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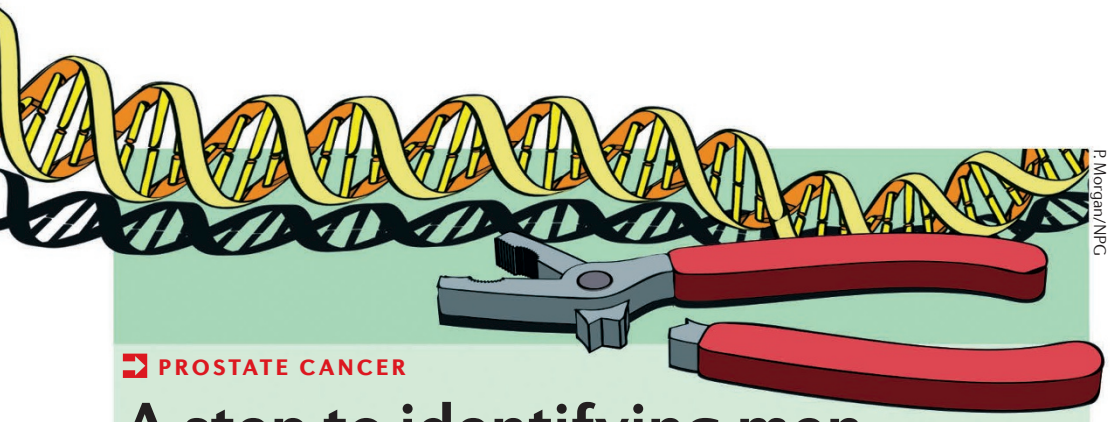

P. Morgan/NPG

PROSTATE CANCER

A step to identifying men at high risk of metastatic disease

> “…11.8% of patients with metastatic prostate cancer carry germline DNA mutations…”

New research shows that 11.8% of patients with metastatic prostate cancer carry germline DNA mutations in genes encoding proteins involved in DNA repair, in contrast to only 4.6% of men with localized disease.

Many men diagnosed with prostate cancer do not develop aggressive disease and might not require definitive treatment. Identifying those patients whose tumour has the potential to metastasize is critical to provide the best possible treatment and improve patient outcomes. However, a tool to effectively identify men with prostate cancer who have a high risk of developing metastatic disease is lacking.

The new report, which was published in *The New England Journal of Medicine*, includes data from seven case series of men with metastatic prostate cancer ($n=692$) enrolled at centres in the UK and the USA, independent of age or family history. Most men were of self-reported nonhispanic white background and 66% of men with known Gleason score had a score of 8–10 (unknown in 111 patients). As comparators, data from 499 men with localized disease from The Cancer Genome Atlas (TCGA) and from a population of 53.105 individuals without a reported cancer diagnosis from the Exome Aggregation Consortium (EAC) database were used.

The investigators focussed their analysis on 20 genes that have functions in maintaining DNA integrity and have been linked to autosomal dominant hereditary cancer syndromes. In 82 of the 692 men (11.8%), they found a total of 84 mutations (two men carried two mutated genes). Aberrations were localized in 16 of the 20 investigated genes — most commonly in *BRCA2*, *ATM* and/or *CHEK2* (37, 11 and 10 mutations, respectively). To discover whether the frequency of these DNA repair gene mutations differed depending on cancer stage, the team compared their results with data from TCGA. Of 499 men with localized disease, 4.6% carried mutations in the investigated 20 genes — significantly fewer than in the cohort of men with metastatic tumours ($P<0.001$). Unlike most patients whose prostate tumour is detected through screening, most men registered in TCGA had high-risk disease.

“In my opinion, the high frequency of these mutations warrants inclusion in management guidelines for men with advanced prostate cancer,” comments Peter Nelson, senior author of the study. “First, identifying a DNA repair mutation can assist in guiding treatment — currently, considering platinum chemotherapy and, hopefully in the future, a PARP inhibitor. Second, family members found to have one of these mutations are at risk of cancer predisposition. They should be tested and, if found positive, be considered for intensified screening and, in some, prophylactic treatment.”

Evaluating possible associations between the presence of the DNA mutations and patient characteristics, the team found a possible link for Gleason scores ≥8 versus scores ≤7 ($P=0.04$), but no associations with age younger or older than 60 years or nonhispanic white versus other background. Analysis of a possible connection to familial cancer history showed that 22% of men had a first-degree relative with prostate cancer, regardless of the men’s mutation status. When evaluating all cancer diagnoses except prostate cancer, the team found that 71% of men with, but only 50% of those without DNA repair gene mutations had a first-degree relative with cancer other than prostate cancer ($P=0.001$). In comparison with a large population of individuals without a reported cancer diagnosis from the EAC database, men with metastatic prostate cancer were five times more likely to have germline mutations in these DNA repair genes (OR 5.0, 95%CI 3.9–6.3; $P<0.001$).

The absence of comparison groups as an inherent part of the study protocol impeded matching of patients and individuals according to their characteristics. In addition, the use of varying DNA analysis techniques might have resulted in inconsistencies in the data gathered from the seven case series.

“Further work is needed to characterize other mutations currently classified as variants of uncertain significance and to investigate other DNA repair genes,” points out Nelson. “Also, looking for modifiers of cancer predisposition is important: not all patients with these mutations will develop cancer — they are just at much higher risk.”

Clemens Thoma

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