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LETTER TO THE EDITOR

"Heterozygous versus Homozygous" should be applied for complex diseases

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Dear editor,

Complex diseases are caused by a combination of genetic, environmental, and lifestyle factors, most of which have not yet been identified. The vast majority of diseases, including several congenital defects and a number of adult-onset diseases, fall into complex diseases. Complex diseases do not obey the standard Mendelian patterns of inheritance [1]. In the past few decades, many studies have been performed to relate genetic polymorphisms to complex diseases. In these studies, researchers examined the association between the allele, genotype and complex diseases. They usually select a dominant genetic effect and a recessive genetic effect of the minor allele. However, the two genetic inheritance patterns may not be comprehensive for complex diseases, and there may be another genetic effect of the minor allele.

Recently, we investigated the association between the tumor necrosis factor-α (TNF-α) promoter −238A/G polymorphism (TNF-α −238G>A, rs361525) and systemic lupus erythematosus (SLE) using a meta-analysis [2]. We found that A/A was a risk genotype for SLE susceptibility, while G/A was a protective genotype for SLE susceptibility. When we selected a dominant genetic effect of the A allele, we did not detect the association between TNF-α promoter −238A/G polymorphism and SLE. The result indicates that there may be another genetic effect of the A allele. Currently, we are performing another meta-analysis to evaluate the association between the FK506 binding protein 5 (FKBP5) gene rs4713916 polymorphism and the mood disorders, and we also found that heterozygous had different genetic effects in comparison with homozygous (unpublished). Moreover, similar phenomenon was also found in the field of pharmacogenetics [3, 4]. These results support the view that there may be another genetic effect of the minor allele. In the future genetic epidemiology research of complex diseases, the contrast of "heterozygous versus homozygous" should be applied, and more attention should be paid to the genetic effects of the minor allele.

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