Even after detailed analyses of past events, future events are difficult, if not impossible, to predict. Few are those who could have predicted that a long and monotonous DNA molecule would potentially revolutionize the future of science and medicine. Even after the acceptance of DNA as the basic hereditary material, few predicted either the rapid rate of discovery of genes and mutations that cause the simply inherited mendelian diseases or the speed at which international public and private efforts made it possible to read the complete sequence of the human genome. Today, genes are implicated in all aspects of the human condition, ranging from susceptibility to common diseases to differences in clinical outcomes. Further analysis of the human genome sequence has led to the identification of millions of single-nucleotide variations (single-nucleotide polymorphisms [SNPs]), which form the backbone of individual variations in disease susceptibility, clinical outcome, and response to therapy (pharmacogenetics). Massive efforts are currently underway to unleash the potential usefulness of SNPs in clinical medicine. The ultimate goal is to develop “personalized medicine” by creating SNP profiles for identification of those at increased risk in a preclinical setting, providing information about the pathology of disease in subgroups of patients, and targeting drugs and other treatments to those patients who are most likely to respond.

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We have witnessed (and sometimes participated in) a plethora of association studies exploring susceptibility genes for a diverse array of human diseases and other traits. In this issue of Circulation, Droma et al1 report a susceptibility gene for high-altitude pulmonary edema (HAPE), a life-threatening condition characterized by hypoxemia, pulmonary hypertension, and increased pulmonary capillary permeability.5,3 The pathogenesis of HAPE is not well understood. Clinical studies have implicated genetic background, as well as nongenetic factors, in susceptibility to HAPE.4 Those with higher pulmonary artery pressure at rest or an exaggerated response to hypoxia or exercise are considered to be at higher risk.4 Therefore, one could postulate that genetic variants that affect pulmonary arterial pressure could serve as susceptibility alleles for HAPE. The article by Droma et al1 suggests that variants of the endothelial nitric oxide synthase gene (NOS3) could affect susceptibility to HAPE. They found statistically significant differences in the distribution of genotypes of a glutamic acid to aspartic acid change at amino acid position 298 (E298D) in exon 7 and a 27-bp variable number of tandem repeat (VNTR) polymorphism in intron 4 in 41 subjects with a history of HAPE and in 51 healthy mountain climbers. The findings of this study, implicating NOS3 as a candidate susceptibility gene for HAPE, are in accord with the results of previous studies that suggested involvement of NO in the pathogenesis of HAPE.5,6 HAPE-susceptible persons exhibit decreased levels of exhaled NO, produced by endothelial NO synthase, during hypoxia.5,6 NO, a major endothelium-derived relaxing factor, is a pulmonary vasodilator and could counteract pulmonary arterial vasoconstriction, a ubiquitous finding in patients suffering from HAPE.3 Treatment with inhaled NO improves pulmonary hypertension, arterial oxygenation, and pulmonary edema in patients with HAPE.7,8 Thus, it is plausible that genetic variants that affect the production of NO may also affect susceptibility to HAPE.

Although the report by Droma et al1 provides important and novel observations that deserve replication and further analysis by others, the study has limitations that also deserve attention. First, the sample size is small relative to that expected for most contemporary association studies. Small sample sizes are susceptible to chance variation, and it is notable that the main difference between cases and controls was in the frequency of the heterozygous genotype; there were no subjects homozygous for the risk-raising allele among the cases. HAPE, however, is relatively rare and depends on an unusual environmental trigger, ie, exposure to high altitude. In this context, Droma et al should be commended for sampling all available cases and identifying controls regularly exposed to high-altitude conditions. It is necessary for others with similar opportunities to replicate and validate their findings in other populations. Second, Droma et al do not provide functional data to support the observed association and to substantiate differential effects of NOS3 alleles on NO production. Despite a large number of reports implicating E298D and intron 4 VNTR variants in susceptibility to a variety of clinical syndromes ranging from hypertension9–11 to placental abruption,12 there are insufficient functional data. The few functional studies that have been attempted for the E298D and intron 4 VNTR variants, as well as the results of other clinical association studies, have been discordant.13,14 Therefore, the results of the present study should be interpreted with caution and considered provisional pending confirmation in additional studies and evidence of supportive functional data.
There is little doubt that genes are major determinants of susceptibility to disease, clinical outcome, and response to therapy. What remains less clear is whether we can reliably identify the underlying specific genes and gene mutations. Genetic linkage analyses have proved very successful for localizing and identifying the genes underlying many single-gene disorders. These same methods, however, have not yet proved useful for common chronic diseases, such as cardiovascular disease and its risk factors. Issues such as the small effect size for each gene, genotype–environment interaction, and pathogenic heterogeneity restrict their usefulness. Several alternative approaches have been developed, and association mapping with a large set of SNPs spanning the human genome has emerged as a preferred approach. Such association mapping relies on the underlying association between disease susceptibility alleles and alleles at a marker SNP. This nonrandom association between alleles is called linkage disequilibrium. Unfortunately, the variation in linkage disequilibrium among samples and populations is poorly understood, but it is known to vary widely in samples of small size. This wide sampling variation is at least partially responsible for inconsistent results in genetic association studies. As a result of these limitations, 3 criteria need to be met before the results of genetic association studies can be taken literally: namely, adequate sample size, replication, and functional data. Until these criteria are met, the results of genetic association studies, including the results of Droma et al., should be considered provocative but preliminary. Finally, given the central role of exaggerated pulmonary vasoactive response to hypoxemia in patients with HAPE, studies of uncommon genetic disorders, such as primary pulmonary hypertension, could provide additional information. It is intriguing to postulate that variants of genes responsible for primary pulmonary hypertension, including members of the transforming growth factor-β superfamily, could also serve as susceptibility alleles for HAPE. In any case, large-scale prospective studies in conjunction with detailed functional studies will be needed to identify the susceptibility genes and to delineate whether NOS3 genotypes are predictors of HAPE in those who ascend “into thin air.”

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References

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