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Germline mutations in men with metastatic prostate cancer

Prostate cancer displays great diversity in clinical behavior, ranging from essentially silent, organ-confined disease to rapid and aggressive metastatic spread. The authors know of no clear-cut screening method that can reliably identify those patients whose tumors are likely to behave aggressively and, therefore, may benefit from a more active treatment strategy. Prostate cancer has also been shown to have a significant component of heritability. Previous studies have demonstrated that although common germline variants in numerous genes are associated with increased risk for prostate cancer, only germline mutations in genes controlling DNA damage repair—for example, *BRCA1, BRCA2,* and *MSH2*—have been significantly associated with aggressive local disease and mortality. This study of men with metastatic prostate cancer extends these findings and demonstrates that the incidence of germline mutations in DNA damage repair genes in this setting is significantly higher than in the setting of aggressive localized disease and may provide a useful means of identifying those at risk for aggressive, metastatic disease. The authors examined 692 cases of men with metastatic prostate cancer from seven case series originating at multiple institutions in the United States and United Kingdom. No selection was performed on the basis of family history, age, or information regarding genetic background. For each series of patients, germline DNA obtained from either buccal swabs, saliva, whole blood, buffy coats, or nontumor tissue was subjected to next-generation sequencing, which interrogated a group of 20 genes involved in maintaining DNA integrity. Of the 692 cases studied, 82 (11.8 percent) had at least one presumed pathogenic germline mutation in a gene involved in DNA repair processes. Eighty-four mutations were identified as presumably pathogenic (two of the 84 men studied harbored mutations in two genes), including 79 truncating mutations and five known deleterious mutations. Mutations were identified in 16 of the 20 genes analyzed, of which the most commonly mutated were *BRCA2* (44 percent), followed by *ATM, CHEK2, BRCA1, RAD51D,* and PALB2. No association was found between the presence of a germline mutation in these genes and age at diagnosis of younger than 60 years versus 60 years or older or non-Hispanic white versus other race. To assess the frequency of deleterious germline DNA repair gene mutations in localized prostate cancer, the authors evaluated data from 499 cases included in the Cancer Genome Atlas prostate cancer study. Within this cohort, four of 162 (two percent) men with localized low- to intermediate-risk tumors and 19 of 337 (six percent) men with localized high-risk tumors harbored a deleterious germline DNA repair gene mutation. The odds of deleterious DNA repair gene mutations being present in men with metastatic prostate cancer differed significantly from that for men with localized low- to intermediate-risk tumors (5.3; 95 percent confidence interval [CI], 1.9–20.2; P<.001) and from that for men with localized high-risk tumors (2.2; 95 percent CI, 1.3–4.0; P=.002). Furthermore, an analysis of data from the Exome Aggregation Consortium to assess the frequency of deleterious germline DNA repair mutations in the general population demonstrated that the odds of mutations differed significantly from that for men with metastatic prostate cancer (odds ratio, 5.0; 95 percent CI, 3.9–6.3; P<.001). These findings may provide an improved means of identifying individuals at risk for aggressive disease and for screening family members of affected individuals in order to institute appropriate risk-reduction strategies.

Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer [published online ahead of print July 6, 2016]. N Engl J Med. doi:10.1056/NEJMoa1603144.

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Genomic classification and prognosis in acute myeloid leukemia

Acute myeloid leukemia results from the clonal expansion of myeloid precursor cells that have acquired somatic mutations. Clinically and biologically relevant subcategories of acute myeloid leukemia (AML) were initially defined based on histological variations. However, the advent of genomic profiling has increasingly led to the inclusion of various genetic/genomic qualifiers in the subcategories of AML. As more data from genomic studies of AML become available, it seems clear that AML is a dynamic disease, consisting of various mutationally distinct subclones that evolve over time. Against this backdrop, a recent report by the authors examined genomic data derived from three large clinical trials of AML treatment and proposed a new, fully genomic classification scheme for AML. The authors evaluated genomic profiling data from 1,540 AML patients, ranging in age from 18 to 84 years, who were enrolled in one of three multicenter clinical trials. The genetic information collected included cytogenetic analyses and sequencing data from a group of 111 genes. Variants classified as driver mutations included recurrent fusion genes, aneuploidies, and gene mutations (base substitutions as well as insertions and deletions of less than 200 bp in size). Overall, 5,234 variants categorized as driver mutations from 76 genes or genetic regions were identified in the patient group. Point mutations comprised 73 percent of the total (3,824 of 5,234). At least one driver mutation was identified in 1,478 (96 percent) of the 1,540 patients, with 86 percent of the samples showing two or more driver mutations. From these data, the authors developed a statistical model to subgroup AML patients on the basis of patterns of comutation, which resulted in 11 subclasses of AML. Six subclasses—inv(16), t(15;17), t(8;21), inv(3), t(6;9), and MLL fusions—are identical to those included in the current World Health Organization classification scheme. Two subgroups provisionally added to the WHO classification were also identified: *NPM1*-mutated AML (the largest of the subgroups, accounting for 27 percent of cases) and biallelic *CEBPA*-mutated AML. New subgroups identified in the analysis included a chromatin-spliceosome group with mutations in genes regulating RNA splicing, chromatin, or transcription; a group with mutations in TP53, complex karyotype alterations, copy number alterations, or a combination of these; and a subgroup of AML with IDH2R172 mutations. Using this 11 subgroup scheme, 1,236 (80 percent) of the 1,540 patients were unambiguously categorized into a single subgroup, while only 56 (four percent) patients met criteria for two or more subgroups. Finally, 166 patients (11 percent) with driver mutations could not be classified definitively, suggesting the existence of as yet unrecognized driver mutations. These findings were recapitulated when the classification scheme was applied to AML cases in Cancer Genome Atlas study data. Significantly, distinctions in clinical behavior were also apparent across the subgroups. For example, the chromatin-spliceosome subgroup contained patients with lower white cell and blast counts, lower responses to induction therapy, higher relapse rates, and poor long-term prognosis. Overall, survival was strongly correlated with the number of driver mutations present, suggesting that mutations other than those that define subclasses have a significant impact on disease behavior. This study supports the rationale and continues the trend of using genomic profile information for disease classification. In addition, the significant nature of the data may inform future therapeutic options and prognostication for AML patients.

Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med.* 2016;374:2209–2221.

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