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Phenotype Variations of Polymorphic Sites: Genotyping against Haplotyping

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Since nucleotide modifications including Single Nucleotide Polymorphisms (SNPs) may influence gene phenotypes thus, their studies highlight the distinctive features in pathogenesis of diseases. The reports on prediction of sequence profiles and patterns, as indicated in Prosite database (http://prosite.expasy.org), suggest that the function of elements and motifs is related to cumulative effect of the conserved signatures so that the polymorphic changes could affect inter- and intra molecular interactions (Kd value) leading to phenotype variations. Additionally, self-assembling proteins on several separate nucleotide elements shows that the phenotype variations may be depend on the function of other involved elements. Our knowledge of the involvement of numerous elements on the gene phenotype is limit. Furthermore, in most genotype reports obtained from multi SNPs studies, the heterozygote distribution of polymorphic sites on homologue chromosomes is not identified so that, they could not exactly show the phenotype variations. Theoretically, the number of their two-allele haplotypes can be estimated n! (n indicates the number of polymorphic sites), when the linkage failure exists between the sites. Thus, the phenotype reports based on the genotypes without consideration of haplotypes are not exactly estimated.

The haplotyping methods are able to determine the allele positions on the homologue chromosomes. Some of these methods estimate statistically the allele linkage between polymorphic positions (PHASE software) [1]. The precision of these methods are limit since the substitution rate, gene region and, tolerance level as considered in PAM and BLOSUM scoring matrices, are not summed in their outputs. Other methods based on the direct techniques such as single nucleotide dilution [2,3], typing somatic hybrids and cloning fosmid/cosmid pools [4] are experimentally able to identify the allele haplotypes. These procedures are labor-intensive and expensive, so that their application is not possible in population studies. We developed the direct haplotyping procedure based on ARMS-PCR technique [5] and applied it in descriptive cross sectional studies [6,7]. Although the approach is suitable and feasible in population studies but, some limitations exist on the number of polymorphic sites and the specificity of long ARMS-PCR protocol. The procedure is depend on a key step in which the homologous chromosomes are separated with help of specific primers. It is a specificity-limiting step so that its development could highlight the better conception of haplotype and phenotype relationships of polymorphic sites.

In conclusion, the polymorphic modifications occur independently from another so that, the phenotypes are exactly related to cumulative effects of the modified sites. These effects could be considered with the haplotyping techniques, usable in epidemiological studies. The progression in the direct procedures could markedly highlight the role of haplotypes in pathogenesis of diseases.

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