Scientists report genetic test to help predict men at most risk from aggressive prostate cancer

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Scientists are reporting a test which can predict which patients are most at risk from aggressive prostate cancer, and whether they suffer an increased chance of treatment failure. This test, reported at the European Association of Urology conference in London, and published in the *Journal of the National Cancer Institute*, may give men a better view on how to deal with their prostate cancer risk.

Prostate cancer is the most common male cancer, killing almost 100,000 men each year in Europe. But it is not invariably fatal, in fact more men die with prostate cancer than of prostate cancer. Current screening methods, and in particular the well known PSA blood test, can identify prostate cancers, but are not good at identifying how dangerous they are or even whether they should be treated. This makes if difficult to identify which men with prostate cancer are at real risk and need rapid treatment, and which don't.

Prostate cancer is has a genetic component but it has until now been impossible to understand how aggressive the cancer might be Now a new multi-national study has discovered the basis of a simple blood test which can predict whether a man is susceptible to aggressive prostate cancer.

Recent years have seen extensive research on the genetics of prostate cancer, with over a hundred mutations identified, however most of these

are only present in a small number of men. Recently there has been a particular focus on the "Kallikrein" region of chromosome 19. This is a group of 15 closely-linked genes which code for proteases – molecules which break down proteins. In fact, the well-known test for prostate cancer, the PSA test (prostate specific antigen), is based on one of the Kallikrein genes, KLK3.

The researchers, led by Dr Alexandre R. Zlotta, of the Lunenfeld-Tanenbaum Research Institute (Toronto, Canada) and Paul Boutros (Ontario Institute for Cancer Research) intensively searched for small single-point inherited mutations in the whole Kallikrein region, in a large group of 1858 men with aggressive prostate cancer (defined as having a Gleason score above 8). The men came from three independent groups, in Switzerland (part of the European Randomized Screening Study for Prostate Cancer, Pr Recker and Dr Kwiatkowski), Canada, and the USA. They were able to show that variants of the Kallikrein 6 gene were associated with more aggressive prostate cancer.

"These genes are found in between 6 and 14% of men," said Alexandre Zlotta, "This makes it one of, if not the, most common genes yet found to be associated with aggressive prostate cancer. Even if we take the lower, 6% figure, then that means around 17m North American men and 22m European men carry these gene variants."

The KLK6 variants also independently predicted treatment failure after surgery or radiation for prostate cancer in a Canadian cohort of men from the International Cancer Genome Consortium (ICGC).

Dr Zlotta said "We found that in those men with prostate cancer treated by surgery or radiation, who had these inherited gene variant mutations had a three-fold increase in the risk of treatment failure, which means that after treatment, they were three times more likely to have the cancer recurring than the rest of the population. This is really a quite significant

increase in risk. Similarly men with these gene variants were three times more likely to be diagnosed with aggressive prostate cancer (Gleason 8 or more). To put this into context, around 10 to 15% of all prostate cancers are the aggressive prostate cancer we are dealing with here, but of course they lead to a greater mortality.

"What does this mean? Firstly the test has only just been developed – it's still science, rather than something which is generally available. So it needs to be further validated and costed. It should mean that if you have a high PSA level but are unsure about having a biopsy to confirm whether you have cancer, this test could help you decide. It also means that we can begin to look at better screening for those who are at risk, for example among those men with a family history. As the test is refined we may be able to move towards more intelligent prostate screening."

Prof Ros Eeles of The Institute of Cancer Research London commented:

"It is very important to try to identify markers of aggressive disease in prostate cancer patients as these will help us to target treatments to those most likely to benefit. Genetics is increasingly being brought into the management pathway and this result if validated will be important in adding to the algorithm of a panel of genetic variants which may be become part of routine testing in the coming years."

More information: Laurent Briollais et al. Germline Mutations in the Kallikrein 6 Region and Predisposition for Aggressive Prostate Cancer, *JNCI: Journal of the National Cancer Institute* (2017). DOI: 10.1093/jnci/djw258

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