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Discovery may help to explain mystery of 'missing' genetic risk

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A new study could help to answer an important riddle in our understanding of genetics: why research to look for the genetic causes of common diseases has failed to explain more than a fraction of the heritable risk of developing them.

Susceptibility to common diseases is believed to arise through a combination of many common genetic variants that individually slightly increase the risk of disease, plus a smaller number of rare mutations that often carry far greater risk.

However, even when their effects are added together, the genetic variants so far linked to common diseases account for only a relatively small proportion of the risk we know is conveyed by genetics through studies of family history.

But the major new study, published today (Thursday) in the journal *PLOS Genetics*, shows for the first time in cancer that some common genetic variants could actually be indicators of the presence of much more influential rare mutations that have yet to be found.

Scientists at The Institute of Cancer Research, London, led an international consortium made up of more than 25 leading academic institutions on the study, which was funded by the European Union.

The research, involving 20,440 men with prostate cancer and 21,469 without the disease, identified a cluster of four common genetic variants

on chromosome 17 that appeared to give rise to a small increase in prostate cancer risk, using the standard statistical techniques for this type of study.

But the study found an alternative explanation for the risk signal – a small proportion of the men with these common variants were in fact carriers of a rare mutation in the nearby HOXB13 gene, which is known to be linked to prostate cancer. Under this 'synthetic association', the number of people carrying a cancer risk variant was much lower than had been assumed, but those people who did inherit a variant had a much higher risk of prostate cancer than had been realised.

The discovery shows that the prevailing genetic theory – that common cancers are predominantly caused by the combined action of many common genetic variants, each with only a very small effect – could potentially underestimate the impact of rare, as yet undiscovered mutations.

The results are important because they show that there is a need for renewed effort by geneticists to find the causal variants, whether common or rare, behind the many common cancer-associated variants identified in recent years.

Identifying any underlying rare mutations with a big effect on disease risk could improve the genetic screening and clinical management of individuals at greater risk of developing cancer, as well as other diseases.

Study co-leader Dr Zsofia Kote-Jarai, Senior Staff Scientist at The Institute of Cancer Research (ICR), said: "As far as we are aware, this is the first known example of a 'synthetic association' in cancer genetics. It was exciting to find evidence for this theory, which predicts that common genetic variants that appear to increase risk of disease by only a modest amount may indeed sometimes be detected purely due to their

correlation with a rarer variant which confers a greater risk.

"Our study does not imply how widespread this phenomenon may be, but it holds some important lessons for geneticists in cancer, and other common diseases. It demonstrates the importance of identifying the causal genetic changes behind the many common variants that have already been shown to influence risk of disease.

"Our study also demonstrates that standard methods to identify potential causal variants when fine-mapping genetic associations with disease may be inadequate to assess the contribution of rare variants. Large sequencing studies may be necessary to answer these questions unequivocally."

Study co-leader Professor Ros Eeles, Professor of Oncogenetics at The Institute of Cancer Research and Honorary Clinical Consultant at The Royal Marsden NHS Foundation Trust, said: "One important unanswered question in cancer genetics – and in genetics of common disease more generally – is why the genetic mutations we've discovered so far each seem to have such a small effect, when studies of families have shown that our genetic make-up has a very large influence on our risk of cancer.

"Our study is an important step forward in our understanding of where we might find this 'missing' genetic risk in cancer. At least in part, it might lie in rarer mutations which current research tools have struggled to find, because individually each does not affect a large number of people."

More information: www.plosgenetics.org/doi/pgen.1004129

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