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Inherited Bone Marrow Failure Syndromes in Children

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Abstract

Inherited bone marrow failure syndromes are disorders of hematopoiesis that are mostly encountered in childhood. Taking the basis from genetics, they are characterized by pancytopenia, increased risk of developing myelodysplastic syndrome and malignancy. Extrahematopoietic presentations are observed often in addition to symptoms related to defective hematopoiesis (also known as bone marrow failure). The biology, clinical features, and management of the main syndromes such as Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond syndrome, congenital amegakaryocytic thrombocytopenia, Diamond-Blackfan anemia, and severe congenital neutropenia are briefly summarized in this review.

Keywords: Inherited bone marrow failure syndrome, children, pancytopenia, fanconi anemia, dyskeratosis congenita

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Introduction

Inherited bone marrow failure syndromes (IBMFS) are rare syndromes of defective hematopoiesis that are associated with extra-hematopoietic manifestations. There can be a broad range of clinical presentations of IBMFS from immune deficiency to structural abnormalities.[1] Besides this spectrum of symptoms, there is also an increased risk of malignancies. IBMFS show diminished or total absence of hematopoietic precursors in the bone marrow, therefore generation of hematopoietic lineages gets affected. Early diagnosis of these conditions is crucial to prevent systemic complications while taking precautions for life-threatening complications that require urgent intervention. Furthermore, with the help of early diagnosis and earlier intervention, we may delay the disease progression and that would give us the necessary time to plan further optimal management options.

With the recent developments in molecular genetics, the disease-causing mechanisms have been better elucidated. Currently, more than 100 genes linked with these syndromes have been identified. Understanding the genetic background has made it easier to classify these diseases and then tailor the treatment accordingly. It was found that Fanconi anemia (FA) is related to deoxyribo nucleic acid (DNA) repair genes, dyskeratosis congenita (DC) is related to telomere maintenance genes, Shwachman-Diamond syndrome (SDS) and Diamond-Blackfan Anemia (DBA) are related to ribosome biogenesis or function genes. A better comprehension of these diseases improves the optimal management of the related complications.

Currently, hematopoietic cell transplantation (HCT) is the only viable curative treatment for the hematological manifestations of most IBMFS; with that being said, it doesn't treat the non-hematological findings and it should be kept in mind that, during the HCT there is a significant increase in malignancy development risk in addition to HCT related complications.[2] In the future, we may hopefully see gene therapies' successful implementation from the lab to the clinic. Finally, a holistic approach to patients is the clinician's duty which includes genetic counseling, psychological support and palliative care.

Fanconi Anemia

FA is a chromosomal instability disease that is mostly related to autosomal recessive mutations but on top of that some types have autosomal dominant and X-linked recessive forms.[3-5] To the best of our knowledge, there are at least 22 DNA repair genes in the FA/BRCA pathway that are implicated in the pathogenesis of FA. They take part in aldehyde detoxification, oxidative phosphorylation, proinflammatory and myelosuppressive cytokine homeostasis, and cell cycle regulation via p53/p21. Deterioration of these functions in hematopoietic stem cells causes bone marrow failure (BMF).[4,6]

Generally, patients with FA have variable levels of pancytopenia in childhood. Besides thumb and radial ray malformations, microcephaly or hydrocephaly, renal malformations, short stature, and café-au-lait spots are the most frequent clinical features, however 35% of the patients do not have any of those.[3-5] FA can present with acute myeloid leukemia (AML), cancers of the head & neck, vulva, esophagus and brain; developmental malformations, extreme sensitivity against the proinflammatory cytokines and alkalizing agents besides BMF.[4,6] Among various IBMFS, FA has the highest cancer incidence which is a consequence of defective DNA repair.[5] Since the cells of FA patients are sensitive to crosslinking agents like diepoxybutane (DEB) and mitomycin C (MMC) this quality is used as a screening test that involves controlled exposure of these agents to the cells derived from the peripheral blood for most of the time. A positive result which is defined as having a significant increase in chromosomal breakage; will require genetic testing to confirm and identify the defect precisely. If DEB and MMC test results came back negative although there is a high pre-test probability, a second test using skin fibroblast should be considered which can be of use because there can be false negatives due to the possibility of normal DNA repair in T-cells due to somatic mosaicism or revertant mutations as well as patients which already undergone HCT.[4,7] But at the summit of diagnostic tools stays the molecular genetic tools. With the wide availability of next generation sequencing in which sequencing is done at multiple DNA fragments in a parallel way, much faster and cheaper compared to conventional Sanger sequencing. Now single DNA sequencing with a promise of eliminating errors of amplification and offering a more detailed picture of the genome is on the way. These molecular tools started to change clinical practice in many areas and will keep being.[8]

Following the diagnosis of FA, patients should undergo baseline extensive multiorgan assessment and enter a monitoring plan designed with follow-up by an experienced hematology-oncology center. Currently, the only cure for BMF is HCT although ongoing research and development in gene therapy utilizing gene-corrected $CD34^+$ stem cells from FA patients have been found to be engrafted in immune-deficient mice can be a promising option but clinical application efficacy is not yet demonstrated.[9,10] The goal of the BMF monitoring plan is to intercept at the best time for the HCT and to evaluate the severity of cytopenia, dysplastic or neoplastic features in the bone marrow, the presence and type of cytogenetic abnormalities, infections, transfusion loads, types of available donors, availability of stem cells, and effectiveness of treatment without HCT. HCT increases the risk for secondary malignancies therefore patients who are considered to undergo or already underwent HCT should be evaluated carefully.[2,6]

Dyskeratosis Congenita

DC is a rare multisystemic inherited disorder of telomers that is characterized by BMF, and ectodermal features. Shortening of telomers causes genetic damage whereas normally long repetitive sequences of TTAGGG at the end of chromosomes prevent the loss of genetic material during each cell division.[11] DC has been associated with 12 different genes. The most common mutation is in the *DKC1* gene with X-linked recessive inheritance (20%-

25%). Other related genes are *TERT, ACD* and *RTEL1* which are inherited as (Autosomal Dominant, Autosomal Recessive) // *TERC, TINF2* (Autosomal Dominant) // *NHP2, NOP10, PARN, WRAP53, DCLRE1B* (Autosomal Recessive) // *TYMS* (Digenic Dominant).

DC is characterized by a dysplasia triad consisting of unusual skin pigmentation (Reticulated skin pigmentation, generally on the upper body and the neck), nail dystrophy and leukoplakia of oral mucous membranes. This triad is useful for diagnosis but not always all 3 findings present at the same time. Skin pigmentation and dystrophic nail changes are usually the first recognized features.[5,11]

The leading causes of mortality in DC are complications related to pancytopenia with 60-70%, pulmonary disease with 10-15%, and malignancies with 10%.[11] BMF can develop at any age and it may even be the first clinical manifestation of DC. Epiphora (tear duct obstruction), learning difficulties, developmental delay, mental retardation, pulmonary disease, short stature, esophageal strictures, hair loss at an early age (whitening), tooth decay, and tooth loss can be seen.[11] Cerebellar hypoplasia can be encountered in radiological studies. Patients with DC are at high risk of developing various cancers. While this rate is less than 10% before the age of 20, it increases to 20-30% at the age of 50. The average age of cancer diagnosis is 29 (up to 1.5-68 years old).[12]

Hoyeraal-Hreidarsson Syndrome (HHS) is a clinically severe form of DC. Symptoms of the disease begin in early childhood. HHS is a multisystem disease characterized by BMF, immunodeficiency, and severe growth retardation. HHS is associated with the *DKC1* gene. Also, the *DKC1* gene which encodes the dyskerin protein is the cause of X-linked DC. Most of those with the pathogenic variants of *DKC1* have the classic DC phenotype. Subgroups of some *DKC1* variants have the HHS phenotype.[11,13]

Molecular sequencing confirmed with functional tests such as telomere length analysis, short telomeres, and clinical findings can be counted among the best diagnostic modalities.

As the treatment, blood transfusions, antimicrobials, and antifibrinolytic agents can be considered. Currently, HCT is the only viable curative option for BMF in DC patients.

Androgens, Granulocyte colony-stimulating factor (G-CSF), and erythropoietin treatment can be used in patients who cannot be treated with HCT, but the responses are temporary.

Diamond-Blackfan Anemia

Genes related to DBA are essential for ribosome assembly and function.[5] In DBA, the most common disease driver variants are autosomal dominant missense mutations involving the *RPS19* gene.[14,15] Besides that *GATA1*-related and *TSR2*-related DBA are inherited in an X-linked manner.[15] As a result of these mutations, small or big subunits of ribosomes are affected and the number of functional ribosomes in cells is decreased.

DBA is generally characterized by erythroid hypoplasia and 95% of diagnosis is made in the first two years of life. Typically patients have macrocytic anemia and reticulocytopenia however granulocyte, lymphocyte, and megakaryocyte counts are normal.[5,14,15] Along with it, erythroid colony-forming units are extremely reduced and erythrocyte adenosine deaminase levels are usually elevated.[14] Craniofacial anomalies (cleft palate and lip), thumb deformations, and growth failure are the most frequent physical anomalies seen in DBA patients. Besides, the risk of developing cancer and myelodysplastic syndrome is increased in these patients.[14,15] Steroids, chronic red blood cell transfusion, and HCT are some options that could be considered in the treatment of DBA.

Shwachman-Diamond Syndrome

SDS, the third most common IBMFS after FA and DBA; is an autosomal recessive disorder that is characterized by the triad of BMF, exocrine pancreas deficiency, and skeletal anomalies.[16,17] The most common gene in association with SDS is the *SBDS* gene which is found in the majority of patients.[17] Although the role of the *SBDS* gene is not fully understood, it plays a role in ribosomal maturation, cell proliferation, and the hematopoietic microenvironment. Studies showed that the *SBDS* gene is also involved in telomere length maintenance and even heterozygous variants in *SBDS* has shown to be related to acquired aplastic anemia.[18] Other than the *SBDS* gene; *DNAJC21, EFL1,* and *SRP54* genes are also involved in ribosome assembly and protein translation. Patients with mutations of these genes present with the SDS phenotype.[17] In addition to skeletal anomalies in patients with *DNAJC21*; gingivitis, dental caries, and microdontia are also observed on oral examination.[19]

MDS and AML have been seen in up to one-third of SDS patients. (OMIM260400)[20] Exocrine pancreatic insufficiency is usually the first complaint in patients with SDS although systemic manifestations include nervous, cardiac, endocrine, immune and skeletal systems.[21]

The mean age at diagnosis for SDS is 1.3 years (0-35.6 years).[22] Neutropenia and steatorrhea are seen in 51% of those with mutations in the *SBDS* gene. In the other 14%, there was no evidence of cytopenia at the initial admission. Pancreatic lipomatosis is also seen in imaging. Normal fecal elastase levels and normal skeletal imaging do not exclude the diagnosis of SDS.[17] Typically, neutropenia is observed but other cytopenias can also be present. Neutrophil chemotaxis and migration defects can also be observed in addition to neutropenia.[23] With exocrine pancreatic insufficiency, problems occur in the digestion of fats and fat-soluble vitamins. Therefore, steatorrhea, foul-smelling defecation, and growth retardation are seen. Pancreatic findings appear at 6-12 months of age. Over time, the medical condition of patients improves and they stop taking pancreatic enzyme (NE) therapy.[24] Diabetes mellitus and endocrine pancreatic disorders are unrelated to SDS. Hepatomegaly and elevated transaminases can also occur. Short stature, osteopenia, metaphyseal dysplasia, thoracic and pelvic dysplasia,

short extremities can be seen. Worm-like skull bones can be observed due to abnormal bone turnover and decreased osteoclast and osteoblast activity. Mineral deficiency due to pancreatic insufficiency causes an increase in bone findings. Vertebral compression fractures may occur.[17] Some patients may have learning and behavioral disorders like attention deficit hyperactivity disorder.[25]

Once the diagnosis is confirmed, patients should be initiated pancreatic NE replacement. Fat-soluble vitamin levels should be checked every 6-12 months and replaced if needed. If anemia or thrombocytopenia develops appropriate transfusions are recommended. As a result of transfusions, iron chelation should be considered if necessary. In the presence of severe neutropenia, prophylactic antibiotics can be used. G-CSF can also be used to raise white blood cells. HCT is the only curative treatment option that may be done in selected cases.

Congenital Amegakaryocytic Thrombocytopenia (CAMT)

CAMT is associated with a very low number of megakaryocytes in the bone marrow starting from the neonatal period. At first, a problem solely in the thrombocytic series arises, but in the progress of time, the condition worsens and all lineages are affected resulting in pancytopenia. CAMT is an autosomal recessive disease and has been classified into two types; type 1, the severer form, in which variants in *MPL* gene as frameshift or stop codon mutations causes a complete loss of receptor function leading to decreased bone marrow activity and early-onset low platelet count around 2 years of age.[26] Whereas in type 2 the milder one, platelet numbers are generally normal in infancy, later leading to BMF around 4 years of age which is due to variants that cause splicing defect or amino acid substitution that can lead to the problem in *MPL* receptor's glycosylation resulting to decreased response to thrombopoietin or causes hydrogen bonds to be lost within the *MPL* receptor making it unstable although residual receptor function is preserved.[26-29]

CAMT usually arises in consanguineous marriages, more commonly in women. A misdiagnosis as neonatal alloimmune thrombocytopenia (NAIT) is a possibility. For this reason, the incidence appears to be less. The incidence of NAIT is 1 in every 1,000 live births. On the other hand, approximately 100 CAMT cases have been reported so far.[29,30] CAMT is not accompanied by skeletal anomalies which is an important thing to consider in the differential diagnosis of IBMFS.[31]

CAMT usually presents with thrombocytopenia in the first month of life or fetal life leading to petechiae, intracranial hemorrhages, recurrent rectal hemorrhages, and pulmonary hemorrhages.[28] Also growth and developmental retardation, strabismus, central nervous system anomalies, cerebral malformations, and cortical dysplasia can accompany. If any congenital anomaly is found on physical examination, the diagnosis of CAMT should be re-evaluated.[29]

The mean platelet count in patients with CAMT is 20,000/mm^3. Bone marrow biopsy should be evaluated in every child with congenital thrombocytopenia. *MPL* gene test should be performed according to the results of megakaryocyte evaluation in the biopsy. Platelet transfusions can be needed as a supportive treatment. If anemia or neutropenia has also developed, antimicrobials or red blood cell transfusions can be performed in proper conditions. Antifibrinolytic agents can be used for bleeding control. HCT is the only curative treatment option. HCT should be done as early as possible. It should be done before pancytopenia develops however there is no exact optimal time.

Severe Congenital Neutropenia (SCN)

In SCN in which there is a mature neutrophil deficiency in the bone marrow, the average absolute neutrophil count is less than 200/μL and it often coexists with the elevated number of monocytes.[32] The mode of inheritance can be single gene mutation, X linked or sporadic. The most frequent mutation seen in patients in the population of non-consanguineous marriage emerges on the *ELANE* gene which encodes the neutrophil elastase NE whereas in a population with high consanguineous marriage *HAX1* gene is determined to be the most common one.[5,33,34] NE is a serine protease that can hydrolyze some bacterial and extracellular matrix components and it is essential in innate immunity. Pathogenicity of ELANE mutations is mostly explained by mutant NE which causes developing neutrophils to go apoptosis which leads to low neutrophil counts.[33] Also *GFI1, CSF3R*, *G6PC3, VPS45, WAX, SRP19, SRPRA* genes are reported. Studies keep revealing novel genetic variants related to SCN.[35-37]

Patients with SCN have an increased risk of developing MDS and AML. Persistent severe neutropenia, (<500/μL) recurrent bacterial infections, and maturation arrest in bone marrow can be established in patients with SCN as clinical symptoms and no other congenital malformations are present.[5,33] Preventing infections is extremely important in the treatment of SCN. Therefore, the first-line drug in SCN is G-CSF, with a response rate of approximately 90%.[33]

Conclusion

IBMFS are rare and critical illnesses. It is crucial to perform a physical examination and take a family history in patients who are not expected to have cytopenia especially in the pediatric population. For management, the level of the disease should be determined by performing genetic studies and laboratory tests. Clinicians should be vigilant about the increased risk of malignancy. Prompt evaluation and initiation of the treatment are essential.

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References

1. Gök V, Erdem Ş, Haliloğlu Y, et al. Immunodeficiency associated with a novel functionally defective variant of SLC19A1 benefits from folinic acid treatment. *Genes Immun*. 2023;24:12-20. *[Crossref]*
2. Shakila K, Myers KC, Newburger P (ed), Negrin RS (ed), Rosmarin AG (ed). Hematopoietic cell transplantation (HCT) for inherited bone marrow failure syndromes (IBMFS). In: *UpToDate*.; 2021. Accessed March 15, 2023. *[Crossref]*
3. Fiesco-Roa MÓ, García-de Teresa B, Leal-Anaya P, et al. Fanconi anemia and dyskeratosis congenita/telomere biology disorders: Two inherited bone marrow failure syndromes with genomic instability. *Front Oncol*. 2022;12:949435. *[Crossref]*
4. Green AM, Kupfer GM. Fanconi Anemia. *Hematol Oncol Clin North Am*. 2009;23:193-214. *[Crossref]*
5. Park M. Overview of inherited bone marrow failure syndromes. *Blood Res*. 2022;57(Suppl 1):49-54. *[Crossref]*
6. Dufour C, Pierri F. Modern management of Fanconi anemia. *Hematol Am Soc Hematol Educ Program*. 2022;2022:649-657. *[Crossref]*
7. Olson TS, Newburger P (ed), Rosmarin AG (ed). Clinical manifestations and diagnosis of Fanconi anemia. In: *UpToDate*.; 2022. Accessed March 15, 2023. *[Crossref]*
8. Hulick PJ, Raby BA (ed), Tirnauer JS (ed). Next-generation DNA sequencing (NGS): Principles and clinical applications. In: *UpToDate*.; 2022. Accessed March 15, 2023. *[Crossref]*
9. Olson TS, Newburger P (ed), Rosmarin AG (ed). Management and prognosis of Fanconi anemia. In: *UpToDate*.; 2022. Accessed March 18, 2023. *[Crossref]*
10. Tolar J, Adair JE, Antoniou M, et, al. Stem Cell Gene Therapy for Fanconi Anemia: report from the 1st international Fanconi anemia gene therapy working group meeting. *Mol Ther*. 2011;19:1193-1198. *[Crossref]*
11. Dokal I. Dyskeratosis congenita. *Hematology Am Soc Hematol Educ Program*. 2011;2011:480-486. *[Crossref]*
12. Alter BP, Giri N, Savage SA, Rosenberg PS. Cancer in dyskeratosis congenita. *Blood*. 2009;113:6549-6557. *[Crossref]*
13. Glousker G, Touzot F, Revy P, Tzfati Y, Savage SA. Unraveling the pathogenesis of Hoyeraal-Hreidarsson syndrome, a complex telomere biology disorder. *Br J Haematol*. 2015;170:457-471. *[Crossref]*
14. Kim HY, Kim HJ, Kim SH. Genetics and genomics of bone marrow failure syndrome. *Blood Res*. 2022;57(Suppl 1):86-92. *[Crossref]*
15. Sieff C. Diamond-Blackfan Anemia. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed February 5, 2023. *[Crossref]*
16. Tsangaris E, Klaassen R, Fernandez CV, et al. Genetic analysis of inherited bone marrow failure syndromes from one prospective, comprehensive and population-based cohort and identification of novel mutations. *J Med Genet*. 2011;48:618-628. *[Crossref]*
17. Nelson AS, Myers KC. Diagnosis, Treatment, and Molecular Pathology of Shwachman-Diamond Syndrome. *Hematol Oncol Clin North Am*. 2018;32:687-700. *[Crossref]*
18. Calado RT, Graf SA, Wilkerson KL, et al. Mutations in the SBDS gene in acquired aplastic anemia. *Blood*. 2007;110:1141-1146. *[Crossref]*
19. Alsavaf MB, Verboon JM, Dogan ME, et al. A novel missense mutation outside the DNAJ domain of DNAJC21 is associated with Shwachman–Diamond syndrome. *Br J Haematol*. 2022;197:e88-e93. *[Crossref]*
20. Shwachman-Diamond Syndrome 1; SDS1; MIM Number: {260400}. In: *Online Mendelian Inheritance in Man, OMIM®*. 22/3/2021 ed. Johns Hopkins University. *[Crossref]*
21. Dror Y, Freedman MH. Shwachman-Diamond syndrome: An inherited preleukemic bone marrow failure disorder with aberrant hematopoietic progenitors and faulty marrow microenvironment. *Blood*. 1999;94:3048-3054. *[Crossref]*
22. Cesaro S, Pegoraro A, Sainati L, et al. A Prospective Study of Hematologic Complications and Long-Term Survival of Italian Patients Affected by Shwachman-Diamond Syndrome. *J Pediatr*. 2020;219:196-201.e1. *[Crossref]*
23. Stepanovic V, Wessels D, Goldman FD, Geiger J, Soll DR. The chemotaxis defect of Shwachman-Diamond Syndrome leukocytes. *Cell Motil Cytoskeleton*. *[Crossref]*
24. Mack DR, Forstner GG, Wilschanski M, Freedman MH, Durie PR. Shwachman syndrome: exocrine pancreatic dysfunction and variable phenotypic expression. *Gastroenterology*. 1996;111:1593-1602. *[Crossref]*
25. Booij J, Reneman L, Alders M, Kuijpers TW. Increase in central striatal dopamine transporters in patients with Shwachman-Diamond syndrome: additional evidence of a brain phenotype. *Am J Med Genet A*. 2013;161A:102-107. *[Crossref]*
26. Geddis AE. Congenital amegakaryocytic thrombocytopenia: Congenital Amegakaryocytic Thrombocytopenia. *Pediatr Blood Cancer*. 2011;57:199-203. *[Crossref]*
27. Fox NE, Chen R, Hitchcock I, Keates-Baleeiro J, Frangoul H, Geddis AE. Compound heterozygous c-Mpl mutations in a child with congenital amegakaryocytic thrombocytopenia: Functional characterization and a review of the literature. *Exp Hematol*. 2009;37:495-503. *[Crossref]*
28. King S, Germeshausen M, Strauss G, Welte K, Ballmaier M. Congenital amegakaryocytic thrombocytopenia: a retrospective clinical analysis of 20 patients. *Br J Haematol*. 2005;131:636-644. *[Crossref]*
29. Tirthani E, Said MS, De Jesus O. Amegakaryocytic Thrombocytopenia. In: *StatPearls*. StatPearls Publishing; 2022. Accessed March 12, 2023. *[Crossref]*
30. Norton T, Newberry D, Jnah A. Neonatal Alloimmune Thrombocytopenia: A Concise Review. *Adv Neonatal Care Off J Natl Assoc Neonatal Nurses*. 2021;21:115-121. *[Crossref]*
31. Muraoka K, Ishii E, Tsuji K, et al. Defective response to thrombopoietin and impaired expression of c-mpl mRNA of bone marrow cells in congenital amegakaryocytic thrombocytopenia. *Br J Haematol*. 1997;96:287-292. *[Crossref]*
32. Coates TD, Newburger P (ed), Rosmarin AG (ed). Congenital Neutropenia. In: *UpToDate*.; 2022. Accessed March 15, 2023. *[Crossref]*
33. Wang J, Zhang H, Wang Y, et al. Severe congenital neutropenia caused by ELANE gene mutation: A case report and literature review. *Medicine (Baltimore)*. 2022;101:e31357. *[Crossref]*
34. Yılmaz Karapınar D, Patıroğlu T, Metin A, et al. Homozygous c.130-131 ins A (pW44X) mutation in the HAX1 gene as the most common cause of congenital neutropenia in Turkey: Report from the Turkish Severe Congenital Neutropenia Registry. *Pediatr Blood Cancer*. 2019;66:e27923. *[Crossref]*
35. Triot A, Järvinen PM, Arostegui JI, et al. Inherited biallelic CSF3R mutations in severe congenital neutropenia. *Blood*. 2014;123:3811-3817. *[Crossref]*
36. Goktas S, Azizoglu ZB, Petersheim D, et al. A Novel Intronic Mutation Reduces HAX1 Level and is Associated With Severe Congenital Neutropenia. *J Pediatr Hematol Oncol*. 2022;44:e62. *[Crossref]*
37. Linder MI, Mizoguchi Y, Hesse S, et al. Human genetic defects in SRP19 and SRPRA cause severe congenital neutropenia with distinctive proteome changes. *Blood*. 2023;141:645-658. *[Crossref]*