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LETTER TO THE EDITOR

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Letter to the Editor regarding: Epistatic effects in pathophysiology of asthma and the "missing heritability" of this disease

Re: Yoshikawa T, Kanazawa H, Fujimoto S, Hirata K.: Epistatic effects of multiple receptor genes on pathophysiology of asthma – its limits and potential for clinical application. Med Sci Monit, 2014, 20: 64–71

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We are probably only at the beginning of the road leading to explanation of how some genetic variants can cause chronic disease. It seemed that the so-called "genome-wide association studies" (GWAS) would clarify this issue. Takahiro Yoshikawa et al., however, at the outset of their recent paper wrote that "most of these studies have only managed to explain a small additional percentage of hereditability estimates" [1]. These researchers are convinced that the mechanisms of genetic conditioning of chronic diseases will be explained more effectively by so-called "epistatic analyses" [1]. They remember that, contrary to Mendel's classical law of heredity in which each gene locus exerts an independent effect on a single phenotype, it has been proven that 2 different gene loci can affect the same phenotype and that the action between 2 *loci* is classically defined as 'epistasis' [1].

It turns out that investigations of the genetic determinants of various chronic diseases (e.g., atherosclerosis, coronary heart disease [CAD], or Parkinson's disease) encounter similar phenomena [2,3]. This means that the consideration of individual genetic variants, in particular the so-called "single-nucleotide polymorphisms" (SNPs) using the simple additive model of their impacts, does not explain the genetic conditioning of these diseases.

Marian drew critical conclusions from all previous genome-wide association studies related to atherosclerosis and CAD [4]. He stressed that GWA studies have successfully led to identification of over 100 different *loci* for susceptibility to coronary atherosclerosis, yet the clinical outcomes of GAWS studies are modest [4]. He justified his opinion by citing the fact that the identified SNPs account for a relatively small fraction of the heritability of atherosclerosis [4]. In his next paper he raised the question of „missing heritability" and stated that gene-gene (epistasis) and gene-environmental (G-En) interactions might explain only a fraction of the heritability of complex traits [5].

In fact, epistatic analyses is just one of several possible approaches that try to explain the so-called "missing heritability' [2,6].

The "missing heritability" phenomenon can be defined as the inability of individual genes to account for most heritability of diseases. Most variants of genes identified so far that are specific for a chronic disease often confer relatively small increments of risk and familial clustering [6].

In addition to the epistatic influences and gene-environmental interactions, the "missing heritability" is explained by transgenerational epigenetic changes, regulated in part by microRNAs [2,5].

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Eichler et al. hypothesized that a plausible explanation of the "missing heritability" might be the presence of uncommon and rare variants in the genome that have not been discovered by GWAS, but that might have a great effect on the risk of development of chronic diseases [2]. Surprisingly, Eichler et al. included possible deletions, duplications, and inversions of polynucleotides among these possible uncommon variants [2]. They wrote that these large variants are individually rare but collectively common in the human population [2]. They emphasized that multiple genetic variations interact through different layers of genomic complexity and that the modern definition of the epistatic mechanisms recognizes the complexity of gene networks and biochemical systems [2]. This led to the idea that "a significant proportion of the missing heritability is not due to single common variants, nor single rare variants, "**but rather to rare combinations of common variants"**.

Eichler et al. stated that solving a part of the missing heritability problem will require the application of new "statistical and computational methods" that will detect patterns of epistasis across the genome, implemented in a complex biological system [2].

Yoshikawa et al. concluded that:

"... a genetic approach using quantitatively measurable parameters is well suited for the identification of risk factors in individuals who are likely to have disease prior to the complete development of significant symptoms and signs. Furthermore, it seems worthy to combine this style of genetic approach with prospective research to follow individuals at risk for disease...".

This is an important and significant statement. Asthma is a clinical condition that is diagnosed or suspected in the course of occurrence of symptoms, which does not allow unequivocal diagnosis of this disease. Such states are often referred to as spastic or obstructive bronchitis, chronic obstructive bronchitis, or bronchitis with an obstructive component. It seems that the precise recognition of the specific genetic profile of these patients (the status of expression of genes recognized as pathogenic, as well as their epistatic interactions) will improve the possibilities of treatment and prevention. It must be realized, however, that such a practical diagnostic approach must be continually modified in light of the results of future trials explaning the "missing heritability".

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