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PROSTATE CANCER

Turning the COGS—23 new susceptibility loci identified

The Collaborative Oncological Gene-environment Study (COGS) recently reported—in 13 separate publications—the results of their large-scale analysis of more than 200,000 single nucleotide polymorphisms (SNPs) in prostate, breast and ovarian cancer. Using individuals included in four large European consortia, the COGS work has identified more than 70 new susceptibility loci across the three hormone-related cancers, 23 of which are associated with prostate cancer.

The COGS consortia conducted meta-analyses of genome-wide association studies (GWAS) on tens of thousands of cases and controls across the three cancer types. Using their results, a custom genotyping array (the iCOGS array) was developed to validate the findings in a follow-up analysis. The array includes SNPs thought to be associated with an increased risk of these cancers from GWAS, as well as specific SNPs associated with breast and ovarian cancers, SNPs associated with survival after diagnosis, SNPs in regions known to harbour susceptibility variants for one of the target diseases and functional candidate variants, such as rare variants in known susceptibility loci (for example, *BRCA1*).

The prostate cancer validation studies were conducted on samples from approximately 20,000 men with prostate cancer and a similar number of controls. The genotyping of more than 70,000 SNPs enabled the identification of 23 new loci susceptible to variation in prostate cancer. Combined with the 53 previously known loci, the COGS researchers estimate that the proportion of familial risk that can now be explained by common genetic loci is 30% for prostate cancer.

Furthermore, fine-mapping of the 5p15 locus (on which the *TERT* gene is located) in more than 22,000 cases revealed several SNPs that are associated with increased risk of prostate cancer. *TERT* encodes telomerase reverse transcriptase, the catalytic subunit of the enzymatic complex that extends the ends of telomeres.

Clearly, only a large collaborative effort such as COGS could be sufficiently powered to examine low-penetrance variants. However, identification of the SNPs associated with prostate cancer is only the first stage. Focused investigation is needed to unravel the mechanisms by which these SNPs are involved in carcinogenesis, progression and, possibly, resistance to therapy.

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Arguably, the results of the COGS work represent hope for refining current screening methods. Douglas Easton, director of the Cancer Research UK Genetic Epidemiology Group, was involved in the COGS work and told *The Guardian*: "...it is quite possible that including this type of risk assessment may not cost much and may even save money, because it may reduce... the number of men at low risk getting unnecessary PSA tests or biopsies."

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Original articles Eeles, R. A. *et al.* Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat. Genet.* doi:10.1038/ng.2560 | Kote-Jarai, Z. *et al.* Fine-mapping identifies multiple prostate cancer risk loci at 5p15, one of which associates with *TERT* expression. *Hum. Mol. Genet.* doi:10.1093/hmg/ddt086
Further reading Nature Genetics. *iCOGS Collection* [online], http://nature.com/icogs/ (2013)