than that of the general population, and this is the best-case scenario for patients with good compliance who receive treatment in industrialized countries.[4] In a survey of 30 adults with SCD on their feelings toward receiving a reduced-intensity bone marrow transplantation for the management of their disease, 50% were willing to accept infertility, and 62% were ready to accept a transplant-related mortality greater than 10%.[5] Although that was a small study, among select individuals, it gave an idea of the quality of life of patients with SCD who had reached adulthood. Another report described post-SCT quality of life and demonstrated results identical to those of unaffected siblings.[6]

SCD is recognized as a global public health issue with an average lifetime cost of care of $460 151 per patient.[7] However, taking into consideration disease chronicity, recurrent hospital admissions, surgical and nonsurgical treatment of complications, use of intensive care facilities, and multidisciplinary approach to management, the actual cost estimation is closer to $9 million for 50 years of life expectancy per patient.[7] In terms of economics, the earlier the transplantation, the greater the savings.

Another evolving field that offers a cure is gene therapy, using various exciting techniques, from gene addition by lentiviral vector to gene correction or reactivation of fetal hemoglobin.[8] Although very attractive and having the potential of proving utility in the future, these techniques are not yet common practice and cannot offer an immediate solution for patients with SCD.

Historically, it took 32 years and many small series between the time of the first successful transplant in a patient with SCD in 1984[9] and the appearance of this important article by Gluckman et al, summarizing 1000 patients. Those authors revealed that early intervention with transplantation in patients with SCD using a matched sibling donor can save the patient from years of chronic treatment and significant incapacities. A similar conclusion was reached many years ago for patients with thalassemia major. The first transplantation performed in thalassemia major took place in 1981, and by 2001, the group in Pesaro had already transplanted about 900 patients with homozygous β thalassemia, using marrow as the stem cell source, learning and understanding the pitfalls associated with transplantation in thalassemia, including the importance of age and associated comorbidities.[3] This led to a survival rate of above 90% in patients with class I thalassemia.

The importance of the paper by Gluckman et al is the collaboration among the European Blood and Marrow Transplant Group, Eurocord, and the Center for International Blood and Marrow Transplant Research to report the results of 1000 patients who had undergone transplant for SCD and to arrive at concrete conclusions that can help physicians benefit their patients. It takes a leader in the field to promote treatment progress. Yet, in the real world, most patients do not have a sibling donor. As in other nonmalignant disorders, it is time to move forward using matched unrelated donor (MUD) for SCT. The data regarding MUD transplants in SCD are sparse. The largest study treated 29 patients with reduced-intensity conditioning with good engraftment but with high incidence of chronic graft-versus-host disease.[10] Eligible patients had a median age of 14 years and severe SCD. Learning from matched sibling SCT, age and disease severity are important and should be taken into account when suggesting MUD SCT to a patient with SCD.

Pediatric hemato-oncologists often encounter reluctance on the part of hematologists to refer their patients with SCD for transplantation. With an overall survival rate of 95% among young patients with SCD using matched sibling donor, there is no need to perform controlled clinical trials for comparing chronic transfusions, hydroxyurea, and SCT. Planning controlled prospective clinical trials to explore the best conditioning regimen, either myeloablative or reduced intensity, in the setting of matched unrelated donor is the next challenge that needs to be faced.

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● ● ● PHAGOCYTES, GRANULOCYTES, AND MYELOPOIESIS

Comment on Dhanraj et al, page 1557

DNAJC21: the new kid on the SDS block

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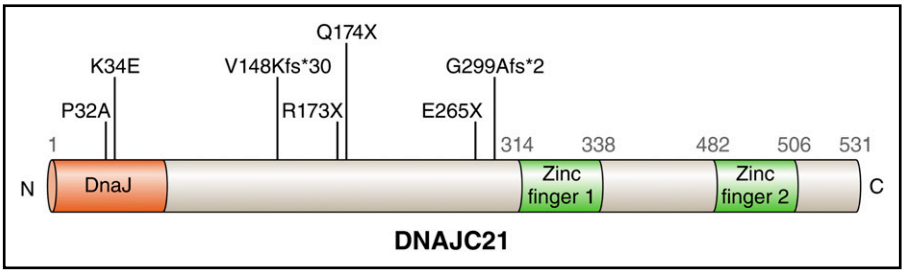
In this issue of *Blood*, Dhanraj et al identify biallelic mutations in *DNAJC21* in patients with phenotypical Shwachman-Diamond syndrome (SDS) who tested negative for mutations in the *SBDS* gene, thus extending the genes that can be mutated in SDS.[1]

SDS was described originally in 1964[2] and classically presents with short stature, exocrine pancreatic insufficiency, cognitive and behavioral impairment, and bone marrow failure, with predisposition to myeloid malignancies (Online Mendelian



Functional domains within DNAJC21 are disrupted by homozygous mutations in individuals with the clinical bone marrow failure SDS. The J domain at the extreme N-terminus mediates interaction with heat shock protein 70 to stimulate its ATPase activity and is likely disrupted within its critical H-P-D motif by the P32A and K34E missense mutations. Nonsense mutations encoding premature stop codons are likely to result in nonsense-mediated decay of messenger RNA, and frameshift mutations caused by splicing mutations truncate the protein before the predicted C-terminal zinc finger domains. Professional illustration by Patrick Lane, ScEYEnce Studios.

Inheritance of Man [OMIM] 260400).[3-5] SDS is an autosomal recessive disorder. The majority of patients who present with phenotypic SDS are found to have biallelic mutations in the *SBDS* gene, which encodes a protein with multiple functions, including the maturation of the 80S ribosome by the release of eIF6.[4]

Two recent articles now describe expansion of the molecular pathology in SDS to include biallelic mutations in *DNAJC21*, collectively observed in 8 individuals from 7 families.[6] These patients showed classic features of bone marrow failure with peripheral pancytopenia. Tummala et al described additional features in their patients, which included intrauterine growth restriction, short stature, and a myeloid malignancy in a 12-year-old child.[6] In the paper published in this issue of *Blood* by Dhanraj et al, the patients underwent detailed phenotypic characterization including analysis of pancreatic function to confirm the SDS phenotype.

The mutations identified in these patients encode mutations in the N-terminal half of the DNAJC21 protein (see figure). Missense mutations are found in the extreme N-terminus: P32A and K34E, which are likely to disrupt the function of the highly conserved H-P-D motif that is critical for function of the J domain. The 5 other mutations, if expressed, would be expected to truncate the protein before the 2 predicted C-terminal zinc finger domains: R173X, Q174X, E265X, and 2 splicing defects that result in frameshift mutations, V148Kfs*30 and G299Afs*2. The 3 nonsense mutations may be subject as well to nonsense-mediated decay of the corresponding messenger RNAs, although Dhanraj et al provide evidence for expression for at least 1 of the truncating frameshift mutations, V148Kfs*30.

The DNAJC21 protein associates with ribosomal RNA and contributes to 60S ribosomal subunit maturation. Tummala et al showed that mutant proteins have decreased interaction with cofactors HSPA8 and ZNF622 as well as cytoplasmic accumulation of the export factor PA2G4, resulting in late cytoplasmic maturation of 60S subunit, aberrant ribosome profiles, and increased cell death.[6]

These 2 papers are emblematic of a new trend in molecular diagnostics: the adaptation of next-generation sequencing techniques to determine the molecular basis of disease based on rare patients who phenocopy a well-described syndrome. With 10% to 20% of patients diagnosed with a clinical syndrome of SDS testing negative for *SBDS*, it is unclear what fraction of those cases has *DNAJC21* mutations, leaving open the exciting possibility that there are other causative gene mutations for SDS. Moreover, in the past, when clinical criteria were used to define a syndrome, it is likely that the most apparent phenotypes that were described corresponded to the strongest disrupting alleles. Now that next-generation sequencing and molecular testing of individuals are more accessible and affordable, we are likely to expand our clinical definitions of syndromes, including the ribosomopathies.[7]

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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