)	0	None reported
Diamond–Blackfan anemia	766	Birth–30 years	4 (0.5)	0	0	None reported
Familial platelet disorder	65	Birth–63 years	15 (23.1)	2 (13.3)	1 (6.7)	None reported
Congenital amegakaryocytic thrombocytopenia	171	Birth–4 years	1 (0.6)	0	0	None reported
Severe congenital neutropenia	934	Birth–13 years	18 (1.9)	2 (11.1)	1 (5.6)	2 total: 1 (+21), 1 (complex)

TABLE 2

Patients inherited bone marrow failure syndromes and their progression to AML with consideration of cytogenetic abnormalities

Inherited bone marrow failure syndrome	Total number of diagnosed patients	Age of diagnosis	AML development (% of total number of diagnosed)	AML with −7 (% of AML development)	AML with complex karyotype 7 (% of AML development)	AML with other cytogenetic abnormalities
Severe congenital neutropenia	934	Birth–13 years	80 (8.6)	6 (7.5)	3 (3.8)	6 total: 3 (chr 21 abnormality), 2 (complex) 1 (t18;21)
Fanconi anemia	932	21 months–42 years	131 (14.1)	15 (11.5)	6 (4.6)	43 total: 2 (other), 17 (+1q), 11 (+3q), 1 (+13q), 3 (−20q), 2 (del5), 1 (11q−), 1 (21), 1 (+10), 1 (2), 1 (9p+), 2 (8 abn), 2 (del17), 1 (complex)
Diamond–Blackfan anemia	766	Birth–30 years	3 (0.4)	0	0	None reported
Dyskeratosis congenita	618	3–61 years	1 (0.2)	1 (100)	0	None reported
Shwachman–Diamond syndrome	581	Birth–37 years	40 (6.9)	3 (7.5)	3 (7.5)	4 total: 1 (del 20q), 3 (complex)
Congenital amegakary-ocytic thrombocy-topenia	171	Birth–4 years	2 (1.2)	0	0	None reported
GATA2 deficiency	226	4 years–76 years	36 (16)	2 (5.6)	12 (33.3)	4 total: 1(+8), 1 (del3), 1 (del(11)(q13q23)), 1(+8,del(11)(q22q23))
Familial platelet disorder	65	Birth–63 years	19 (29.2)	1 (5.3)	0	None reported

TABLE 3

Survival outcome for patients with inherited bone marrow failure syndrome and MDS

Inherited bone marrow failure syndrome	Total number of patients reported with progression to MDS with data on survival outcomes	Total number of patients with progression to MDS who have died (% of total patients with MDS)
Fanconi anemia	79	52 (65.8)
Shwachman–Diamond syndrome	27	13 (48.1)
GATA2 deficiency	25	5 (20)
Dyskeratosis congenita	3	0 (0)
Diamond–Blackfan anemia	3	1 (33.3)
Familial platelet disorder	10	3 (30)
Congenital amegakaryocytic thrombocytopenia	0	0
Severe congenital neutropenia	6	1 (16.7)

TABLE 4

Survival outcome for patients with inherited bone marrow failure syndrome and AML

Inherited bone marrow failure syndrome	Total number of patients reported with progression to AML with data on survival outcomes	Total number of patients with progression to AML who have died (% of total patients with AML)
Fanconi anemia	19	10 (52.6)
Shwachman–Diamond syndrome	10	5 (50)
GATA2 deficiency	25	17 (68)
Dyskeratosis congenita	0	0
Diamond–Blackfan anemia	3	3 (100)
Familial platelet disorder	17	14 (82.4)
Congenital amegakaryocytic thrombocytopenia	2	2 (100)
Severe congenital neutropenia	22	15 (68.2)