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At the Origin of a Never-ending Story

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Et nous allons, suivant le rythme de la lame,

Berçant notre infini sur le fini des mers

Charles Baudelaire, "Le Voyage", 1857

Pharmacogenetics, and its recent hypostasis Pharmacogenomics, has been in existence as a separate discipline for about five decades. In spite of multiple cases where the pharmacogenetic approaches successfully resolved complex problems of pharmacotherapy, and proved to be beneficial for the patients, we witness its slow integration into medical practice [1]. The basis for Pharmacogenomics is mounted on a solid scientific pedestal, the Human Genome Project. This project brought us an understanding that genetic variability between individual organisms of the same species is a common biological phenomenon, rather than a rare and pitiful deviation from the original plan. Second, we learned that human genome is not stable. Genomic DNA permanently acquires changes and, under certain biological conditions, passes them to the next generations. Therefore, though all 7 billion people on this planet are made up according to the same general blueprint, every single one of us is really unique by multiple parameters including our capacity to acquire, process, and respond to medications.

If so, why is the idea of genetic analysis toward prediction of drug response accepted so slowly by the medical community? The reason is definitely not DNA sampling and genotyping: this process is fast, cheap, and easily automated, with amazing throughput capacity. Just recently, Life Technologies advertised its new sequencing machine which is supposed to sequence a human genome per day, at the price $1,000. Even less fashionable technologies allow interrogating thousands of genomes per day, looking for specific genetic variations. Could the limiting factor be poor correlation between genetic polymorphism and phenotype? Apparently not, if the true association has been found and the causative variation has been identified [2]. In part, the above problem may be related to the methods used to identify the genetic variants responsible for the phenotype in question. At present, the strategies used for finding an association between genetic variants and a phenotype rely on statistical analysis. The outcome of statistical analysis is a probability of a certain phenotype in an individual carrying a given genotype. This works beautifully in an experimental setting when we assess the effect of a mutation in a large group of experimental organisms, e.g. in a clinical trial. When we use a statistically sound association as a biomarker in an individual, this approach may not be fruitful, because statistics does not work on a single case. This is why we need the exact knowledge about the causative genetic variants, i.e. the mechanistic explanation of an effect. This piece of evidence is often missing. There are other problems with the statistical search for association between genotype and phenotype in Pharmacogenomics. First, a poorly defined phenotype could actually be a mix of conditions, each with different etiology and prognosis. Second, the non-genetic contributing factors may obscure the genetic component, as exemplified by warfarin dose requirement, with several demographic, nutritional, and medical factors contributing to warfarin dosing, along with genetic polymorphisms. Another major problem is rare alleles which effects are difficult to evaluate by statistical analysis because of insufficient power of the study. Next, results from GWAS analysis produce a large list of SNPs presumed to be in linkage disequilibrium with the causative allele which often remains cryptic. These SNPs could be more or less tightly associated with the causative polymorphism (and consequently, with the phenotype), and therefore add to uncertainty of results.

In pharmacogenomic studies, the failure to find clearly identifiable causative variations is often explained by moderate effects of multiple genes. But, the number of contributing genes is not necessarily high. For example, initial estimate for the number of genes contributing to warfarin dose requirement included about 30 genes. The GWAS performed in 1,053 individuals identified 3 genes (VKORC1, CYP2C9, and CYP4F2) associated with warfarin dose. No additional significant associations were found [3]. Analysis of the genetic variants associated with phenotype is complicated by interracial differences in allele frequencies. It is quite natural, therefore, that the same genetic variant could have distinct effects in individuals with different genetic background. This notion adds complexity to statistical analysis in patients with distinct genetic background.

Looking back at the first 60 years of Pharmacogenomics, we can clearly see the evolution as well as challenges of this discipline: we have to accept the idea that no chemical stimulus, including medications of the present and of the future, will ever exert the identical effect on all the patients. Hard biological evidence is needed at least for the most common alleles at least of the most important drug transporters, drug-metabolizing enzymes, and drug targets, to predict efficacy and adverse effects of medications. We will never accomplish this quest, because new genetic variants will be formed, and will be found in the genome of the species *Homo sapiens*.

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