Oxidative Stress and Human Genetic Variation¹,²

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EXPANDED ABSTRACT

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Genetic variants, largely in the form of single nucleotide polymorphisms (SNPs) are found in almost every human gene. It is estimated that a base change is present, on average, every 300 nucleotides. If the alteration results in a discernable phenotype, these variants form an attractive tool to study a possible effect on disease in association studies. Considering oxidative stress, many potentially significant genetic variants do exist [for a review, see Forsberg et al. (1)]. Examples include glutathione transferase null allels, a low-activity variant of quinone reductase 1, altered heme oxygenase, nitric oxide synthase, paraoxonase, and mitochondrial superoxide dismutase. However, much effort still is needed to determine the phenotype of newly discovered genetic variants that have been identified in large-scale sequencing and coupled bioinformatic research. It also has to be kept in mind that many SNPs in databases are not yet experimentally verified or are extremely rare (which makes them less suitable for association studies). The actual consequence of a base change can, of course, impinge on gene transcription, mRNA stability, or protein function. Detrimental amino acid changes and altered gene regulation have been the focus of most attention so far. One can obtain the current status of a favorite gene’s SNP content at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=snp and a selected and validated list of genes related to cancer (including most oxidative stress related genes) at http://snp500cancer.nci.nih.gov/.

Basic research on human genetic variation in oxidative stress–related genes could reveal the degree of variability that is tolerated in healthy life (e.g., acatalasemia). Furthermore, the effect of antioxidants on expression levels needs to be determined. When coupled to indices of oxidative stress such as oxidized DNA, lipids, and proteins, the genetic variants can provide mechanistic insight into defense organization. The relation of an intermediate “damage” phenotype to a genotype thus constitutes an important goal.

Experience shows that, although many association studies yield significant results regarding a particular genetic variant and a disease (see Table 1), these results often are not reproduced in subsequent studies (2). A case in point is the initial correlation between the null allele of a glutathione transferase M1 and lung cancer (3). Several studies subsequently yielded conflicting results, but meta-analysis of 43 studies that included >43,000 individuals indicates that lack of the enzyme carries a small but significant risk (4). Clearly, these studies point to an inherent difficulty in association studies involving multigene disease etiology. Nevertheless, the influence of 1 in >20 glutathione transferases could be detected.

The genetic component of various cancers ranges from 10 to 18% for colon, colorectal, and lung cancers and melanoma, as estimated from twin studies (5). Estimates can vary from 10 to 32% for colorectal cancer and be as high as 42% for prostate and 21% for breast cancer, respectively (6,7). Hence, the genetic component affects the possibility of determining the effects of genetic variants that influence the choice of disease for association studies.

In summary, many association studies will be needed to determine whether genetic variants in oxidative stress–related genes can be used to assess the effects of oxidative stress on disease. Careful consideration also should be given when designing association studies, as these can be made more sensitive by several approaches (2). These studies also are complicated by compensatory changes in the expression of protective genes and by possible modulation by antioxidant intake. Research on oxidative stress–related genes, intermediate phenotypes, and their dynamic interplay with dietary antioxidants is anticipated to yield important holistic information on this intricate and highly redundant defense system. As recent results indicate that oxidative stress can play a significant role in cancer development (8), this constitutes an important research area.

A summary of research needs follows:

● Phenotype. Although most genetic variants (SNPs) can be found in databases, new variants need to be characterized with regard to functional consequences.

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Intermediate phenotypes. Genetic variants need to be related to oxidative damage status, e.g., oxidized lipid and DNA.

Homeostasis. The interplay between genetic variants (as well as antioxidants) and compensatory changes in protective genes needs to be studied.

Epidemiology. Larger epidemiological studies and improved statistical methods are needed.

LITERATURE CITED