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Unique study reveals genetic 'spelling mistakes' that increase the risk of common cancers

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More than 80 genetic 'spelling mistakes' that can increase the risk of breast, prostate and ovarian cancer have been found in a large, international research study within the framework of the EU Network COGS. For the first time, the researchers also have a relatively clear picture of the total number of genetic alterations that can be linked to these cancers. Ultimately the researchers hope to be able to calculate the individual risk of cancer, to better understand how these cancers develop and to be able to generate new treatments.

The main findings are published in five articles in a special issue on genetic risk factors for cancer in the prestigious scientific journal *Nature Genetics*. The articles originate from COGS (Collaborative Oncological Gene-environment Study), an EU-based consortium where more than 160 research groups from all over the world are included. In the five COGS studies 100,000 patients with breast, ovarian or prostate cancer and 100,000 healthy individuals from the general population were included.

The scientists performed genetic analyses on all study participants. The composition of the nitrogen bases A, G, C and T was studied on 200,000 selected sections of the DNA strand. When cancer patients had significantly different compositions compared to healthy control subjects, the differences were considered to be relevant to risk of disease. The alterations can be described as a genetic 'spelling mistake',

where A, G, C or T have been replaced with another letter. This 'spelling mistake' is called Single Nucleotide Polymorphism (SNP) – pronounced 'snip'.

For breast cancer the researchers found 49 genetic typos or SNPs, which is more than double the number previously found. In the case of prostate cancer, researchers have discovered another 26 deviations, which means that a total number of 78 SNPs may be linked to the disease. For ovarian cancer 8 new relevant SNPs were found.

'An equally important finding is that we identified how many additional SNPs that could influence the risk of breast cancer and prostate cancer, respectively. For breast cancer the number is 1,000 and for prostate cancer 2,000' says Per Hall, Professor at Karolinska Institutet in Sweden and the coordinator of the COGS consortium. "We also have a picture of where in the genome we should look in future studies'.

SNPs are part of our natural heritage, we all have them. How it affects the individual depends on where on the DNA strand the genetic deviation is found. The researchers now hope to be able to evaluate the importance of the identified deviations, so that it will be possible to more clearly predict which individuals are at high risk of developing one of these cancers.

"We're now on the verge of being able to use our knowledge to develop tests that could complement breast cancer screening and take us a step closer to having an effective prostate cancer screening programme", says Professor Doug Easton of the University of Cambridge, UK, who has led several of the presented studies.

At the same time as these five articles are published in *Nature Genetics*, the Nature Publishing Group publishes another two articles on studies emanating from the COGS collaboration in Nature Communications.

Further five COGS articles will be published simultaneously in other journals. The studies are financed by partly different funders; however the COGS project is mainly funded by the European Commission's 7th Framework Programme. Some of the other financial contributors are the Märit and Hans Rausing Initiative against Breast Cancer, the Swedish Research Council, Cancer Research UK and the Cancer Risk Prediction Center (CRisP).

"COGS is the largest genotyping project in the world targeting identification of genetic alterations that influence the risk of common cancers. The collaborative efforts have been tremendous and key to success", says COGS coordinator Per Hall.

More information: The five publications in *Nature Genetics* are:

'Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array', Eeles et al, doi: 10.1038/ng.2560
'GWAS meta-analysis and replication identifies three novel susceptibility loci for ovarian cancer', Pharoah et al, doi: 10.1038/ng.2564
'Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer', Bojesen et al, doi: 10.1038/ng.2566
'Genome-wide association studies identify four ER-negative specific breast cancer risk loci', Garcia-Closas et al, doi: 10.1038/ng.2561
'Large-scale genotyping identifies 41 new loci associated with breast cancer risk', Easton et al, doi: 10.1038/ng.2563

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