Molecular medicine and bone marrow failure syndromes

In this issue of The Journal, Yaghmai et al[1] have shown the folly of syndromology in this era of molecular medicine. They describe a patient with an unusual phenotype, who clinically appeared to have a rare syndrome, Hoyeraal-Hreidarsson syndrome; they demonstrate that the patient has a mutation in the *DKC1* gene, which makes his disorder a member of the dyskeratosis congenita family. This connection was also made recently by the group who first cloned the *DKC1* gene.[2] The 6 acceptable case reports of HHS all describe males who are growth and developmentally retarded and have microcephaly with cerebellar hypoplasia; each developed aplastic anemia.[3-7] The patient in the report by Yaghmai et al[1] had all of those features, as well as nail dystrophy, mucosal findings, and reticulated hyperpigmentation. He also had esophageal strictures, gastric ulcers, epiphora, thin hair, blood cytopenias, and bone marrow hypocellularity. Patients with DC are primarily male, with dystrophic nails, reticular cutaneous pigmentation, and mucous membrane leukoplakia. In fact, all of the features of HHS have been described with variable frequencies in patients with DC.[8] In addition, the other findings in the patient in this report, such as epiphora, are also features of DC.

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The authors found that their patient, who had clinical features of both HHS and DC, had a de novo mutation (A353V) in the *DKC1* gene for dyskerin, the same mutation that was found in 30% of males with classical DC.[9] They have thus confirmed the link between a somewhat rare bone marrow failure disorder (DC) and an extremely rare one (HHS). Other patients with DC-like disorders, such as those with Coats retinopathy, might also fit into this category, if DNA studies could be done.[10,11]

DC	Dyskeratosis congenita
HHS	Hoyeraal-Hreidarsson syndrome

Genes are rapidly being identified for many other of the genetic bone marrow failure syndromes, such as Fanconi's anemia,[12] Diamond-Blackfan anemia,[13] and amegakaryocytic thrombocytopenia,[14] and are being sought in Shwachman-Diamond syndrome,[15] thrombocytopenia absent radii,[16] and Kostmann's syndrome.[17] The *FA* genes are for newly identified proteins, which may somehow have a role in DNA repair; the *DBA* mutation is in ribosomal protein S19; dyskerin is a nucleolar protein with a role in ribosome biogenesis and a defect in telomere maintenance[18]; and the amegakaryocytic mutation is of *c-mpl*, the thrombopoietin ligand. Patients with Fanconi's anemia and Diamond-Blackfan anemia have more than one gene that produces similar phenotypes. Once all the genes are known, patients who were classified as having additional rare syndromes[19] might find a previously known category, and thus "splitters" could become "lumpers."

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