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Commentary

The association between gene SNPs and cancer predisposition: Correlation or causality?

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In this issue of *EBioMedicine*, Fu and colleagues investigated the association between three BRCA1-associated RING domain protein 1 (*BARD1*) gene single nucleotide polymorphisms (SNPs) and nephroblastoma susceptibility (Fu et al., 2017). Based on the study conducted in a southern Chinese population consisting of 145 cases and 531 controls, they concluded that one of three previously GWAS-identified SNPs, rs7585356 G>A, was significantly associated with nephroblastoma risk. In addition, the risk effect of the three genotypes is additive, in that subjects with three risk genotypes exhibited higher nephroblastoma risk compared to those with 0–2 risk genotypes. While these SNPs have already been suggested to associate with susceptibility of other cancers such as neuroblastoma (Capasso et al., 2009), their association with nephroblastoma risk has not been reported previously. Despite the relatively small sample size and restricted population ethnicity, this study yielded a new and meaningful discovery worthy of further validation. This work also supported the hypothesis that some risk genotypes might be shared by different cancers. Specifically, the neuroblastoma risk-conferring *BARD1* gene SNP also confers nephroblastoma risk in the studied population.

Several points deserve special attention in prospective research design. First, some cancer genes are common to many cancers, while others are quite cancer-specific (Tan et al., 2015; Vogelstein et al., 2013). In addition, there might be hundreds of SNPs in the same gene, and SNPs responsible for some cancers are not naturally applicable to the others. Hence, selection of study object based on comprehensive pan-cancer analysis will be more rational. Second, the demographic factors (e.g., age, gender) may or may not influence the SNP-cancer risk association, but they are definitely useful for stratification analysis. However, clinical stage seems not a good stratification factor. The tumorigenesis is a progressive process, and a patient of clinical stage I + II may eventually progress to stage III + IV. Therefore, the rationale to associate a genotype with clinical stages remains questionable.

The solid statistical techniques and high significance level (*p*-value) adopted in this work, as well as in numerous other similar association studies, indicated the strong correlation between the gene SNP and particular cancers or other diseases. Here we ask the question: does this correlation represent real causality or just co-occurrence of two unrelated events?

To answer this question, two aspects need to be checked: (1) Does this SNP alter the amino acid, or, is it a synonymous or non-synonymous SNP? (2) Does this SNP really change the expression level of its host gene or other transcription unit? In other words, if the underlying molecular mechanisms of the SNP-disease association are clear, the causality can be consolidated. On the one hand, a non-synonymous SNP changes the protein sequence and hence potentially alters the biochemical and biophysical properties of the protein product (Tan et al., 2012). This type of SNP tends to change cell fitness and confer selective growth advantage, and consequently predispose tumorigenesis. On the other hand, a SNP may not alter the protein sequence, but it is able to influence the gene expression at the transcriptional or translational level, through various mechanisms. Therefore, the location of the SNP on the host gene, and its effect on the protein sequence (if it is on the protein-coding region) should be examined. Also, it has great value to check the gene expression profiles of samples with different genotypes if the SNP is located in the untranslated region.

Intriguingly, the SNP studied in this work, and many other SNPs in previous research, are located in the 3′ untranslated region (3′UTR). Since most microRNA (miRNA) binding motifs reside in the 3′UTR of their target genes, it would be of great significance to explore whether these SNPs affect the gene expression levels. In practice, this could be achieved by expression quantitative trait loci (eQTLs) analysis (Rockman and Kruglyak, 2006) based on publically available data, followed by luciferase reporter assay as experimental confirmation (Ebert et al., 2007). Previous efforts have shown that negative selection in humans is stronger on miRNA binding sites than on other conserved sequence motifs in 3′UTRs, and polymorphisms in the binding sites are likely to be deleterious (Chen and Rajewsky, 2006). Experiments further corroborated that SNPs on particular miRNA binding sites in the 3′UTR of its target genemay confer increased or reduced risk of lung cancer (Chin et al., 2008; Ryan et al., 2015). These results imply that the specific location of a SNP is closely related to its function and role in oncogenesis, and hence deserves comprehensive consideration when studying SNP-disease associations.

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Disclosure

No conflict of interest to declare.

References

Capasso, M., et al., 2009. Common variations in BARD1 influence susceptibility to high-risk neuroblastoma. Nat. Genet. 41, 718–723.

Chen, K., Rajewsky, N., 2006. Natural selection on human microRNA binding sites inferred from SNP data. Nat. Genet. 38, 1452–1456.

Chin, L.J., et al., 2008. A SNP in a let-7 microRNA complementary site in the KRAS 3′ untranslated region increases non-small cell lung cancer risk. Cancer Res. 68, 8535–8540.

Ebert, M.S., Neilson, J.R., Sharp, P.A., 2007. MicroRNA sponges: competitive inhibitors of small RNAs in mammalian cells. Nat. Methods 4, 721–726.

Fu, W., et al., 2017. BARD1 gene polymorphisms confer nephroblastoma susceptibility. EBioMedicine http://dx.doi.org/10.1016/j.ebiom.2017.01.038.

Rockman, M.V., Kruglyak, L., 2006. Genetics of global gene expression. Nat. Rev. Genet. 7, 862–872.

Ryan, B.M., et al., 2015. Identification of a functional SNP in the 3′UTR of CXCR2 that is associated with reduced risk of lung cancer. Cancer Res. 75, 566–575.

Tan, H., Bao, J., Zhou, X., 2012. A novel missense-mutation-related feature extraction scheme for 'driver' mutation identification. Bioinformatics 28, 2948–2955.

Tan, H., Bao, J., Zhou, X., 2015. Genome-wide mutational spectra analysis reveals significant cancer-specific heterogeneity. Sci. Rep. 5, 12566.

Vogelstein, B., et al., 2013. Cancer genome landscapes. Science 339, 1546–1558.