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Diamond Blackfan Anemia: A Cheshire Cat of Hematology

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With mysterious origins, an unpredictable hematological combination of intransigence—with resulting corticosteroid- or transfusion-related toxicity—and the capriciousness of remission, a broad but potentially subtle array of physical abnormalities, and the lurking malevolence of a cancer predisposition syndrome, Diamond Blackfan anemia (DBA) has both vexed and fascinated hematologists for more than four generations. Although many aspects of DBA remain enigmatic, careful laboratory and clinical investigation, accelerating over the past 15 years, have led to substantial progress in improving our understanding of the genetic origins of DBA.

Following the initial discovery of a child harboring a translocation disrupting component of the small ribosomal subunit, a series of studies have shown the ribosome to be a common culprit in DBA. Autosomal dominant mutations or single copy deletions are now recognized in DBA involving at least 11 genes encoding ribosomal proteins (RP) that are components of either the small (denoted “RPS”—*RPS7*, *RPS10*, *RPS17*, *RPS19*, *RPS24* and *RPS26*) or large (denoted “RPL”—*RPL5*, *RPL11*, *RPL15*, *RPL26* and *RPL35A*) subunit of the ribosome.[1–4] In retrospect, these discoveries have followed a parallel arc to findings in other inherited bone marrow failure syndromes, with recognition that a large but related group of genes intersect at a common biological pathway, such as DNA repair pathways in Fanconi anemia or telomere maintenance pathways in dyskeratosis congenita and related disorders. In DBA however, there have also been troubling signs of potential failure in this thesis. While the flurry of sequencing studies focusing on all the known structural components of the ribosome identified novel DBA genes, these studies also suggested that approximately 40% of patients with a clinical diagnosis of DBA do not have an identifiable RP gene abnormality.

Lacking further obvious candidates for targeted sequencing in this sizeable minority of DBA patients, Sankaran et al. employed a genome-wide approach to identify the first non-ribosomal genetic abnormality in DBA. [5] Using the wide net of exome sequencing in a pair of DBA brothers, and subsequently confirmed in one of 62 additional probands tested, they identified mutations of the hematopoietic transcription factor, *GATA1*. These patients share a specific category of mutation which alters mRNA splicing in a way that preserves production of a short isoform (GATA-1s) while abrogating production of the longer isoform (GATA-1 or GATA-1 FL). As a key transcription factor required for hematopoiesis, mutation of *GATA1* in DBA makes an intuitively attractive gene candidate, but several

aspects of *GATA1* biology and of the DBA phenotype in these individuals raised additional questions (see additional excellent commentary in [6]). Somatic mutations of *GATA1* identical to these DBA mutations are characteristic in Down syndrome-associated transient myeloproliferative disorder and acute megakaryoblastic leukemia.[7] A prior report identified this precise mutation in a large family manifesting hereditary anemia with multilineage dysplasia similar to, but not fully typical for DBA.[8] Additionally, more distant mutations of *GATA1* are associated with a congenital dyserythropoietic anemia and thrombocytopenia largely distinctive from DBA.[9] In addition to the abundance of phenotypes associated with mutations of *GATA1*, the proband phenotypes were somewhat atypical for DBA. All had moderate neutropenia, a reported, but not a classical feature of DBA. None had associated physical abnormalities or elevated erythrocyte adenosine deaminase activity (eADA), seen in 40-50% and 80% of DBA patients, respectively.

In this issue of *Pediatric Blood & Cancer*, Parrella et al. report identification of a hemizygous mutation of *GATA1* in the male proband of an additional family out of 23 tested from the Italian DBA registry.[10] Although the precise mutation in this case is distinct from that identified in prior studies, the predicted functional consequence, preservation of GATA-1s with abrogation of full-length GATA-1, is identical. This independent finding with converging molecular consequences lends further strong support to *GATA1* as a *bona fide* DBA gene. Notably, though this child also lacked congenital abnormalities, he was found to have moderately elevated eADA, suggesting that eADA may vary from other modifiers rather than directly with *GATA1* genotype. More alarmingly, this child developed early myelodysplastic syndrome with multiple clonal abnormalities, a well-documented adverse event in DBA for which the underlying biological basis remains unclear.[11]

These findings not only enlarge the growing repertoire of DBA genes, but potentially challenge the current view that failure to adequately synthesize ribosomes leads, *per se*, to the erythroid and possibly the non-hematologic manifestations of DBA. That is, if ribosome-determined and GATA1-determined DBA are more than serendipitous phenotypic similarity, how do they relate? Could changes in GATA-1 somehow directly alter ribosome synthesis? Does a paucity of functional ribosomes in the differentiating red cells preferentially impact on translation of full length GATA-1? Or might abortive ribosome assembly and *GATA1* abnormalities converge later, in the regulation of key pro- and anti-apoptotic mediators in a developing erythroid precursor? Identification of the gene is the first among many steps to answering these important questions.

Rarity is one characteristic of the DBA-associated *GATA1* mutations that is similar to several of the DBA-associated RP genes. With 1/23 males identified in the Parrella study and 1/62 additional male probands in the Sankaran study, the frequency of *GATA1* mutations appears unlikely to exceed more than 1-2% of what is currently genetically uncharacterized DBA, with less than half of that frequency more broadly in DBA, an estimate that is similar in magnitude to several of the less commonly mutated RP genes. A positive interpretation of this finding is that other gene(s) remain to be discovered, which may clarify the relationship between the ribosome, erythron and bone marrow failure. However, with 12 genes identified in 15 years of genetic discovery in DBA, it seems fair to wonder: How deep is this rabbit hole?

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