Published in final edited form as:

Pediatr Clin North Am. 2013 December ; 60(6): . doi:10.1016/j.pcl.2013.09.007.

The Inherited Bone Marrow Failure Syndromes

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Abstract

In spite of the rarity of inherited bone marrow failure syndromes (IBMFS), they represent diseases for which the molecular pathogenesis may be elucidated. Their study and presentation of the details of their molecular biology and biochemistry is warranted not only for appropriate diagnosis and management of afflicted patients but also because they lend clues to the normal physiology of the normal hematopoiesis and, in many cases, mechanisms of carcinogenesis. Several themes have emerged within each subsection of IBMFS, including the ribosomopathies that entail both ribosome assembly as well as ribosomal RNA processing. The Fanconi anemia (FA) pathway itself has become interdigitated with the familial breast cancer syndromes. The sections that follow present a more detailed analysis of the diseases that account for the majority of IBMFS diagnoses.

Keywords

ribosomopathies; Fanconi anemia; Diamond Blackfan anemia; dyskeratosis congenita; Shwachman Diamond; Bone marrow failure; DNA repair; Ribosome biogenesis; Cancer susceptibility

In spite of the rarity of inherited bone marrow failure syndromes (IBMFS), careful studies of the molecular pathogenesis of these disorders has led to a deeper understanding of normal and aberrant bone marrow function. Understanding the molecular biology and biochemistry of IBMFS helps in the appropriate diagnosis and management of afflicted patients and also lends clues to the physiology of normal hematopoiesis and, in many cases, elucidates mechanisms of carcinogenesis. Several themes have emerged within each subsection of IBMFS, including the ribosomopathies that include both ribosome assembly as well as ribosomal RNA processing. The Fanconi anemia (FA) pathway itself has become interdigitated with the familial breast cancer syndromes. The sections that follow present a more detailed analysis of the diseases that account for the majority of IBMFS diagnoses.

A. The Ribosomopathies

In recent years, the subset of patients affected with Diamond-Blackfan anemia (DBA), Shwachman-Diamond-Bodian Syndrome (SDBS), dyskeratosis congenita (DC), and cartilage hair hypoplasia (CHH) have all been shown to have mutations in ribosomal proteins and in proteins responsible for processing of ribosomal RNA[1]. The reports of

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amelioration of a DBA-like phenotype in the p53 deficient mouse and zebrafish imply that defects in the ribosome assembly pathway and imbalances in protein synthesis lead to cell stress that can activate the p53 pathway and cause subsequent apoptosis, resulting in a depletion of sensitive cell populations such as the hematopoietic stem cell pool[2][3]. Even though the biology of these syndromes does not completely overlap (i.e., DC involves biology directly at the telomere), several investigators have organized these diseases into a linear or cooperative pathway in which ribosomal RNA is assembled in a multistep process. [4]

1. Diamond-Blackfan Anemia (DBA)

The most common disease of isolated inherited red cell production failure is DBA, with an incidence is approximately 5–7 cases per million live births in North America. Presentation of the disease can be at any age but the majority of patients are diagnosed in the first year of life with at least 10% in one series presenting at birth and 25% within the first month of life. [5][6][7][8][9].

DBA is a genetic disease with evidence of mixed inheritance, although sporadic cases comprise the majority of all cases. A significant portion of inherited cases is autosomal dominant with equal sex frequency. This group of patients appear to have fewer physical anomalies. Another portion of cases is autosomal recessive with disproportionately more males than females, implying an X-linked form of the disease[10][11][12]. Approximately 50% of DBA patients exhibit physical abnormalities, including dysmorphic facies, short stature, eye, kidney, and hand abnormalities[13][14][15]. Patients first present typically with macrocytic anemia and reticulocytopenia and associated pallor, often in the setting of failure to thrive. In the neonatal period, diagnosis can be uncertain, as the normal newborn proceeds through the physiological nadir of erythropoiesis over the first 4–8 weeks and the normal newborn RBC is macrocytic at birth. Thus, most commonly, patients present between 2 and 4 months of age. The confirming finding is reticulocytopenia and decreased erythroid activity in the bone marrow [16][17].

In addition, significant minorities of patients present with neutropenia, thrombocytosis, or thrombocytopenia, even though DBA is thought of as a pure red cell aplasia[18]. Other non-specific abnormalities include elevations of fetal hemoglobin, red cell antigen i, iron, folate, and B12[16][17]. An elevated erythrocyte adenosine deaminase level has been proposed as a good diagnostic test for DBA with a sensitivity of 84% and specificity of 95%. However, 16% of affected people will have a normal erythrocyte adenosine deaminase[19].

The two most common therapeutic options are corticosteroids or transfusion therapy for patients that are symptomatic from their anemia. Corticosteroids may be initiated with anemia that causes cardiovascular and developmental compromise. Prednisone is usually the first line agent at a dose of 2 mg/kg/day. If the child has a response to steroids, the goal is to reach a hemoglobin of 10 g/dl and sustained reticulocytosis after which the steroids can be slowly tapered off. A bit more than half of DBA patients are steroid responders; within this group, many can be weaned to a very low dose or off prednisone completely[20][15][21]. Corticosteroids may become problematic with chronic use, leading to growth retardation, weight gain, gastritis, and decreased bone mineralization. Interestingly, those who are positive responders display a distinctive gene expression signature that may characterize the underlying difference in response as host related.

For patients who do not respond to steroids or cannot tolerate them, transfusion therapy is an effective option. As is the case with chronic transfusion therapy for any disease, iron overload becomes the chief difficulty, resulting in cardiac, endocrine, and pulmonary disease. Chronic iron chelation using subcutaneous desferoxamine has been poorly tolerated

and adherence limited. Since 2006, deferasirox, a daily oral chelator, has been available for treatment of iron overload and in more recently, deferiprone, an oral agent given three times a day was FDA approved for use in this setting[22].

Any discussion of transfusion and iron overload must be balanced against the role of bone marrow transplantation (BMT) as a curative modality with its associated side effects. The side effects of BMT include graft versus host disease (GVHD), infections, and chemotherapeutic toxicity involved with conditioning. With matched sibling donors, the risk of GVHD has become markedly lower with long term survival of over 80%. The optimal timing of BMT in DBA is not known. The younger patient is more likely to exhibit less GVHD and better long-term survival but have more late effects, leading some to argue for waiting for additional time to allow for late remissions [23][24].

Growth factors have also been used in DBA. Erythropoietin has been the logical choice without any evidence of efficacy[25]. IL-3 has shown some modest benefit amongst transfusion-dependent patients, along with side effects of deep venous thromboses and constitutional symptoms[26][27]. In recent years additional agents have been shown to be at least anecdotally beneficial, including leucine and metaclopropamide.

Patients with DBA have a reduced life expectancy from causes largely related to treatment side effects and long term risks of malignancy. In addition, hematologic malignancy is a major cause of death as DBA patients have a risk of AML with a lifelong risk of up to 25% [28]. Anecdotally ALL, Hodgkin's, and MDS have all been reported in DBA [29][30][31][32]. Reports of osteogenic sarcoma and hepatocellular carcinoma, which are likely associated with concomitant viral hepatitis infection, have also been published [33][34]. An overall risk of 5.4 odds ratio for developing cancer in DBA has been calculated, with predominance in MDS, AML, colon cancer, osteogenic sarcoma, and genital cancer.

Often mentioned in the differential diagnosis of DBA are transient erythrocytopenia of childhood (TEC) and infection with parvovirus. TEC and parvovirus induced aplasia should resolve within a month and both are unusual in the newborn period.

The science of DBA has exploded in the last decade. The first gene identified as mutated in DBA, ribosomal protein RPS19, was cloned positionally by analyzing a patient with DBA who had a translocation interrupting the RPS19 locus. Twenty-five percent of DBA patients have RPS19 mutations in the heterozygous state, which implies that the allele acts in a dominant negative fashion or that a dosage effect exists and that the presence of 2 mutated alleles may be lethal [35][36]. As many as 8 additional mutations in ribosomal genes have been identified, both in the large as well as the small subunit of the ribosome (RPL5, RPL11, RPL15, RPL35, RPS7, RPS10, RPS17, RPS24, RPS26), leaving almost 50% of DBA cases having no identified mutation [37]. A recent report detailed the first non-ribosomal mutation found in a DBA patient, exhibiting a GATA splice site mutation [38].

The cloning of these genes alone does not answer the basic question of why DBA occurs. In general, reduced colony forming activity in DBA patients has been observed, but this has not proven to be a reliable predictor of DBA [39][40][41][42]. Progenitors have been marked by accelerated apoptosis [43]. Defects in the microenvironment of the marrow have also been proposed as contributors to pathogenesis because of inhibition of erythropoiesis by bone fragments from a DBA patient. Other affected functions include growth factors, their receptors, and transcription factors [44].

A mouse with an RPS19 knockout showing the DBA phenotype has been made and is being studied. As noted above, increased understanding of DBA came through amelioration of its phenotype in a p53 knockout background in both the mouse and the zebrafish, leading to a

lower rate of apoptosis and suggesting that the imbalance of ribosome synthesis and/or inefficiency of protein translation leads to cell stress. In addition, RPS26 has been demonstrated through an RPL11 mediated pathway to stabilize p53 via interaction in an inhibitory fashion with MDM2, which is the E3 ubiquitin ligase for p53, thus leading to the stabilization of p53 [45].

An interesting overlap with adult MDS has been characterized in the identification of the etiology of the 5q- syndrome, which arises as a result of deletion of the RPS14 gene. This acquired defect leads to a lower risk MDS that has been treated with lenalidomide[46][47].

2. Dyskeratosis Congenita

Dyskeratosis congenita (DC) is a genetically heterogeneous disorder related to defects in telomere maintenance. The classic X-linked recessive form in particular appears to be associated with the classic DC findings of hyperpigmented reticular lacy pigmented skin, dystrophic nails, and leukoplakia. Up to 90 percent of patients develop bone marrow failure, although the time to recognition of classic findings is quite variable. The inheritance pattern can also be autosomal dominant or autosomal recessive. Two particularly severe variants are Hoyeraal-Hreidarsson (HH), presenting as systemic DC with cerebellar hypoplasia and developmental dysfunction and Revesz syndrome, similar to HH coupled with exudative retinopathy. Reported cases have included probands with intrauterine growth retardation and microcephaly. In addition, these patients have a predisposition to myelodysplasia, myeloid leukemia, and an assortment of solid tumors, including squamous cell cancers of the head, neck, and anogenital region[48][49][20][50]. As in numerous genetic cancer predisposition syndromes, sporadic mutations have been found in DC genes in cancers, suggesting the importance of the telomere broadly in cancer outside of DC.

On a cellular level DC cells are characterized by progressive telomere shortening that accumulates in an age-dependent fashion, thus leading to variability in the phenotype. In fact, the age of presentation has been reported to be as high as 75 years. When a patient with bone marrow failure does present, given the clinical heterogeneity of many of these disorders in question, telomere analysis should be a part of the workup for all bone marrow failure. While some variability exists in telomere length analysis, overall it is a sensitive test for DC, and combination analysis with flow cytometry to measure telomeres in multiple cell subsets can enhance its utility[51].

The first identified gene DKC is X linked (and the most common form of DC), encoding the dyskerin protein that resides in ribonucleoprotein (RNP) complexes at the telomere as well as in ribosomal RNA. This implies a duality in mechanism of the proteins involved in DC. Dyskerin binds to the RNA that serves as the template for the TTAGGG repeats found at telomeres. Other members of the telomerase RNP found to be causative when mutant in DC include NOP10, NHP2, TCAB1, TERC and TERT (telomerase reverse transcriptase), all of which are autosomal recessive inheritance[52][53][51]. Dyskerin also appears to be involved in the pseudouridylation of rRNA, but the specific function in the ribosome of this modification is unclear[54].

The other genes responsible for DC reside in the shelterin complex that protects telomeres from degradation. Shelterin is a 6-member protein complex that includes the DC causative gene TIN2. The function of the shelterin complex is to protect telomeres from exonuclease activity, thus enabling the integrity of telomere length[52].

The classical presentation of DC includes two of the three following findings: dystrophic nails, a reticular lacy rash, leukoplakia. Other features recognized to be part of the DC spectrum include premature graying hair, pulmonary fibrosis, liver disease, leukemia or

MDS, esophageal stenosis, urethral stenosis, short stature and developmental delay. Recently described is the high prevalence of neuropsychiatric disorders in this population, which has previously been reported as 25% in children but in a recent small prospective study done by the NCI, the lifetime risk for children with DC was 83% for disorders including ADHD, PDD, anxiety and mood disorders[55].

The diagnosis of DC can be difficult with still close to 50% of patients lacking a known mutation in the DC pathway. The measurement of telomere lengths in lymphocyte subsets has become an important element that supports a diagnosis of DC. Patients with DC have very short telomeres well below the normal range in contrast to other IBMFS patients who often have short telomeres compared to the general population but are not significantly shorter than the first percentile. Clinicians must use a combination of physical exam findings, family history, and features of leukemia or bone marrow failure and/or very short telomere lengths. Often, the family history can be particularly useful in anticipating new patients who may have worse disease than their forebears, perhaps because the telomere inheritance gets shorter and shorter with each generation.

Management of DC generally centers around treating the symptoms of marrow failure. Because the treatment options have significant morbidity, a watch and wait approach is often employed. When cytopenias cause symptoms, androgens can be used to good effect despite masculinizing side effects and the need for careful monitoring for liver tumors later in life. The use of growth factors has achieved some temporary improvement in counts and related symptoms, but worry of malignant transformation in the resultant stressed marrow remains a concern[56][57].

If those therapies do not help, BMT can be considered. Unfortunately, outcomes for BMT have been poor based both on patients' sensitivities to conditioning regimens as well as the underlying disease. DC patients are unique in having very late pulmonary and liver complications, likely due to their underlying disease, that may be worsened or accelerated by the transplant process. Recent data from 2013 looking at 34 patients treated from 1981 to 2009 reported a 10 year survival probability of 30%. Unrelated donors or mismatched related donors and regimen intensity were independent risk factors for early mortality[58][59][60].

3. Shwachman-Diamond syndrome

Shwachman-Diamond syndrome (SDS) is a syndrome of neutropenia, pancreatic exocrine function insufficiency, and metaphyseal dysostosis. Anemia and thrombocytopenia can indeed accompany the neutropenia. SDS patients also can have a wide array of physical findings, including short stature, failure to thrive, skin rashes and macules, teeth and palatal defects, and syndactyly[7][61][62]. The putative gene which when mutated leads to SDS is the SBDS gene, encoding a 250 amino acid protein with predicted functions in RNA metabolism. Its widespread expression may be the basis of the multiple organ involvement of SDS [63]. A recent model using induced pluripotent stem cells as a model for SDS manifests exocrine and hematopoietic cell dysfunction that phenocopies SDS[64]. Recent work demonstrates the defective processing of rRNA into ribosome assembly, suggesting that SDS is closely associated with the molecular pathogenesis of DBA [65]. A majority of SDS patients do not display a mutation in the SBDS gene, suggesting additional genes underlying the pathogenesis of SDS. The diagnosis of SDS can be difficult, as many patients do not have an identifiable mutation in SBDS gene. Clues can be found by examining trypsinogen, isoamylase, and obtaining an ultrasound of the pancreas. Family history may provide a clue but is less useful than in DC.

No definitive therapy exists for SDS neutropenia, except for bone marrow transplantation, while pancreatic insufficiency is managed by administration of exogenous pancreatic enzymes. Supportive care is indicated with transfusions in the 20% of SDS patients who develop pancytopenia. Some efficacy has been reported with the use of granulocyte-stimulating growth factors, with 6 out of 7 responding to G-CSF in one series. Like other IBMFS, the diagnosis of SDS confers a 5% risk of leukemia, including ALL, CML, and AML, making the use of growth factors a difficult decision for fear of stimulating a clonal expansion, despite minimal data to support this concern [66][67][68].

4. Cartilage hair hypoplasia

Cartilage hair hypoplasia (CHH) is a recessive disease with a constellation of skeletal abnormalities consisting of short stature, lordosis, scoliosis, and chest wall deformities. The disorder was first described amongst the Old Order Amish. Sparse, fine hair is the other consistent feature [69][70]. Growth failure occurs prenatally with shortness of limbs or stature noted on fetal ultrasound or perinatally. CHH patients also have increased risk of Hirschsprung's disease [71]. Mutations in the RNA component of RNAse MPR endoribonuclease involved in mitochondrial and nucleolar RNA processing has been reported to be responsible for CHH [72]. Together with TERT, the telomerase reverse transcriptase, RMRP forms a complex that produces double strand RNA that participates in small interfering RNAs [73]. RMRP works in parallel with Diamond-Blackfan anemia defects, upstream of Shwachman-Diamond, and downstream of dyskeratosis congenita in the processing of the 80S unit of the ribosome [74].

Anemia and macrocytosis occurs in the variable context of pancytopenia [75]. Lymphopenia is reported along with defective cellular immunity [76]. Corticosteroids and transfusion have been used temporarily with some patients outgrowing marrow failure [77]. However, increased malignancy risk was also reported throughout infancy, childhood, and adulthood [69][78]. T cell lymphoproliferative disease has been seen as a consequence of immunodeficiency [79].

B. Fanconi anemia (FA)/BRCA Pathway

Fanconi anemia (FA) is an autosomal and X-linked recessive disorder characterized by bone marrow failure, acute myelogenous leukemia (AML), solid tumors, and developmental abnormalities. At the molecular level, cells derived from FA patients display hypersensitivity to DNA cross-linking agents, resulting in increased numbers of chromosomal abnormalities including translocations and radial chromosomes. This hypersensitivity has made successful treatment for FA patients a challenge in the past because traditional treatments of symptoms resulted in more harm than good. In recent years, care of the FA patient has improved with modern blood banking, antibiotics, and hematopoietic stem cell transplantation (SCT), which has been used in performed in FA patients for almost 30 years [80]. Despite greater survival of children into adulthood as a result of SCT, the specter of the potential for solid tumors, such as squamous cell carcinomas of the head, neck, and genitourinary track, remains a serious problem [81][82].

Even though the classic features of thumb abnormalities and radius absence generally characterize these patients, FA children typically present in the first decade of life upon recognition of aplastic anemia [83][84][85]. Even more interesting is the fact that a sizable subset of FA patients has no discernible abnormalities at all. As a result, the index of suspicion of the clinician must be high to recognize the diagnosis of FA in the differential diagnosis of aplastic anemia.

The gold standard tests for FA quantify chromosomal breakage in cells exposed to cross-linking agents to which FA cells are hypersensitive, typically diepoxybutane[80,85]. On occasion, despite the strong suspicion of FA being present in a patient, the chromosome fragility test can be negative due to somatic reversion[86][87]. In the face of this possibility, if a negative diepoxybutane or mitomycin C result has been obtained in the setting of strong suspicion of an FA diagnosis, then a skin biopsy should be obtained for culture and subsequent diepoxybutane testing.

Ninety percent of FA patients first present with bone marrow failure, but a percentage present nonetheless first display AML. These cases of AML are typically M1-M4 FAB subtype and display no characteristic cytogenetic or molecular abnormality, although numerous translocations, deletions, and other aneuploidogenic changes can be found[88]. Some report distinctly different clones in FA-associated AML versus sporadic AML [89]. Patients treated in a fashion similar to other AML patients experience intolerance to standard doses of alkylating agents. Thus, morbidity precludes an aggressive approach. In addition, analysis of cells derived from these AML cases suggests that some are paradoxically resistant, perhaps a result of the underlying genomic instability of FA cells that could allow acquisition of resistance[90].

FA patients are at markedly increased risk of squamous cell carcinomas (SCC) of the head and neck and genitourinary tract. These tumors have been only sporadically positive for human papilloma virus, although vaccination for HPV is strongly encouraged in the FA population. In addition, routine laryngoscopy and ENT follow up is considered standard of care for FA patients[81][82][91]. Breast cancer is also typical of adult FA patients, which is in line with the fact that 5 FA genes are actual familial breast cancer genes: BRCA2, PALB2, RAD51C, SLX4, and BACH1[92,93][94][95][96].

FA genes have also been implicated in sporadic cancers by virtue of detection of non germline mutations in tumors such as lung, pancreatic, ovarian, and breast. It has been proposed that such tumors can be targeted by using agents specifically inducing hypersensitivity in FA mutant cells[97].

Because the FA patient is at increased risk of toxicity from SCT regimens, clinicians must time the procedure before the onset of leukemia, avoiding the long-term effects of blood product provision or unaffected by serious infections from invasive organisms like *Aspergillus*. The complementation group and gene mutation should be identified in order to assess the suitability of a family member stem cell donor, averting the possibility that a matched donor has a subclinical case of FA. It has become clear from the experience of FA clinicians that FA-D1 and those with the Ashkenazi FANCC mutation patients are at significant and early risk of progression to AML, often before the presentation of aplastic anemia[98][98]. In general terms, it is thought that such a risk of early AML progression is coincident with a more severe FA phenotype[99][100][101].

Historically, the challenges of SCT in FA patients have been numerous. The issue of graft failure has a prevalence of 10%, but use of fludarabine has reduced this risk to < 1%. As a result, efforts at reduction of conditioning have been steady and the use of total body irradiation has been diminished down to doses of 400 to 600 cGy. In addition, the use of cyclophosphamide has also been decreased in recent years. With an allogeneic-related transplant, the long-term survival is often greater than 80%[102][101].

Matched-unrelated transplants have posed a greater challenge with a greater incidence of graft-versus-host disease. Toxicity-associated graft-versus-host disease occurs with greater intensity in the FA patient, perhaps because of the greater degree of toxicity caused by

conditioning. Such toxicity is synergistic with the increased graft-versus-host disease risk. With diminished toxicity has come greater graft-versus-host disease control and subsequent increased survival for FA patients undergoing matched-unrelated transplants[101][103].

Secondary effects of SCT have important consequences for FA patients presumably because of their underlying issues of growth delay, endocrine dysfunction, and increased risk of malignancy, all of which are associated with long-term consequences of undergoing SCT. A markedly increased risk of acquisition of SCC is seen post-transplantation beyond that observed in untransplanted FA patients; these SCC are only somewhat linked to human papillomavirus [82]. GVHD greatly increases the risk of SCC in FA patients and patients undergoing unrelated stem cell transplant.

The idea that FA cells are hypersensitive to endogenous and exogenous stimuli suggests that FA stem cells in the bone marrow are susceptible to a sort of “natural selection.” This is probably why somatic reversion is observed in some FA patients. As a result, it has been postulated that gene therapy is an ideal approach to treatment of FA. Clinical trials targeting the most common complementation group, FA-A, have been instituted using a lentiviral transduction system of hematopoietic stem cells from FA patients, manipulated *ex vivo*. *In vitro* data suggest that hematopoietic stem cells can be transduced with subsequent colony-forming assays suggesting increased growth and reconstitution. Such trials have been disappointing, however, because lack of permanent transduction of progenitors has led to failure to establish long-term hematopoiesis[104][105].

Traditionally, androgens have proved to be an efficacious treatment in some bone marrow failure patients, FA patients included. Androgens can stimulate more effective hematopoiesis, resulting in an increase in peripheral blood counts. The use of androgens has been marked by their limitations in females, given the masculinizing side effects. In addition, their use has been associated with increased risk of liver adenomas[106,107].

The FA pathway is composed of at least 16 genes[108]. Each of these genes, when biallelically mutated, causes FA, except for the X linked FANCB. The encoded proteins (Table 1) can be subdivided within the FA pathway into three groups: (1) proteins that make up the core complex; (2) the FANCD2 and FANCI proteins, which compose the ID complex; and (3) five downstream effector proteins, FANCD1/BRCA2, FANCF/BRIP1/BACH1, FANCN/PALB2, FANCO/SLX4, and FANCP/RAD51C. Many of the FA proteins contain no recognizable motifs, which has made discovering their contributions to the FA pathway and the main function of the FA pathway more challenging[108][109][110][111].

Teleologically, the involvement of very specific developmental abnormalities in FA patients implies that the FA proteins have the potential for other functions aside from those they perform in protecting the genome. Some have argued that the main function of the FA pathway is to regulate oxidative stress, because reactive oxygen species have been documented to be involved in bone marrow failure[112][113], cancer[114], endocrinopathies[115], abnormalities in skin pigmentation[116], and malformations[117]. This explanation becomes even more plausible when considering the redox-related functions of some FA proteins[118][119]. Recent provocative work has supported the idea that acid aldehydes are the toxic metabolite *in vivo*, as mouse models knocking out enzymes that detoxify such chemicals phenocopy FA[120].

Several lines of evidence have shown that excessive apoptosis and consequent malfunction of the hematopoietic stem cell compartment lead to progressive bone marrow failure in FA patients. The FANCC protein functions independently of the FA core complex to suppress apoptosis in hematopoietic cells in response to environmental cues, which induce expression

or secretion of certain cytokines[121]. FA patients exhibit altered expression levels of some growth factors and cytokines, including unusually high levels of intracellular tumor necrosis factor- α (TNF- α), a cytokine capable of initiating the apoptotic pathway. Neoplastic stem cell clones, however, which are resistant to these cytokines, frequently evolve in FA patients and result in leukemia. Cells from TNF- α -treated *fancd1*^{-/-} mice also showed increased levels of chromosomal aberrations and decreased levels of repair of DNA damage caused by reactive oxygen species, indicating that FANCC may also play a role in the cellular response to oxidative DNA damage[122,123][124].

C. Mitochondrial Diseases

1. Pearson Syndrome

Pearson syndrome is a rare sideroblastic anemia with associated exocrine pancreatic dysfunction, liver dysfunction, and renal tubule defects[125][126]. Often patients are diagnosed in the neonatal period, and Pearson syndrome has been reported as a cause of hydrops. Rarely these patients can have physical abnormalities such as retinopathy, ataxia, or muscle weakness but often present with failure to thrive or poor growth along with persistent, macrocytic anemia[127]. These cases, numbering no more than 40 reported in the literature, have been diagnosed histologically with vacuolization of bone marrow precursors[20][128]. In the 1990s, the molecular defect of Pearson syndrome was characterized, involving deletions and duplications of regions of mitochondrial DNA[129][130]. As a result of the mitochondrial defect, the enzymes of the oxidative respiration cascade are compromised, and thus acidosis is the major component of the disease. In patients with the disease who survive the neonatal period, the anemia improves and in fact, elevations in hemoglobin have been observed. Recently, induced pluripotent stem cells have been produced that serve as a new primary cell model for Pearson's[131]. Growth factors have been used in the therapy of Pearson's but have not proved effective. Transfusions remain the mainstay of therapy, but mortality is high in early childhood from acidosis, sepsis, or liver and kidney failure. Malignancy has not been associated with this disease[132].

B. Reticular dysgenesis (RD)

This extremely rare disease almost exclusively presents in the neonatal period with leukopenia and lymphopenia and no myeloid and lymphoid precursors but usually not complete marrow aplasia[133][134][135][136]. Lymphoid tissue is generally absent. Early progenitors are probably the defective cells since two distinct lineages are affected. However, a subset of patients has anemia and thrombocytopenia. Genetic analysis has demonstrated that RD is of mitochondrial origin with mutations found in the adenylate kinase 2 gene[137]. The action of this gene has been postulated to be involved with the unfolded protein response, whose absence may lead to imbalance in secretory protein load. BMT has been curative in RD patients who clinically act like severe combined immune deficiency patients. Mixed results occur because of the difficulty of infant BMT, and the resulting mortality is high[138][139].

D. Congenital Thrombocytopenias

1. Amegakaryocytic thrombocytopenia

A handful of cases with isolated thrombocytopenia have been reported in patients who display none of the classic findings of FA or thrombocytopenia/absent radii syndrome (TAR). These patients exhibit a range of developmental defects, including microcephaly, low birth weight, delay, cardiac defects, central nervous system defects, and orthopedic anomalies. The presentation of most patients includes thrombocytopenia without

megakaryocytes on marrow examination. Progressively, an increasingly hypocellular picture emerges over time, suggesting that pancytopenia is a bigger issue than at initial presentation. A familial pattern has emerged in these patients, which fits both autosomal recessive and X-linked inheritance. Several candidates have been identified as the causative gene, including MPL, RUNX1, ANKRD26, MYH9, and PTPN1, but the large majority of cases of mutations has been in MPL, the thrombopoietin receptor. Forty percent of patients develop pancytopenia along a variable timeline and are at risk of leukemia. Corticosteroids have been used with limited success and little BMT experience exists in this disease[20][7][140][141].

2. TAR syndrome

Thrombocytopenia with absent radii (TAR) is an autosomal recessive disease with preserved thumbs. Thrombocytopenia is usually evident from birth and almost certainly by 4 months of age and is accompanied by significant hemorrhagic events. Megakaryocytes are absent, classifying it as a progenitor disease only affecting the platelet lineage. Some patients exhibit a leukemoid reaction, but this subsides in infancy. Because of the lack of malignancy, genomic instability, and no reports of FA mutations, this disease entity is likely not an overlap with FA nor a premalignant syndrome, although sporadic cases of leukemia associated with TAR exist. Platelet counts improve after infancy; thus afflicted patients do relatively well after the first year of life, requiring platelet transfusions only during infancy. Other modalities have not been shown to be effective[20][142][143].

F. Congenital Dyserythropoietic Anemia (CDA)

The CDAs are a group of isolated red cell production disorders characterized by morphological abnormalities of erythroid precursors in the bone marrow, a consequence of dyserythropoiesis and ineffective erythropoiesis[144][145]. In addition, distal limb malformations, including syndactyly, absence of phalanges and nails, an additional phalanx, and duplication or hypoplasia of the metatarsals, have been reported in several cases of CDA I[146]. Other congenital abnormalities found include café au lait spots, short stature, flattened vertebral bodies, hypoplastic rib, Madelung deformity, deafness, and retinal angioid streaks[147][148].

On the basis of morphological abnormalities of the bone marrow, CDAs have been classified into three different types: type I, type II, and type III, but additional variants requiring further characterization have also been identified. Approximately 600 cases of CDA have been reported worldwide, CDA II being the most common[149]. CDA II in particular has been associated with the HEMPAS phenotype (**h**ereditary **e**rythroid **m**ultinuclearity with **p**ositive **a**cidified **s**erum). CDA I and II are inherited in an autosomal recessive pattern, and CDA III exhibits autosomal dominant inheritance and a sporadic form[144]. The disease-related genes for CDA I, II, and III have been localized by linkage analysis, and the disease-causing genes have been identified for CDA I, II, and III. Additional reports suggest other distinct forms of CDA. Most of these have been tentatively assigned to four phenotype-based groups designated CDA group IV, V, VI, and VII, with varying degrees of anemia and erythroid dysplasia. They have been designated as groups rather than types as there is evidence of phenotypic and/or genetic heterogeneity within each group. In addition to these groups, each of which includes three or more families, there are cases with unique features reported in only one or two families.

The ineffective erythropoiesis of CDA leads to intermittent jaundice, splenomegaly, hepatomegaly, and iron overload, also a result of blood transfusion therapy[145][150][151]. Dyserythropoiesis results in abnormal features of marrow erythroblasts such as

internuclear chromatin bridges, multinuclearity, vacuolization, and duplication of the plasma membrane.

CDA I is an autosomal recessive disease marked by mutations in *cdan1*, whose encoded protein has no obvious function[152]. Additional variants of CDA I have demonstrated mutations in the erythroid transcription factor *KLF1* in a dominant fashion[153]. CDA I is marked by spongy heterochromatin, suggesting a role for *cdan1* in chromatin, and a link to the chromatin binding protein HP1 has been made[154]. CDA II is also autosomal recessive, with mutations reported in the secretory pathway gene *SEC23B*[155]. CDA III is an autosomal dominant disease with reported mutations in the *KIF23* gene, a kinesin[156]. Given the lack of a cancer phenotype and the involvement of these gene products in chromatin and in the secretory pathway, these genes suggest a pathway for regulation of nuclear extrusion and red cell maturation and the lack of involvement in early erythropoiesis.

Treatment varies amongst groups of CDA, although generally attention to gallstones and iron overload is warranted. Splenectomy is often indicated for CDA II; less so for other groups. Interferon alpha has been shown to be efficacious, especially in CDA I[149].

E. Workup of a patient with bone marrow failure

The clinical signs of pancytopenia include infection, bruising, and pallor. A blood count, usually done by the primary care physician or emergency department, will then reveal pancytopenia. Sepsis or viral suppression can result in neutropenia and thrombocytopenia, and thus the clinical situation must be considered anytime one considers the diagnosis of hypoplastic marrow. In the absence of sepsis, a complete blood count and manual examination of the peripheral smear is mandatory. In addition, a bone marrow aspiration and biopsy are crucial to determine a primary cause. Samples should be sent for:

1. Cytogenetics

Culturing of mononuclear cells and examination of chromosomes for cytogenetic abnormalities is required for aplastic presentation. An abnormality indicative of malignancy, myelodysplasia, genetic syndrome (e.g., Down's), or clonal process would alter therapeutic interventions.

2. Diepoxybutane(DEB) chromosome fragility assay

This assay involves the incubation of a mononuclear fraction of blood cells in the presence of a bifunctional alkylating agent, that is an agent which can cause an inter or intrastrand DNA crosslink. The cells are then treated with colchicine to arrest them in mitosis and are dropped onto a slide for a karyotype-like analysis. Increased chromosome breaks in this setting are pathognomonic for Fanconi anemia. The test is very sensitive and specific. The DEB test is crucial because many FA patients bear none of the classic physical findings of FA.

3. Flow cytometry

Delivery of mononuclear cells into the FACs machine after fluorescent detection of surface antigens demonstrates the full panel of normal mature and precursor cells in bone marrow and peripheral blood. Detection of abnormal groups of cells reveals potential clonality or malignant process. Flow for CD55, the paroxysmal nocturnal hemoglobinuria(PNH) clone, should be performed. It is common to find a clone at low percentage but consensus is that more than approximately 15% clone would be concerning for PNH.

4. Genotype analysis

Cases in which an inherited transmission is responsible and for which a gene has been likely cloned should be analyzed for presence of mutation. For example, 16 FA genes have been cloned, and retroviral gene correction is available can establish the genetic complementation subgroup for FA as well as focus the search for mutations. Once the mutation is described, then effective genetic counseling may be provided for the family. CLIA-approved genetic sequencing panels now exist whereby genes in the FA, DC, DBA, and other syndromes may be interrogated for mutations, assuming some clinical suspicion.

5. Infectious etiologies

Titers for suspected viral causes of aplasia may be sent for IgG and IgM so the source and status of infection can be determined and followed. In some cases, PCR may be used to directly test for presence of pathogens associated with marrow aplasia. Such viruses include hepatitis, parvovirus, CMV, EBV, HHV6, and others.

6. Telomere length analysis

Similar to DEB testing, telomere length analysis is a functional assay to screen for dyskeratosis congenita. The test should be done on lymphocyte subsets and not simply granulocytes or all white blood cells combined. If the results are well below the first percentile of the normal population for age then there is a high likelihood the patient has DC. Also, many patients with IBMFS have shorter telomere lengths closer to the first percentile and so it may also give some support to a clinical suspicion of an inherited process even if it is not DC.

7. Research

The physician should consider the collection of additional blood or marrow for research purposes per approved institutional protocol, given the rarity of marrow failure syndromes.

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Key Points

1. In spite of the rarity of inherited bone marrow failure syndromes (IBMFS), they represent diseases for which the molecular pathogenesis may be elucidated.
2. Their study and presentation of the details of their molecular biology and biochemistry is warranted not only for appropriate diagnosis and management of afflicted patients but also because they lend clues to the normal physiology of the normal hematopoiesis and, in many cases, mechanisms of carcinogenesis.
3. Several themes have emerged within each subsection of IBMFS, including the ribosomopathies that entail both ribosome assembly as well as ribosomal RNA processing.
4. The Fanconi anemia (FA) pathway itself has become interdigitated with the familial breast cancer syndromes.

Table 1

Syndrome	Inheritance pattern	Genes	Physical findings	Laboratory testing
Fanconi Anemia	AR, XLR	FA-A---FA-P Breast cancer genes	Short stature, radial limb, thumb,	Diepoxybutane (DEB) chromosome breakage MMC breakage assay Gene testing
Dyskeratosis Congenita	AR, AD, XLR	TERT, TERC, DKC, TINF2, NOP10, TCAB1, NHP2	Nails, skin, leukoplakia	Telomere lengths lymph subsets Gene testing
Shwachmann Diamond	AR	SBDS	Pancreatic insufficiency, skeletal abnormalities	Serum trypsinogen, Isoamylase, fecal elastase, pancreatic imaging Genet testing
Diamond Blackfan anemia	AD	RPS7 RPL5 RPS17 RPL11 RPS19 RPL15 RPS24 RPL35a RPS26	Short stature, head, upper limbs, urogenital	Erythrocyte adenosine deaminase (ADA) Gene testing
Congenital Amegakaryocytic thrombocytopenia	AR	C-MPL		Gene testing