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Inherited Bone-Marrow Failure Syndrome

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INHERITED BONE MARROW FAILURE SYNDROMES

James Joseph Southern Maine Community College, Spring 2021

Abstract

The inherited bone marrow failure syndromes are heterogeneous group of rare genetic disorders characterized by bone marrow failure, congenital anomalies, and cancer predisposition. This includes disorders associated with pancytopenia, such as fanconi anemia and dyskeratosis congenita, as well as disorders with predominantly, but not exclusively, single lineage cytopenias.

These syndromes are associated with mutations in 33 genes, and this has led to further understanding of hematopoiesis and how this is disrupted in patients with bone marrow failure. Other fundamental biological pathways were examined in patients, such as the DNA repair-fa/BRCA pathway. Fanconi anemia/BRCA is a human tumor suppressor gene also known as a caretaker gene and is responsible for repairing damage DNA or destroy cells if DNA cannot be repaired. Another pathway examined was the telomere maintenance of dyskeratosis congenita, an inherited bone marrow failure syndrome characterized clinically by the triad of abnormal nails, reticular skin pigmentation, that has been found to have x-linked recessive, autosomal dominant and autosomal recessive subtypes. There is also a mutated gene in x-linked DC (*DKC1*) which encodes a highly conserved nucleolar protein called dyskerin. Dyskerin associates with the H/ACA (human anti-chimeric antibody) a class of small nucleolar RNA in small nucleolar ribonucleoprotein particles (snornp), which are important in guiding the conversion of uracil to pseudouracil during the maturation of ribosomal RNA.

This poster will review recent literature about the mutations that are most directly associated with this rare genetic disorder.

Bone marrow failure (BMF) disorders are characterized by presentation with pancytopenia or single lineage cytopenias. Although acquired aplastic anemia (AA) is the most common BMF disease at all ages, children and adults may have an inherited BMF (IBMF) disease that must be diagnosed if present, because this is critically important not only for treatment choices but also to monitor for progression to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). MDS and AML occur with increased frequency through acquisition of somatic mutations in medically treated patients with acquired AA but have a much greater likelihood in patients with germline.

This reviewed article presents the cases of pancytopenia associated with acquired aplastic anemia and bone marrow failure syndromes. These disorders has been differentiated for the presentation of treatment decisions. Identification of new inherited germline cell diseases as a result of genetic testing intervention in patients presented with inherited bone marrow failure disorder was made possible. In patients, evidence as shown that many individuals with this disorder may appear to be normal with fewer or no symptoms in clinical settings. The prognostic value of somatic mutation may vary in different stages of individual level of advancement of the disease. The proliferative defect observed in inherited bone marrow failure syndrome can be reversed using hematopoietic stem cells, which may still furtherly develop somatic mutations and may progress to myelodysplastic syndrome or acute myeloid leukemia.

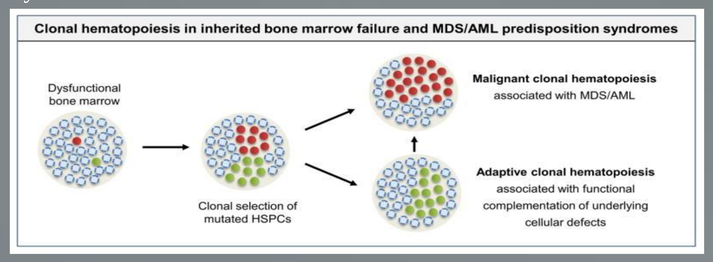

Fig.1. Image adapted from Hematol Oncol Clin North Am. 2018 Aug; 32(4): 643–655.

Bone marrow failure syndromes are associated with dysfunctional hematopoiesis that may drive a strong selective pressure that favors mutated hematopoietic stem and progenitor cells with enhanced fitness. as seen in the fig. above (red) some mutations may result in leukemic transformation, others may enable clonal expansion due to functional complementation of disease specificity to cellular defects (green). The latter may involve biological pathways that are distinct from leukemic transformation and not associated with elevated risk of progression to MDS or AML.

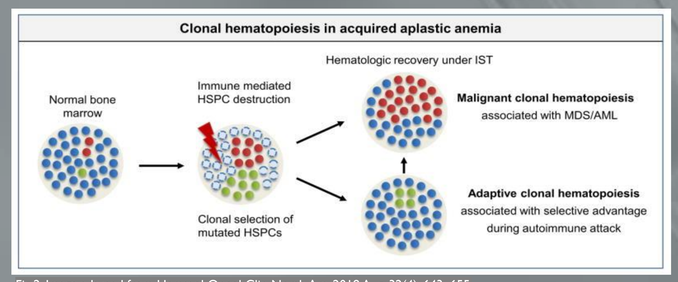

Fig.2. Image adapted from Hematol Oncol Clin North Am. 2018 Aug; 32(4): 643–655.

Immune mediated selection pressure drives the expansion of HSPCs (Hematopoietic stem and progenitor cells) with context to specific growth advantage.

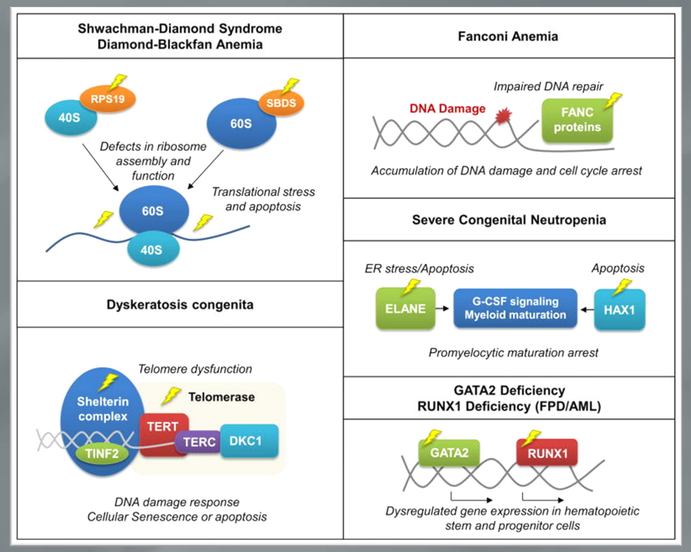

Fig.3 Image adapted from Hematol Oncol Clin North Am. 2018 Aug; 32(4): 643–655.

The Image above fig. depicts the pathways affected in inherited bone marrow failure and MDS/AML predisposition syndromes. The abnormal chromosomal breakage, if present mutation are seen in one of the genes 14. This also shows presence of a mutation in the DCK1, TERT or TERC genes 16, by increased erythrocyte adenosine deaminase (eada) activity and/or by mutation in the RPS19, RPS24, RPS17, RPL5, RPL11 or RPL35A genes 18. Presence of neutropenia associated with exocrine pancreatic insufficiency and, if possible, by mutation in the SBDS gene 6.
An onset of thrombocytopenia, typical bone marrow findings, and mutations in the thrombopoietin receptor (cmpl) gene 7.
In AA, number of tests demonstrated that untreated AA leads to the apoptosis of CD3+, inhibits CD34+ cell which is crucial for HSPCs

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Fanconi anemia is a rare but serious blood disorder that prevents bone marrow from making enough new blood cells for body to perform normal functional activities. It can cause to bone marrow (the sponge-like tissue in the bones), to make abnormal blood cells. It is an inherited autosomal recessive caused by mutation in the genes known as the FA genes, which provides instruction to repair certain types of DNA damage.

Myelodysplastic syndrome (MDS) is one of a group of cancers in which immature blood cells in the bone marrow do not mature, cannot form healthy blood cells.

Dyskeratosis congenita (DC) is an inherited bone marrow failure syndrome characterized clinically by the triad of abnormal nails, reticular skin pigmentation, and oral leukoplakia, and associated with very high risks of developing aplastic anemia, myelodysplastic syndrome, leukemia, and solid tumors. Patients have very short germline telomeres, and approximately half have mutations in one of six genes encoding proteins that maintain telomere function.

Severe congenital neutropenia is characterized by profound peripheral neutropenia. Individual with the congenital disorder usually present with recurrent, life-threatening infections in infancy. Bone marrow examination usually reveals a maturation arrest in the myeloid lineage. The disease can progress to myelodysplasia and leukemia, usually with acquisition of secondary mutations including mutations in the granulocyte colony-stimulating factor receptor. Heterozygous mutations in the neutrophil elastase gene (*ELA2*) have been demonstrated in the majority of patients. These mutations are thought to lead to the accumulation of a non-functional protein which in turn triggers an unfolded protein response leading to maturational arrest. The original family described by Kostmann, had autosomal recessive severe congenital neutropenia, which has been shown to be associated with biallelic mutations in the *HAX1* gene predicted to lead to defects in cell death. Mutations in other genes (*GFI1*, *WASP*) are also known to be associated with severe congenital neutropenia, demonstrating genetic heterogeneity

Interconnected pathways that cause bone marrow failure

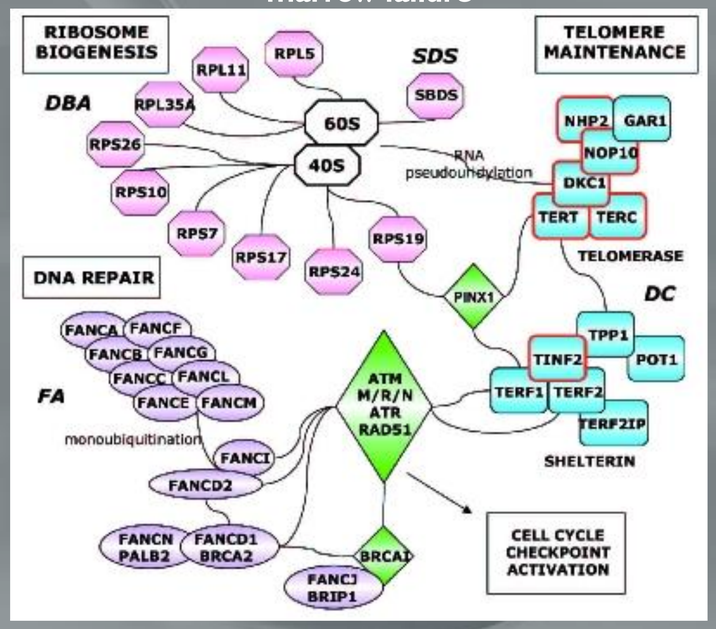

Fig.4. Image adapted from Ferrata Storti Foundation

Genes known to be mutated in the different pathways that lead to bone marrow failure are highlighted in the interconnected pathways. Genes mutated in the telomere maintenance pathway are circled in purple. The mutated gene and other interconnecting proteins are: RP ribosomal protein; FANC, Fanconi anemia complementation group; DKC1, dyskeratosis congenita 1, dyskerin; NOP10, nucleolar protein 10 homolog; NHP2, non-histone ribonucleoprotein 2 homolog; GAR1, glycine and arginine rich riboncleoprotein 1 homolog; TERF1, telomeric repeat binding factor 1; TERF2, telomeric repeat binding factor 2; TINF2, TERF1-interacting nuclear factor 2; TERF2IP, TERF2 interacting protein (RAP1); POT1 protection of telomeres 1 homolog; TPP1, TIN2 interacting protein 1 (ACD, adrenocortical dysplasia homolog); PINX1, PIN2 (TERF1) interacting protein; ATM, ataxia telangiectasia mutated; M/R/N: MRE11/RAD50/NBS1, meiotic recombination 11 homolog A/radiation resistance 50 homolog/Nijmegen breakage syndrome 1; ATR, ataxia telangiectasia and Rad3 related (Seckel syndrome); BRCA1, breast cancer 1. BRIP1, BRCA1 interacting protein C-terminal helicase 1; PALB2, partner and localizer of BRCA2.

Lastly, numbers of evidence shows that individual presented with bone marrow failure were suspected to have inherited bone marrow failure by the combination of various factors observed at young age, low birth weight, macrocytosis and high levels of hemoglobin F. However, most individual shows a normal chromosomal breakage test, normal telomere length, and no mutations in SBDS or c-mpl genes. Furthermore, The BRCA1/2 majorly play a huge role in the regulation of telomere maintenance and a mutation in this gene may result in BMFS, in addition, there are still some ongoing research been tested.