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Commentary

On the Protective Effects of Gene SNPs Against Human Cancer

Hua Tan *

School of Biomedical Informatics, The University of Texas Health Science Center at Houston, Houston, TX 77030, USA

Most existing genotype-phenotype association studies in cancer research were designed to detect cancer-causing (pathogenic) genetic variants, i.e., those showing strong linkage with cancer susceptibility, but rarely to focus on the protective variants. In the current issue of *EBioMedicine*, Zhu et al. [1] explored the impact of single nucleotide polymorphisms (SNPs) within base excision repair (BER) genes on the Wilms tumor susceptibility, based on 145 cases and 531 healthy controls from Chinese Han children. They concluded that three SNPs, *hOGG1* rs1052133, *FEN1* rs174538 and rs4246215, showed protective effects against Wilms tumor, a common pediatric kidney cancer. Since this is the first time to investigate the association between BER polymorphisms and Wilms tumor risk, the conclusions brought new knowledge and insights into the field. This pioneer work also addressed (at least partially) the current paucity of research pertaining to the protective effects of gene SNPs against human cancer.

Complete information about overall risk-modifying variants, including both cancer-risk and cancer-preventive ones, facilitates better genetic definition of population subgroups and potentially expedites personalized treatment according to their genetic profiles [2, 3]. The current work represents a good example to report cancer-protective variants in a particular population with clinical translational potential. This potential is further consolidated by a previous relevant study, in which one of the currently studied SNP, *hOGG1* rs1052133, was reported to be a strong protective factor for head and neck squamous cell carcinomas among north Indian populations [4]. More encouragingly, owing to the continuing progress in the next-generation sequencing technologies and high-throughput genotyping platforms, it is becoming more feasible and efficient to pursue such goals than ever before. Similar work aiming to identify general human disease-protective variants has been emerging, including those targeting breast cancer [5], type 2 diabetes, multiple sclerosis and rheumatoid arthritis [6]. Therefore, efforts towards identification and characterization of disease-protective SNPs would be increasingly promising in the near future.

When talking about a protective variant, one point should be clarified. The statement that a SNP showed protective effects against tumor is inaccurate, and subjects to a conceptual and semantics mistake. Every disease-associated SNP involves two alleles, with one considered "risk-associated" and the other by default referred to as "disease-protective". In the context of the current paper, and as presumed in general cases, the protective factor implicitly referred to the derived (i.e. the mutant) allele, rather than the ancestral (i.e. the wild type) allele or the SNP itself. It is assumedly safer to claim that "the mutant (or minor, contingent on specific contexts) allele" of a SNP is protective from disease. In addition, since a minor allele does not necessarily equal the derived (mutant) allele, it is essential to confirm which allele is derived and which is ancestral before determining the protective nature of a SNP [2, 6].

While the findings regarding protective effects of these SNPs are exciting, they are barely correlation analysis based on a relatively small sample size. The causative roles of the SNPs in cancer predisposition remain to be confirmed, and a deeper understanding of the molecular mechanisms is critical to ensure the biological significance of this discovery [7]. The three significant SNPs detected in this study are located in different types of genome region. The *hOGG1* rs1052133 variant (C8069G) is located in the coding region (CDS) and results in an amino acid alteration (Ser326Cys). This nonsynonymous SNP (nsSNP) changed the protein product of this gene, and the biophysical properties as well as function of the protein might be accordingly altered [8]. The other two SNPs are located in the untranslated region (5'UTR and 3'UTR, respectively) of the host gene *FEN1*. Although a SNP in UTR would not influence the protein sequence, it might have an impact on the transcription activity of host or distal genes by affecting the binding affinity of related transcription factors or microRNAs. Since these SNPs displayed negligible influences on the host genes based on expression quantitative trait loci (eQTL) analysis, they are supposed to exert their protective effects not via affecting the expression of their host genes, but through indirect mechanisms. Besides the potential influence on regulators binding as mentioned, the eQTL-linked target genes are likely to play a vital role in determining the function of the SNPs. In this sense, a further bioinformatics and wet-lab experimental study on the function of these eQTL-associated genes would be beneficial for elucidating the mechanisms underlying the protective phenotypes.

Finally, it should be recognized that a genetic signature such as a SNP and its implications in oncogenesis can be highly cancer-specific [9, 10]. While the rs1052133 variant showed protective function against Wilms tumor and head and neck carcinomas in respective populations, as mentioned above, it has also been implicated in increased risk of various other cancers [4]. Therefore, a conclusion addressed from one cancer type should be interpreted in that specific context, and in most cases cannot be directly parallelized to a different cancer. On the other hand, multiple protective SNPs on genes participating the same biological process (such as the BER pathway) can be analyzed together to

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* Corresponding author.
E-mail address: Hua.Tan@uth.tmc.edu.

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detect their combinatorial effects, synergistically or antagonistically, on cancer susceptibility. Such kind of analysis is expected to provide more comprehensive information regarding the variation among genes and pathways contributing to tumorigenesis, and hence enables more precise therapeutics to the carriers of referenced SNPs.

Disclosure

No conflict of interest to declare.

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