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PROSTATE CANCER

Genomic drivers of *BRCA2*-mutant tumours

Aggressiveness of localized prostate tumours with *BRCA2* mutations is driven by specific genomic changes, resulting in a metastatic-like phenotype at diagnosis, according to a study published in *Nature Communications*.

An association between germline *BRCA2* mutation and prostate cancer risk is well known: *BRCA2*-mutant prostate tumours arise at a younger age than sporadic cases, progress more quickly, and are particularly hard to treat. They quickly become castration resistant and 5-year cancer-specific survival is poor. "Germline *BRCA2*-mutant prostate cancer is not particularly common, but it remains a key clinical conundrum," explains corresponding author Paul Boutros.

Whole-genome sequencing and copy number analyses were used to investigate genomic alterations in localized prostate tumours from 14 men carrying germline *BRCA2* mutations at the point of diagnosis, when they had not received treatment. These genomic data were compared to mutational profiles of 200 sporadic prostate tumours. Measurement of percent genome alteration revealed increased genomic instability in the *BRCA2*-mutant tumours, as well as increased numbers of single-nucleotide variants and genomic rearrangements, compared with sporadic tumours. Genomic changes associated with an aggressive phenotype, such as gains in the *MYC* oncogene, *MYCN*, *GSK3B,* and *MTOR* were more common in *BRCA2*-mutant prostate cancer than sporadic tumours. The most prominent rearrangement noted was an inversion on 3p26.1, which encodes the metabotropic glutamate receptor GRM7, inactivation of which is suggestive of loss of negative regulation of NMDA signalling, known to be associated with a neuroendocrine phenotype. Furthermore, *BRCA2*-mutant tumours showed global hypomethylation compared with sporadic cancers, particularly in pathways associated with aggressive neuroendocrine disease.

The team went on to investigate a region of amplification on chromosome 3q observed in 61% of *BRCA2*-mutant tumours, but only 6.8% of sporadic tumours, which contains *MED12L*, a WNT/β-catenin pathway modulator. *MED12L* is amplified in 44% of *BRCA2*-mutant tumours, but only 0.1% of sporadic tumours; in this study, *MED12L* amplification was particularly notable in *BRCA2*-mutant cancers containing intraductal carcinoma. Intraductal carcinoma in *BRCA2*-mutant tumours was associated with increased mortality and aggressive disease, as evidenced by preferential amplification or deletion of genomic regions indicative of poor prognosis.

"Bearing in mind our tumours were from treatment-naive men, these results were quite a surprise," corresponding author Gail Risbridger comments. "However, it explains why these tumours are aggressive: they already exhibit features of aggressive tumours at the get-go".

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