Comment on Molteni et al, page 643

Germ line risk variants: beyond cancer

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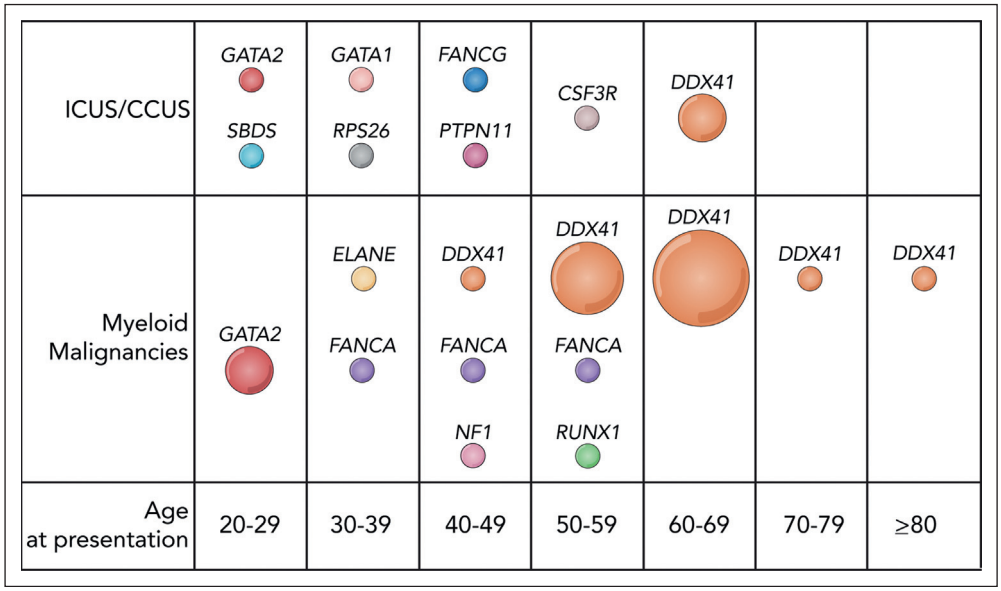
In this issue of *Blood*, Molteni et al address how often deleterious germ line variants are associated with unexplained cytopenias and bone marrow hypocellularity.[1] They determined the frequency of these alleles in 402 consecutive adults evaluated for cytopenias and age-adjusted hypoplastic bone marrows. The authors considered the mode of inheritance for each condition, such that single deleterious variants were considered causative for autosomal dominant conditions but 2 deleterious variants were required for autosomal recessive disorders. DNA variants were curated according to the criteria outlined by the American College of Medical Genetics and Genomics (ACMG), the Association of Molecular Pathology (AMP), and ClinGen, which require rigorous assessment of functional, case/segregation, population, and computational/predictive data for each variant.

Molteni et al examined the variants in 60 genes important in hematopoiesis or known to confer risk for inherited hematologic malignancies (HMs) and/or bone marrow failure and identified that 6% to 7% of individuals in their cohort had a deleterious germ line variant. Those with a pathogenic (P) or likely pathogenic (LP) germ line variant were younger at the time of presentation than those without such alleles. However, of note, the oldest person identified with a causative germ line variant in *DDX41* came to medical attention at age 84 years. Among the 402 individuals studied, 27 people were identified with deleterious germ line variants: 18 of 173 (10%; age range, 23-84 years) had a myeloid neoplasm, and 9 of 229 (4%; age range, 24-51 years) had idiopathic or clonal cytopenia of undetermined significance (ICUS/CCUS) (see figure). The most frequently mutated genes included *DDX41* (6% of apparently sporadic myelodysplastic syndrome [MDS]/acute myeloid leukemia [AML]), *FANCA*, and *GATA2*. Among the myeloid neoplasms that developed in these individuals, the somatic mutation profile was similar to that seen in de novo diseases, meaning that somatic mutation profiles cannot predict which individuals are likely to have germ line predisposition (unless the gene affected in the germ line happens to be on the somatic profiling panel). Germ line *DDX41* mutations were associated with hypocellular bone marrows, a median age at diagnosis of 63 years, and male gender more than female, as described previously.[2] Of note, one of these patients also developed colon cancer, an association seen in prior studies[2] and one worthy of further investigation.

The frequency of LP/P germ line variants found in this cohort are consistent with previous studies. Our group has examined the frequency of deleterious germ line variants in patients diagnosed with MDS, AML arising from a background of MDS, or aplastic anemia (AA), given the diagnostic overlap with hypoplastic MDS. In those diagnosed at age 40 years or younger, we detected such alleles in 19% of those with MDS/AML with prior history of MDS and 15% of those with AA.[3] In a more recent study, we used paired peripheral blood samples from patients with MDS across the entire age range of life and their related allogeneic hematopoietic cell transplant (HCT) donors to estimate that the frequency of these alleles is ≥7%.[4] Analyzing a similar cohort of patients diagnosed with severe AA who underwent HCT, McReynolds et al analyzed 104 genes associated with inherited bone marrow failure syndromes in 732 patients and found that 16.5% of individuals had causative LP/P germ line variants in 42 genes.[5] A recent study from a Chinese patient cohort of 788 individuals diagnosed with AA and HMs found that 8% were positive for these variants in the 5 genes analyzed (*BRCA2*, *FANCA*, *FANCC*, *FANCD2*, and *FANCG*), with *FANCA* being the most frequently mutated gene followed by *BRCA2*.[6] Pediatric groups have also examined germ line variants in their populations of patients with MDS, finding P/LP germ line variants in *SAMD9/SAMD9L* in their youngest patients and *GATA2* in teenage/young adult patients, especially with MDS associated with monosomy 7.[7] What emerges is the observation that the age at which MDS is diagnosed is a surrogate for the biological pathway(s) driving the malignancy, with DNA repair and telomere biology genes dominating in adult age ranges and *DDX41* in older patients.

It is important to note that variant curation performed according to ACMG/AMP/ClinGen guidelines is not a static entity, meaning that interpretation of DNA variants changes with new knowledge. Over time, DNA variants can move from deleterious categories (LP/P) to non–clinically actionable designations, such as variant of uncertain significance (VUS). Alternatively, variants can be upgraded from VUS into LP/P range. Variant curation criteria were intended to be specified in a gene-specific manner, but such curation rules are available only for a small number of genes considered in this study, including *RUNX1*. Therefore, as gene-specific curation rules are developed and implemented for genes examined in this study and as additional functional characterization is performed for specific variants, it is likely that some of the designations presented in this work will change. This is inherent in the nature of variant curation. In fact, the authors found that 13 germ line variants were close to LP designation, suggesting that the frequency of causative germ line variants in this population could climb to 10% or even higher, a figure consistent with other studies as cited above.

Importantly, the finding of 6% to 7% deleterious germ line alleles in adults with unexplained cytopenias and hypocellular bone marrows is clinically relevant today. Clinical guidelines by the National Comprehensive Cancer Network and the



Correlation of age of disease presentation with affected gene. Molteni et al describe deleterious germ line variants causing cytopenias and hypocellular bone marrows that vary across the age spectrum, with alleles in *GATA2* and Fanconi anemia genes common in younger individuals and *DDX41* in older individuals. Genes in which these alleles were identified are plotted as a function of age of presentation (on the x-axis) vs the diagnosis of the individual (top, ICUS/CCUS; bottom, myeloid malignancies; on the y-axis). Professional illustration by Somersault18:24.

ACMG recommend germ line genetic testing when the pretest probability of a positive finding is >5%.[8-10] Therefore, we should be offering genetic counseling and testing to a larger and larger population of patients: patients with MDS aged <40 years; patients with MDS of any age going to related HCT; and, now based on this study, individuals with unexplained cytopenias and hypocellular marrows. These investigators had limited ability to predict those with germ line predisposition based on demographic data, clinical presentation, or family history, demonstrating that it is not obvious a priori who will have germ line risk. Thus, one wonders if/when we will have sufficient data to justify germ line genetic testing as standard of care for all patients undergoing evaluations for persistent cytopenias, HMs, and/or allogeneic HCT.

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

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PHAGOCYTES, GRANULOCYTES, AND MYELOPOIESIS

Comment on Rhee et al, page 658

Progenitor diversity defines monocyte roles

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In this issue of *Blood*, Rhee et al[1] provide evidence that individual monocytes and their progeny may not be as plastic as previously thought. Instead, their data suggest that the apparent flexibility of monocytes to respond appropriately to diverse stimuli reflects selection of functionally diverse monocyte subtypes that arise from heterogeneous preprogrammed myeloid progenitors (see figure).