5

Individual Susceptibility and Gene–Environment Interaction

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5.1. INDIVIDUAL SUSCEPTIBILITY

It has always been clear that individual human beings differ widely in their susceptibility to the toxic effects of environmental agents (Bois 1995; Harris 1989). There are many factors that play a part in determining the particular degree of susceptibility for each individual to the effects of toxic agents. Susceptibility factors that originate from the person at risk are called host factors, and they include aspects of the individual’s health, weight, habits and genetic make-up. Host factors include some characteristics that are under total or partial control by the individual, such as diet, weight, sexual habits, medication or drug use and general health status. Other host factors, such as hormonal levels and a great number of genetic factors, are beyond the control of the individual. Identifying risks associated with environmental and host factors that are subject to change is of obvious value, since preventive strategies can be identified. The identification of risks associated with host factors that are not subject to alteration by the will of the individual raises more complex issues (VanDamme et al. 1995; Schulte et al. 1999).

The study of host factor-related susceptibility has been mostly focused on the genetic variation that is known to be prevalent in human populations (Vineis et al. 1999; Fryer et al. 1999; Kelada et al. 2003). Research into the genetic basis of human variability in disease risk has the potential to produce a number of benefits, in addition to the identification of susceptible individuals. The identification of subpopulations who are more susceptible to chemically-induced disease increases our ability to recognize relevant risk factors (Garte 2001), and knowledge of genes involved in the metabolism of a putative aetiological agent strengthens the evidence for its role in toxicity. As discussed later, genetic polymorphisms may be particularly important for low exposure levels (Garte et al. 1997; Taioli et al. 1998; Vineis et al. 1994, 2004; Taioli and Garte 1999; Garte 2006), which could influence the whole process of risk assessment, a process that is now starting to take individual variability in susceptibility into account. This chapter focuses on the effects of genetic background on individual susceptibility and how genetic factors interact with toxic exposures to produce individual variability in the observed effects of such exposures.

5.2. GENETIC SUSCEPTIBILITY

Current knowledge of the human genome, which includes the identity and sequences of the genes that code for the enzymes involved in detoxification of toxins and carcinogens, as well as in drug activity and toxicity, is beginning to make it possible to investigate the basic sources of human variability using new technologies. This field of biomedical research is called “pharmacogenetics” when dealing with the genes controlling drug
metabolism, or 'toxicogenetics' when the emphasis is on detoxification of chemical toxins. Often the same genes are involved in both processes (Idle et al. 1992). When the research is not related to a limited number of known genes, but encompasses the entire genome (e.g. when searching for new targets for a drug or a toxin), the area is defined as 'toxicogenomics' or 'pharmacogenomics'. There is a considerable degree of overlap between the terms 'pharmacogenetics' and 'pharmacogenomics' and they have often been used interchangeably.

Genetic susceptibility is a reality for the large majority of diseases. Because of the interests of the author, this chapter tends to highlight those genes associated with susceptibility to carcinogenesis and interaction of genetic factors with environmental carcinogens. However, it is critical to note that genetic susceptibility is a major and important area of research into many other human diseases, including heart disease (Kaab and Schulze-Bahr 2005; Watkins and Farrall 2006; Bianchi 2005; Ye 2006), infectious diseases (Clementi and Di Gianantonio 2006; Bellamy 2006; Kaslow et al. 2005; Fernando and Britton 2006), psychiatric disorders (Gogos and Gerber 2006), hepatic fibrosis (Day 2005), kidney disease and diabetes (Gohda et al. 2005; Freedman et al. 2006; Maier and Wicker 2005), osteoporosis (Zmuda et al. 2005) and many others (Khoury et al. 1995; Lidral and Murray 2004; Ban and Toner 2005; Libby et al. 2005; Abel et al. 2006).

The genes responsible for differences in susceptibility may be divided into many groups, but each of these genes can be assigned to one of two broad categories. The category I genes act within the mechanistic cellular pathways, and do not generally interact with environmental agents in order to produce effects. For carcinogenesis, these genes, including tumour suppressor genes, such as p53, Rb, BRCA1, other genes involved in inherited cancer susceptibility syndromes, such as ATM or RET, and oncogenes such as ras or myc, may be called 'major cancer genes' (Friend et al. 1988; Frebourg and Friend 1992; Savitsky et al. 1995). The mechanisms of action of these genes do not depend on the presence of any environmental exposures, and they can exert their effects in the absence of such exposures. The second category of genes influence events in the mechanistic pathways of toxicity (such as metabolism or repair), but are not part of the pathway. Because of this, they differ in many ways from the first category of genes.

5.3. METABOLIC SUSCEPTIBILITY GENES

Genetic sequence polymorphisms have been found in these genes that directly affect the function of their gene products, which are usually enzymes that act within the classical two-phase biochemical detoxification pathway (Figure 5.1). In phase I, a toxic agent is metabolized by a complex reaction, usually mediated by a cytochrome P450-containing enzyme, in which an oxygen-containing moiety such as a hydroxyl group is placed on the xenobiotic compound. This reaction has the effect of painting a target onto the foreign molecule and allowing it to be more easily attacked by the conjugating reactions of phase II enzymes. The oxidizing enzymes of phase I are now referred to as CYP genes (for cytochrome P450) and the number and variations of these genes is immense (Hukkanen et al. 2002; Ingelman-Sundberg et al. 2000). The phase II genes include those that code for enzymes that add glutathione, glucuronide or acetyl groups to the targeted (oxidized) xenobiotic agent, and thereby allow for their rapid elimination from the cell and ultimately the organism.

Reports during the past decade have suggested that certain alleles of these xenobiotic metabolizing
**Table 5.1 Differences between categories of cancer susceptibility genes**

<table>
<thead>
<tr>
<th>Category</th>
<th>Major genes</th>
<th>Susceptibility genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category I</td>
<td>Act on mechanistic pathway</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Somatic mutations</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Germline polymorphisms</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Penetrance</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Phenotype requires exposure</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Function (examples)</td>
<td>Biological processes of growth and regulation</td>
</tr>
</tbody>
</table>

In many cases, the presence of a variant of a gene that codes for an enzyme involved in xenobiotic metabolism, such as the metabolic enzymes CYP1A1, CYP1B1, CYP2A6, CYP2D6, CYP2E1, glutathione-S-transferases (GSTM1, GSTT1, GSTP1), myeloperoxidase (MPO), nitroquinoline oxide (NQO1), N-acetyltransferase (NAT1, NAT2) and epoxide hydrolase (EPHX) may be associated with many types of common human epithelial and other cancers of several organs (Hein 2006; Garte et al. 2000; London et al. 2000; Ramachandran et al. 1999; Schnakenberg et al. 2000; Park et al. 2000; Boissy et al. 2000; Sweeney et al. 2000; Wadelius et al. 1999; Wu et al. 2004). There have also been reports of their association with a wide variety of other diseases, especially those in which environmental risk factors play a role in aetiology (Paracchini et al. 2006; Gao et al. 2006; Lea et al. 2005; Okubo et al. 2003; Masetti et al. 2003; Hukkanen et al. 2001; Takeyabu et al. 2000). Because of the relatively high frequency of these allelic variants in the population (1-50%; Garte et al. 2001), the attributable risk for these genes could be quite high, even if their penetrance is low. In some cases effects were only observed in the presence of two or more risk alleles.

Another category of genes that has elicited great interest as low-penetrance susceptibility genes are those that code for DNA repair enzymes (Berwick and Vineis 2000; Goode et al. 2002). These genes, like the metabolic genes, are generally highly polymorphic in humans, and a number of variants of several of these genes have been found to be associated with higher risk for cancer. Gene–environmental interaction between DNA repair gene polymorphisms and specific exposures have also been studied (Hung et al. 2005).

**Table 5.2 Examples of cancer susceptibility genes**

<table>
<thead>
<tr>
<th>Category</th>
<th>Oncogenes</th>
<th>Tumour suppressor genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>c-myc</td>
<td>p53</td>
</tr>
<tr>
<td></td>
<td>H-ras</td>
<td>P16</td>
</tr>
<tr>
<td></td>
<td>c-abl</td>
<td>Rb</td>
</tr>
<tr>
<td></td>
<td>c-fos</td>
<td>VHL</td>
</tr>
<tr>
<td></td>
<td>c-jun</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>Metabolic genes</th>
<th>DNA repair genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 2</td>
<td>CYP1A1</td>
<td>XPG/ERCC5</td>
</tr>
<tr>
<td></td>
<td>CYP2D6</td>
<td>XP/ERCC2</td>
</tr>
<tr>
<td></td>
<td>CYP1B1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GSTM1</td>
<td>XPF/ERCC4</td>
</tr>
<tr>
<td></td>
<td>NQO1</td>
<td></td>
</tr>
</tbody>
</table>
There are many differences between the two classes of susceptibility genes (Caporaso and Goldstein 1995), in addition to their differences in penetrance (Table 5.1). Changes in the category 1 or high-penetrance genes are usually caused by some mutation in one or a few cells, and these mutations then lead to the onset of a disease state, such as malignant transformation of the affected cell. On the other hand, for the low-penetrance genes, somatic mutations are rarely if ever seen, and instead, genetic variation is found throughout the population at these loci. These polymorphic genes may be involved in risk as either homozygotes or heterozygotes. By convention, the most common allele is considered to be the wild-type, although on occasion, the labelling of certain alleles as wild-type and others as variants appears to be arbitrary, especially when the population frequency of so-called variant alleles is very high in the population.

The low-penetrance susceptibility genes are important in understanding the basis of both individual differences in susceptibility and the mechanisms of gene–environment interactions in cancer and other chronic diseases. Most of these genes are polymorphic in the human population (Garte et al. 2001) and a large number of studies have investigated the role of germline variants in metabolic and DNA repair gene polymorphisms in gene–environmental interactions to cause disease (Hemminki and and Shields 2002; Brennan 2002; Thier et al. 2003; Geisler and Olshan 2001; Ishibe and Kelsey 1997; Smith et al. 1994; Cascorbi et al. 1999; Strange et al. 1998; Hirvonen 1999; Autrup 2000; D’Errico et al. 1996). Metabolic susceptibility genes follow the form of ‘type 2’ gene–environment interaction (Ottman 1996; Khoury 1998), whereby the polymorphic genetic risk factor functions only in the presence of an environmental exposure (see below).

Genes that confer differences in susceptibility to toxic or carcinogenic agents in the environment can code for proteins with a great variety of function. For the Category 2 genes, such functions can include the uptake, metabolism, excretion and binding of toxic chemicals or their metabolites. A project devoted to the interplay of genetic susceptibility factors in the context of epidemiological investigations was initiated several years ago under the auspices of the US Centers for Disease Control (CDC) (Khoury and Dorman 1998). This project, the Human Genome Epidemiology (HuGE) project, sponsors review articles that cover all aspects of genetics in the epidemiology of many human diseases, with a focus on both genetic susceptibility, by summarizing results of association studies, and on gene–environment interactions. A more recent outgrowth of the HuGE network is the development of the HuGE Published Literature database, recently described (Lin et al. 2006).

A promise of genetic susceptibility markers is the potential to identify high-risk groups for certain diseases and exposures. This is especially true for individuals who might already be at high risk because of unusual exposures, diet, smoking behaviour or other genetic backgrounds. This does not mean that it is necessarily a good idea to screen the whole population for these genetic markers, since there are good reasons to believe that such an exercise would not be fruitful. For single gene polymorphisms, the penetrance is usually so low and the population frequency is so high that it is generally difficult to make any use of large-scale screening for prevention or public health. For example, if the GSTM1 variant, a gene deletion which is present in roughly half the Caucasian population, confers a significant but minor risk of bladder cancer of < 10%, what message should be given to the 50% of the population who have inherited this variant? To suggest that they are all at higher risk of developing a rare tumour such as bladder cancer is clearly ridiculous and probably counterproductive. On the other hand, if the group being screened were limited to workers exposed to aniline dyes, and the risk of bladder cancer were elevated three- to five-fold in GSTM1 variants among these workers, then it would make sense to screen the subset of these people based on their specific exposure history. Those with the susceptible genotype could then be offered more frequent and regular surveillance to allow for earlier detection of the cancer, thus saving lives.

Combinations of several susceptibility genetic variants have been shown to increase the risk associated with the susceptible genotypes, sometimes to the point where relative risks can reach those found with the major cancer or other disease susceptibility

5.4. STI

Studies in particular have shown that certain genes are related to prostate cancer (e.g. the ASH gene) and may increase the risk of developing this condition in men who are at high risk. The use of genetic susceptibility markers for the general population is not supported, however, because most of the genes involved are polymorphic in the human population.
5.4. STUDY DESIGNS

Studies of susceptibility genes in human disease, particularly cancer and heart disease, generally have employed a case–control study design as the most common approach to investigate the role of these genes in disease aetiology, progression and prognosis (Caporaso et al. 1999; Gelatti et al. 2005). Some advantages of the case–control design are relatively low cost, lower investment of time than, for example, a cohort study, and the ability to use stored or archival DNA tissue banks, including tissue blocks, frozen blood or urine, or other materials such as saliva. This allows for the collection of material from deceased cases, and can allow for studying changes with time and exposure conditions, if the archival material is extensive enough.

A variation of the case–control design that is used in genetic susceptibility studies is the case–case design (Hamajima et al. 1999; Gatto et al. 2004). In this type of study, cases with a polymorphism are compared to cases without it; the outcome variable could be survival or time to relapse or response to therapy. Studies of cases only can also be used to investigate gene–environment interactions, e.g. to determine whether such interaction is present in cases that have better or worse clinical courses.

Just as the case-only design has been used in studies of genetic susceptibility, so has the control-only design. The object of such studies is not to understand the role of the genetic variant in the disease process directly. Instead, by studying healthy populations, it is possible to explore the mechanistic effects of putative susceptibility genes on non-disease end-points or intermediate markers, such as DNA adducts, levels of metabolites, repair processes, etc., that could be related to one or more diseases. This approach, which has been called biochemical susceptibility analysis (Garte et al. 2005), has the advantage of providing information on genotype–phenotype correlations, and giving insights into the mechanisms by which some genetic variants function to increase susceptibility. An example of such a study that would provide important information would be the relative levels of nicotine metabolism as a function of genotype in smokers. It is possible that people with some genotypes might be more or less addicted to tobacco, depending on genotype, and therefore at different levels of risk for continuing smoking and development of any of the numerous diseases associated with smoking exposure. This approach is also particularly useful in studies of intermediate markers that are likely to be involved in a disease process. For example, individuals with different genotypes could be compared as a function of exposure, with respect to the level of DNA adducts or other forms of DNA damage, such as strand breaks, toxic metabolite levels, tissue injury, antibody response and any number of biological effects (Teixeira et al. 2002; Butkiewicz et al. 2000; Georgiadis et al. 2004; Rojas et al. 2000; Neri et al. 2005; Paracchini et al. 2005; Schoket et al. 2001; Palli et al. 2004; Whyatt et al. 2000; Merlo et al. 1998; Fustinoni et al. 2005). This approach not only gives information on the probable identification of susceptibility genotypes, but also provides potentially very useful information regarding the mechanism of action of specific genes and their variants. When the phenotypes of the variants are known, it might be possible to determine mechanistic pathways and refine our knowledge of toxic mechanisms. Until recently such detailed studies of biochemical and molecular
mechanisms of toxicity, involving specific gene products and genetic alterations, were only done in animal and cell-culture models. The use of genetic variability in the human population now make it possible to explore such mechanistic questions in human beings in vivo.

5.5. GENE–ENVIRONMENT INTERACTION

The interaction of environmental and genetic risk factors in the production of human disease is an important and well-studied area of molecular epidemiology. Many approaches have been taken in order to clarify these interactions and to try to understand the underlying basis of such interactions, as well as to further refine the identification of subpopulations who could be at higher risk. Small case–control studies are not usually useful for such investigations, since it is unlikely that sufficient power will be available to test hypotheses once stratification and division of a relatively small population (100–300 individuals) into subgroups is done. Larger case–control studies, as well as cohort and prospective studies involving populations in the thousands, can address issues of gene–environmental interactions, depending on the prevalence of the exposure as well as the frequency of the putative at-risk genotype (Matullo et al. 2006; Gormally et al. 2006). An approach that has proved extremely valuable in such studies is the use of very large networks of databases (Ioannidis et al. 2006) for pooled analyses, in which data from tens of thousands of cases and controls are collected from various laboratories, using the same or similar methodology for genotyping and exposure analysis. This approach is exemplified by the long-standing international project on Genetic Susceptibility to Environmental Carcinogenesis (GSEC) (Taioli 1999; Gaspari et al. 2001; Raimondi et al. 2005; Vineis et al. 2004b; Hung et al. 2003), which has resulted in a great many interesting results related to gene–environment interactions because of the unusually high power of the study. A more detailed discussion of this project is provided in Chapter 15.

Very few chronic diseases are caused solely by environmental or solely by genetic factors. Even in cases where one type of risk factor is clearly more important (such as smoking and lung cancer, or BRCA1 mutation and breast cancer), there is usually some effect of the other type of risk factor in determining individual susceptibility to the disease. As we know, not all smokers get lung cancer, and not all women with an inherited BRCA1 and BRCA2 mutation develop breast cancer. In the former case it is quite likely that low-penetrance metabolic and DNA repair genes play a role in determining relative susceptibility to disease occurrence, and in the latter case there are a number of hypotheses, that some lifestyle or exposure factors, as well as other genes (Pharoah et al. 2002; de Jong et al. 2002; Conway et al. 1995), influence the likelihood of carriers coming down with the disease. Since for the great majority of human chronic illnesses, including cancer (Lichtenstein et al. 2000; Mucci et al. 2001; Shields and Harris 2000), heart disease (Imumorin et al. 2005; Hegele 1992), diabetes (Wareham et al. 2002), lung diseases (Kleeberger and Peden 2005; Sengler et al. 2002; Caramori and Adcock 2006) and others (Brennan and Silman 1994; Caspi and Moffitt 2006; Liangos et al. 2005; Whitcomb 2006; Cummings and Kavlock 2004), both genetics and environmental factors are presumed to play some role, it is prudent to be interested in the possible ways that such factors could interact with each other (Kraft and Hunter 2005; Daly et al. 1994). In addition to the field of gene–environment interaction, which has become a major field of research recently, there are studies on gene–gene, and gene–gene–environment interactions as well as gene–hormone–environment interaction, etc. (Manuguerra et al. in press; Szolnoki and Melegh 2006; Taylor et al. 1998). Not all publications or studies that examine more than one gene or single nucleotide polymorphism (SNP) at a time, necessarily find evidence for gene–gene interaction or synergistic effects between different loci. A number of examples of gene–gene interactions, where various genetic variants combine to give strong associations with a large variety of disease and other phenotypic end-points, are shown in Table 5.3.

Gene–environment interaction is not a new idea in medicine. The great geneticist J. B. S. Haldane published a classic paper entitled 'The interaction of natural selection and the sub-type of indeterminate type of COPD. For example, observations on the interaction of the lung in med.
Table 5.3  Examples of gene–gene interaction in disease susceptibility

<table>
<thead>
<tr>
<th>Genes</th>
<th>Disease or end-point</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYPIA1 and GSTM1 and GSTT1</td>
<td>Lung cancer</td>
<td>Taioli et al. 2003</td>
</tr>
<tr>
<td>CYPIA1 and GSTM1 and GSTT1</td>
<td>Lung cancer</td>
<td>Vineis et al. 2004</td>
</tr>
<tr>
<td>GSTP1 and GSTM1 and GSTT1 and CYPIA1</td>
<td>DNA adducts</td>
<td>Teixeira et al. 2002</td>
</tr>
<tr>
<td>CYPIA1 and GSTM1</td>
<td>Lung cancer</td>
<td>Hung et al. 2003</td>
</tr>
<tr>
<td>GCR and ESR2</td>
<td>Osteoporosis</td>
<td>Xiong et al. 2006</td>
</tr>
<tr>
<td>XRCC1 and APE1</td>
<td>Cutaneous melanoma</td>
<td>Li et al. 2006</td>
</tr>
<tr>
<td>ALDH2 and ADH2</td>
<td>Colorectal cancer</td>
<td>Matsuo et al. 2006</td>
</tr>
<tr>
<td>MTHFR and GSTM1</td>
<td>Male infertility</td>
<td>Paracchini et al. 2006</td>
</tr>
<tr>
<td>FAS and FASL</td>
<td>Cervical carcinogenesis</td>
<td>Lai et al. 2005</td>
</tr>
<tr>
<td>GSTM1 and GSTT1 and GSTP1</td>
<td>Bladder cancer</td>
<td>Srivastava et al. 2005</td>
</tr>
<tr>
<td>CARD15 and TNFα promoter</td>
<td>Crohn’s disease</td>
<td>Linderson et al. 2005</td>
</tr>
<tr>
<td>Cyclin D1 and XPD</td>
<td>Aero-digestive tract cancer</td>
<td>Buch et al. 2005</td>
</tr>
<tr>
<td>PPARY and 2 ADRB3</td>
<td>Obesity</td>
<td>Ochoa et al. 2004</td>
</tr>
<tr>
<td>CYP2D6 and NAT2</td>
<td>Multiple chemical sensitivity</td>
<td>McKeown et al. 2004</td>
</tr>
<tr>
<td>Tyrosine phosphatase 1B and LEPR</td>
<td>Body mass index</td>
<td>Santaniemi et al. 2004</td>
</tr>
<tr>
<td>GSTM1 and matrix metalloproteinase 9</td>
<td>COPD</td>
<td>Yanchina et al. 2004</td>
</tr>
<tr>
<td>Cyclin D1 and thymidylate synthase</td>
<td>Childhood ALL</td>
<td>Costea et al. 2003</td>
</tr>
<tr>
<td>Prothrombin and factor XIII-A</td>
<td>Myocardial infarction</td>
<td>Butt et al. 2003</td>
</tr>
<tr>
<td>CYPIA1 and GSTM1</td>
<td>DNA adducts</td>
<td>Firozi et al. 2002</td>
</tr>
<tr>
<td>NQO1 and MPO and CYP2E1</td>
<td>Childhood ALL</td>
<td>Krajnovic et al. 2002</td>
</tr>
<tr>
<td>NAT2 and GSTM1</td>
<td>Adducts, lung cancer</td>
<td>Hou et al. 2001</td>
</tr>
<tr>
<td>NAT2 and GSTM1 and CYPIA1</td>
<td>Childhood ALL</td>
<td>Krajnovic et al. 2000</td>
</tr>
<tr>
<td>NAT2 and GSTM1</td>
<td>Bladder cancer</td>
<td>Schnakenberg et al. 2000</td>
</tr>
<tr>
<td>GSTM1 and GSTT1</td>
<td>Breast cancer</td>
<td>Park et al. 2000</td>
</tr>
<tr>
<td>GSTP1 and CYPIA1</td>
<td>DNA adducts</td>
<td>Whyatt et al. 2000</td>
</tr>
<tr>
<td>GSTM3 and GSTM1</td>
<td>Larynx cancer</td>
<td>Jourenko-Mironova et al. 1999</td>
</tr>
<tr>
<td>NAT1 and NAT2</td>
<td>Bladder cancer</td>
<td>Taylor et al. 1998</td>
</tr>
</tbody>
</table>

aFor details on gene and allele definitions, see the referenced publications.
bCOPD, chronic obstructive pulmonary disease; ALL, acute lymphoblastic leukaemia.

do concept of 'nature and nurture', published in 1946, on this topic (Haldane 1946). In later literature on the subject, Khoury and co-workers (Khoury and James 1993; Khoury and Wagener 1995) and Ottman (1995, 1990, 1996) described a number of types of gene–environment interactions, which differ from each other on the basis of the degree of independence of action of the two factors. For example, in some cases, disease causation is observed only when both risk factors are present; alternatively, one factor might act independently of the other, which can, however, exert a mediating influence. In one particular type of gene–environment interaction, termed ‘Type 2’, genetic risk factors function to exacerbate (or sometimes mollify) the toxic effects of an exposure (Garte et al. 1997; Taioli et al. 1998). The exposure by itself acts as a risk factor for the disease, even in the absence of the genetic factor. On the other hand, in the absence of exposure, simply being a carrier of the genetic variant that is considered to be the risk factor should have no effect on disease risk. This type of gene–environment interaction can be applied to the metabolic susceptibility genes, whose function is to modify the effective dose of an environmental exposure, increasing risk. Of course if the exposure is absent, then no increased risk should be seen. More details on the different types of gene–environment interaction is given in Box 5.1.
Box 5.1 Types of gene–environment interactions
Various forms of gene–environment interaction (GEI) have been applied to molecular epidemiological studies. Khoury and his co-workers have described six types of gene–environment interactions (Khoury et al. 1988, 1993, 1995; Khoury and James 1993; Khoury and Wagener 1995). In type 1, neither the environmental nor the genetic risk factor have any effect on disease (or other end-point) in the absence of the other. However, when both environmental and genetic risk factors are present, an interaction between them produces an effect. An example often given for type 1 GEI is that of phenylalanine exposure in the diet, and the phenylketonuria genotype. Type 2 GEI is defined as one in which the genetic variant has no effect on disease in the absence of the relevant environmental exposure, but the environmental risk factor by itself can affect risk, even in the absence of the genetic factor. This is the most important type of GEI for environmental carcinogenesis related to metabolic susceptibility genes. Type 3 GEI is the converse of the second, in that the genetic variant can produce an effect in the absence of environmental exposure, and the exposure by itself plays no role in disease etiology. This type of interaction may be important in human disease if a specific toxicant acts only on people with a particular genetic make-up. Type 4 GEI occurs when both the environmental exposure and the genetic factor carry some risk for disease, but the combination is interactive and/or synergistic. Cancers associated with DNA repair gene deficiencies, such as ataxia telangiectasia or xeroderma pigmentosum, are examples. Most category 1 cancer genes (c-myc, p53, etc.) belong to this type of GEI, since the gene mutations themselves produce increased risk which is exacerbated by exposure to environmental carcinogens. Types 5 and 6 GEI refer to cases in which the genetic risk factor is protective.

Ottman (1990, 1994, 1995) has described five similar types of GEI. In the first, the disease may be caused by either the genetic or the environmental agent, but the genotype increases the expression of the agent. The second and third are the same as Khoury’s. In the fourth type, both environmental and genetic risk factors must be present to cause the disease, equivalent to Khoury’s type 1. In the final model, both factors influence risk by themselves, but with interaction between them.

Both groups make the point that the term ‘interaction’ covers a variety of biological phenomena. The type of gene–environment interaction is as important as the fact that an interaction occurs. Further understanding of mechanistic and practical or clinical aspects of GEI depend on knowledge of which type of GEI is operative in any particular situation.

5.6. EXPOSURE DOSE EFFECTS IN GENE–ENVIRONMENT INTERACTIONS
There are a number of interesting theoretical and practical implications of the type 2 model of gene–environment interactions (Garte et al. 1997), one of which relates to the role of exposure dose. It has been found in many studies that some genetic risk variants seem to exert relatively more significant effects on disease or other end-point, when the interactive level of exposure is low. This phenomenon, which we have termed a low-exposure gene (LEG) effect (Taioli et al. 1998), is defined as the situation when the degree of interaction with a particular genetic variant decreases as a function of exposure. A number of examples of LEG effects have been reported for a variety of diseases and for a number of gene and environmental exposure combinations (Belogubova et al. 2004; Kiyohara et al. 2003; Alexandrie et al. 2004; McNamara et al. 2004; Ordovas et al. 2002; Wang et al. 2001). The observation of a LEG effect is not equivalent to an observation of a protective effect, since the relative risk of the exposure associated with the genetic variant is diminished as a function of increasing exposure dose. Thus, individuals with the higher-risk genetic variant will be at a higher relative risk in persons with a low exposure than in persons with a high exposure.

It has been suggested that the phenomenon of the inverse dose or LEG effect might be simply...
Box 5.2 Relationship of functional effects of polymorphisms to dose effects

The genetic variants (polymorphisms) of some genes code for enzymes with either a gain- or loss-of-function phenotype. Using classical Michaelis-Menten kinetics, it has been shown (Garte 2006) that the LEG effect can be predicted to always occur for any gain-of-function polymorphism that affects the $K_m$ of the enzymatic gene product. On the other hand, loss-of-function polymorphisms, such as deletions or loss of enzymatic activity, should always produce a high dose effect. These conclusions are based on a theoretical treatment, and have yet to be confirmed or refuted by experimental data.

due to a saturation phenomenon, so that for people with very high exposure, having a genetic risk factor that increases the effective dose is irrelevant, since saturation of the exposure effect has already occurred. The problem with this explanation is that the LEG effect has also been seen when the exposure levels to environmental risk factors are not high enough to be saturating. An alternative hypothesis is based on the biochemistry of the enzymes coded for by the metabolic susceptibility genes, which make up the majority of genetic risk factors that follow type 2 gene-environment interaction (Vineis et al. 2004; Garte 2006). Box 2 provides some further thoughts on this topic.

5.7. MUTATIONAL EFFECTS OF GENE-ENVIRONMENT INTERACTIONS

In addition to the type 2 gene-environment interactions that are the dominant form of such interactions for the low-penetrance metabolic susceptibility genes, there are many other kinds of such interactions that are well known. The best example is that of somatic mutations caused by the direct chemical interaction of a toxic agent with a regulatory or active site of a critical gene, such as an oncogene or tumour suppressor gene in the case of cancer. It has been shown that certain environmental carcinogens, such as tobacco smoke, UV radiation, aflatoxin and (TCE), produce specific patterns of such mutations in specific genes. In this case, the genes involved tend to be the category 1 high-penetrance pathway-related genes. A good example of such genes is $p53$, an important tumour suppressor gene, which has been found to be involved in a large number of cancer types and is frequently mutated in human cancer cases (Hernandez-Boussard et al. 1998; Olivier et al. 2004). A database of $p53$ mutations in human tumours was originated and is maintained at the International Agency for Research in Cancer (IARC) in Lyon, France, and the website for this database (www-p53.iarc.fr) is very informative concerning the mutational spectra of mutations in this gene with respect to interactions with mutagenic chemicals and other environmental carcinogens. For this type of gene-environment interaction, unlike the type 2 described above, environmental exposure is not required for the gene to have a risk effect. Again, taking the example of $p53$, inherited mutations of this gene, which occur in the rare Li–Fraumeni syndrome, cause cancer in the absence of any environmental exposure. In this interaction, the effect of the exposure is to produce mutations, so that if mutations are present due to other causes, then exposure is no longer relevant.

5.8. CONCLUSIONS

In conclusion, individual susceptibility and gene-environment interaction are closely related areas of intense research into the origins of a number of chronic disease, with a good deal of emphasis placed on environmental carcinogenesis. The study of individual variability due to genetic differences is of critical importance in all aspects of human health care, from the avoidance of adverse drug effects, to protection from environmental exposure to toxic agents and regulations designed to protect human health. With the completion of the Human Genome Project and current progress in haplotype mapping, it is becoming possible to identify and study very large numbers of potential genetic risk factors and variants that could play a role in determining genetic susceptibility to disease. Successful efforts in this area will require careful planning and study designs that take advantage of, and are not confounded by, the vast amounts of data that can now be available using modern technologies related to whole-genome scanning. Of equal importance in
this field are the myriad potential problems associated with ethical and social implications of genetic susceptibility testing, which are covered in other parts of this volume.

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