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Age-related mutations linked to clonal hematopoietic expansion and malignancies

A common practice in molecular profiling of tumors is to subtract mutations detected in DNA derived from blood (representing germline or inherited polymorphisms) from mutations detected in DNA derived from the paired tumor to assess the tumor's somatic molecular profile. The authors conducted a study in which they detected somatic mutations that occurred in DNA isolated from the blood of individuals without hematologic malignancies. The study involved exome sequencing on DNA derived from 2,728 blood specimens that were the paired normal controls to one of 11 diverse solid tumor types from The Cancer Genome Atlas. After filtering out variants with a population allele frequency of greater than one percent in the 1000 Genomes reference and other metrics, a pattern emerged. Blood-specific mutations were found in all 11 cancer types, and the overall frequency of blood-specific mutations increased with age. In addition, 64 of the 77 (83 percent) mutations detected were in one of 19 genes known to be associated with hematologic malignancies, and nine of these genes—DNMT3A, TET2, JAK2, ASXL1, TP53, GNAS, PPM1D, BCORL1, and SF3B1—were recurrently mutated. The age-dependent mutation rate, however, was not even across the genes. TET2, ASXL1, and SF3B1 mutations were primarily found in the oldest age groups—those in their 70s and 80s; DNMT3A mutations were mainly found in those in their 60s through 80s. JAK2 mutations, on the other hand, were found in both the younger and older age groups—40s through 50s and 70s, respectively. The overall blood-specific variant frequencies ranged from 1.2 percent (those in their 40s) to 6.8 percent (those in their 80s). The authors estimate that, collectively, approximately two percent and 3.5 percent of people without hematologic malignancies and who are older than 40 and 60 years, respectively, carry blood-specific mutations that are associated with hematologic malignancies. Yet most of these people likely do not progress to overt disease. The authors suggest that certain genetic mutations may confer an advantage to hematopoietic stem/progenitor cells, resulting in enhanced cell renewal or proliferation resulting in clonal expansion. These findings highlight the potential risk of using blood-derived DNA for a germline surrogate, especially in older patients. Special consideration may be warranted when evaluating mutations in patients with an unclear diagnosis.

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