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GENOMICS

A different view of the landscape

> Inherited germline variants were also associated with somatic mutations

Genomic analyses have provided substantial information about the landscape of somatic alterations in cancer, and genome-wide association studies (GWAS) have identified many germline variants that are linked with cancer predisposition. Although some evidence has emerged linking germline variants to somatic alterations, cancer genome data have not been widely used for dissecting the contributions of germline variants to cancer development. Carter *et al.* integrated pan-cancer data on germline and somatic alterations from The Cancer Genome Atlas (TCGA) to examine whether germline variation can influence tumour development and evolution.

Looking at germline variants present at allele frequencies of 1% or higher, the authors identified more than 700,000 autosomal single nucleotide polymorphisms (SNPs) and 1.6 million haplotypes among 6,908 patients. They then used this information to compare tumours that originated at 22 tissue sites represented in TCGA data, and identified and validated 395 germline markers that were associated with tumour development at a particular site. For example, germline variants at 8q24.13 or 11q22.3 were significantly associated with development of breast cancer.

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Inherited germline variants were also associated with somatic mutations in known cancer genes, suggesting that a person's germ line creates a biological context in which alterations in a particular gene might be more likely to provide a selective advantage in tumour development. Overall, the authors identified 35 such interactions of potential interest, which included 28 germline loci and 20 known cancer genes, and further examined two specific associations.

In the first example, a germline variant at 16p13.3 that included an enhancer region in *RBFOX1* (which encodes an RNA binding protein) was associated with an eight-fold increase in somatic mutations in the splicing factor *SF3B1*. The minor allele at this locus (rs8051518) was shown to increase *RBFOX1* expression in TCGA samples, and splicing patterns in patients who carried both the minor rs8051518 allele and *SF3B1* mutations were substantially different relative to patients who carried the major rs8051518 allele. These data indicate that a germline-driven increase in *RBFOX1* expression creates a context in which cells have greater changes in splicing in response to subsequent *SF3B1* mutation.

The second example involved a germline variant at 19p13.3 that increased somatic mutations in *PTEN*. The minor allele at this locus increased the expression of G protein subunit alpha 11 (*GNA11*), which, like PTEN, functions in the PI3K–mTOR pathway. In HEK293T cells, increasing *GNA11* expression increased mTOR signalling, and this was further magnified by knockdown of *PTEN*, suggesting that people carrying this variant might be more susceptible to loss-of-function *PTEN* mutations.

A larger scale analysis of the genes affected by the 28 germline loci identified by the authors indicated that 20 additional genes with potential cancer relevance had a higher than expected somatic mutation rate in a specific genetic background. As most of these had not been identified as mutated in previous cancer genome analyses, stratification of patients by germline genetic background could enable the identification of new cancer genes.

This study highlights the importance of a person's genetic background in cancer risk and the likely evolutionary trajectory of a tumour, which may have implications for both personalized prevention and precision medicine.

Sarah Seton-Rogers

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