Nature Reviews Genetics | AOP, published online 5 August 2014; doi:10.1038/nrg3801

CANCER GENOMICS

Non-coding mutations in the driver seat

> inherited regulatory variants become active in cancer and are likely to contribute to cancer progression

Cancer research has traditionally focused on deciphering driver mutations (that is, mutations that causally underlie tumorigenesis and that confer a selective advantage during cancer development) in protein-coding regions. Now, researchers from the collaborative European project SYSCOL (Systems biology of colorectal cancer) show that both inherited and somatic (that is, acquired) mutations in non-coding regions of the genome also contribute to cancer development and progression.

Germline variants in non-coding regulatory regions that affect gene expression — known as expression quantitative trait loci (eQTLs) — have previously been implicated in complex diseases. The researchers therefore hypothesized that interactions between eQTLs or non-coding somatic variants and coding variants would also play a part in tumorigenesis.

Colorectal cancer is the third most common cancer type worldwide, and it has an increased prevalence in developed countries versus developing countries. The researchers carried out RNA sequencing of 103 tumour and normal colon mucosa samples from patients with colorectal cancer — 90 of which were also genotyped for germline variants — which were then analysed for allele-specific expression to dissect the effects of individual regulatory variants. About 10% of coding heterozygous sites showed marked allele-specific expression, and there was a significantly higher proportion of such sites in tumour samples than in normal tissues, which the authors propose might be a result of copy-number alterations.

Allelic expression patterns were most similar between tumours and normal tissues from the same patient. This finding suggests that germline genotypes remain important determinants of gene expression even after tumorigenesis. Overall, Ongen *et al.* were able to determine 71 genes with putative somatic *cis*-regulatory driver mutations.

The authors postulated that if non-coding germline variants act as cancer drivers, then "such variants ... would affect gene expression specifically in tumours". Therefore, the researchers carried out a *cis*-eQTL analysis in which they compared differences in eQTLs between tumours and normal tissues (948 and 1,693 eQTLs in tumour samples and controls, respectively). In a series of additional analyses, the team showed that inherited regulatory variants become active in cancer and are likely to contribute to cancer progression.

In the future, the investigators plan to evaluate their findings in other cancer types with the ultimate goal of developing "a model that integrates both protein-coding and regulatory variants, thus giving a much more complete picture, to assess a tumour and its characteristics, as well as to use this information to develop personalized approaches for treatment," concludes Emmanouil T. Dermitzakis (University of Geneva, Switzerland), who led the study.

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ORIGINAL RESEARCH PAPER Ongen, H. *et al.* Putative *cis*-regulatory drivers in colorectal cancer. *Nature* http://dx.doi.org/10.1038/nature13602 (2014)

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