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Common genetic variation in the germline influences where and how tumors develop

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ABSTRACT
Germline variation contributes to individual risk for developing specific types of cancer. Analyzing thousands of tumors, we found evidence that the germline also influences vulnerable tissue sites and the mutations that arise in tumor genomes. These associations provide new clues to unravel the biologic mechanisms underlying cancer predisposition.

Genome-wide association studies (GWASs) have linked hundreds of common germline variants to inherited predisposition for specific cancers. However, determining the precise biologic mechanism by which these loci lead to cancer susceptibility has proven challenging. More recently, there have been reports of specific germline haplotypes that increase the probability that a tumor acquires a specific mutation. For example, among individuals that develop myeloproliferative neoplasms, those with a GG/GC genotype at rs10974944 at the locus encoding Janus kinase 2 (JAK2) are more likely to develop a V617F mutation in JAK2. Among individuals that develop non-small cell lung cancers, the -216T and CA-19 alleles at the epidermal growth factor receptor (EGFR) locus are associated with the occurrence of EGFR exon 19 microdeletions in the tumor genome. The germline has also been shown to influence gene expression in some tumors. These associations, obtained by comparing similar tumors with distinct genomic characteristics, provide a new perspective on cancer risk by tying the germline locus to a specific event in the tumor. These interactions suggest much more specific hypotheses about how a particular germline locus contributes to disease, thereby providing new clues to unravel the biology underlying inherited cancer risk. In addition, the mounting evidence that germline biases the emergence of specific tumor genotypes suggests that it may be possible to predict how an individual’s tumor will develop, potentially allowing a shift from reactionary approaches toward more proactive approaches for planning therapeutic strategies.

Unlike most cancer GWAS studies, The Cancer Genome Atlas (TCGA) has systematically collected both germline and tumor genomic data for cancer patients. Using matched germline and tumor genomic data for nearly 6000 patients, it was possible to systematically screen for and validate 412 associations between germline loci and tumor site as well as for a subset of common tumor genotypes involving known cancer genes. By this approach, we sought to identify inherited factors that could influence where a tumor will emerge and what cancer genes might be involved in the tumor’s development (Fig. 1).

We identified 395 loci that were associated with the site at which a tumor emerges. A minority of these loci had previously been reported by cancer GWAS and several of the novel germline loci are near known cancer genes, including RB transcriptional corepressor 1 and ATM serine/threonine kinase. Because of the rich genomic and clinical data available through TCGA, it was possible to follow up with some loci to evaluate the influence of different genotypes on the expression of genes encoded at the locus or on clinical factors such as age at diagnosis. For example, one allele at 8q24.13 was not only associated with breast cancer, but also with disease occurring nearly 10 years earlier. We also analyzed published GWAS markers within the TCGA cohort to understand how markers identified by traditional approaches comparing healthy individuals to those with a specific cancer type compare with markers associated with tumor site among individuals with cancer. Genotype frequencies were contrasted between individuals with the disease where the genotype was identified and all other cancer types grouped. With the exception of several markers that were very strongly associated with thyroid cancer, glioma and ovarian cancer, published GWAS markers tended to be modestly significant within TCGA, suggesting that these markers may contribute to risk for multiple tumor types.

In addition, we identified 17 markers that influenced the somatic alteration rate of known cancer genes. Interestingly, in contrast to most previous reports, the implicated germline loci were not near the affected cancer genes. It is well established that heterogeneous somatic mutations converge on common biologic processes and pathways, explaining why tumors with very different mutation profiles nonetheless display common
neoplastic phenotypes. We suspect that the same principles could explain germline associations that influence the mutation rate of distant genes. Indeed, we found examples among the identified associations where genes at the germline locus could clearly be tied to a biologic process or pathway involving the somatically altered cancer gene. For example, a locus overlapping an enhancer in an intron of RNA-binding protein, fox-1 homolog 1, a gene encoding an RNA-binding protein involved in alternative splicing, was associated with an increased mutation rate of splicing factor 3b subunit 1 (SF3B1), a cancer gene that recognizes branch points during alternative splicing. Further analysis identified significant differences in splicing among tumors with both the germline minor allele and somatic mutations in SF3B1. Another association involved a locus encoding cancer genes, G protein subunit α11 (GNA11) and serine/threonine kinase 11 (STK11) that appear to influence the mutation rate of phosphatase and tensin homolog (PTEN). All of these genes participate in mechanistic target of rapamycin (mTOR) signaling, and we were able to identify a likely mechanism whereby the minor allele may increase the capacity of GNA11 to drive mTOR signaling conditional on inactivation of PTEN. Finally, we were able to perform an unbiased screen for candidate cancer genes with elevated mutation rates among individuals grouped according to their germline background.

In conclusion, we report evidence of a landscape of common germline variants that influence how and where tumors develop. Due to limited sample sizes, our study was better powered to detect associations with some tumor sites and cancer genes than others, and was underpowered to evaluate associations with mutated cancer genes within specific tumor types, a factor that other studies suggest will be important. For example, Puzone and Pfeffer reported germline SNPs associated with phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (PIK3CA) mutation in estrogen receptor positive breast cancer, whereas our cross-cancer screen did not identify PIK3CA associated loci, suggesting that some associations may only be observable in the correct disease context. Thus we expect that collection of additional data capturing both germline and somatic genotypes and exploration of different study designs will be needed to gain a complete picture of germline’s contribution to cancer.

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