disease mechanism. One profound example actually arises from the recognition of disease associations that are not genetic. Rather, our research is now pointing us to the companion study of *epigenetics*. This can be defined as the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence.⁶ Epigenetic changes are almost certainly responsible for heritable adverse consequences of DES, and recent research points to likely epigenetic roles for the induction of the toxic consequences of herbicide exposure,^{7,8} and asthma and respiratory disease (which are obviously exposure-associated).⁹ Hence, perhaps one of the great contributions of genetics and genomics to occupational health is not in the elucidation of gene-environment interactions and disease associations. Rather, one of the real values of this research is its failure to become a part of practice and, thereby, has opened other complementary paths of research. So it is—the simple becomes complex.

As we move ahead we can be assured that new paradigms will emerge to supplant the old ones, pushing us further towards having the tools we require to more completely understand occupational disease. Genetics is a piece of the puzzle, but only a piece. We have begun to realise this and, importantly, we may soon be ready to incorporate what we have learned and move forward once again to new frontiers. The practice of occupational medicine is ready to incorporate novel approaches and information, but only when it is rigorously tested, medically reliable and ultimately adaptable into our time-tested framework for protecting worker health.

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Genetics

Genetics and occupational health and safety

Harri Vainio

Commentary on the editorial by Schulte (see page 717)

A recent study in China concluded that the incidences of neurasthenia and of ultrasonographic abnormalities in the livers of vinyl chloride-exposed workers increased with increasing cumulative exposure dose.¹ This is an important finding, especially as the exposure to vinyl chloride studied was below the current Chinese permissible occupational limit. The same study also reported that the *CYP2E1 c1c2/c2c2* genotype was significantly associated with liver damage (OR 3.3).

How should occupational health and safety professionals use these data? A further decrease in the occupational health standard for vinyl chloride in China should be the immediate reply. How about the data on polymorphic *CYP2E1*?

We are on the threshold of a new revolution in understanding the interaction of genes with the environment. The relative roles of heritable and environmental causes in occupational hazards are an important scientific issue, with

many practical consequences. Traditional geneticists have emphasised genes, while epidemiologists have argued for the environment. The literature on disease causation is full of overstatements, but recent data from twin and family studies offer more scientifically-based estimates of the apportionment of disease causation. With the emergence of the versatile tool of single nucleotide polymorphisms, studies on “gene-environment interactions” have become popular. The studies have produced a number of reports with no or only modest impacts of gene-environment interaction on environmentally-induced disease.² Furthermore, there are many embedded controversial issues. Mass reporting of results has occurred, with little consideration of the functionality of single nucleotide polymorphisms or the tissue of expression of the relevant genes in subgroups with little biological rationale. It is ironic that the traditional roles of epidemiologists and geneticists appear to have been reversed:

the proponents of gene-environment interactions seem to be stressing the overwhelming importance of genetic factors acting in concert with environmental factors, while geneticists are raising concern.³

The setting of permissible occupational exposure limits is a practical example of the importance of understanding the relative contributions of the environment and genes. The role of polymorphic genes in occupational disease risks has been the subject of extensive research for several decades. Some polymorphic genes do not present a risk in the absence of a given exposure but do so when the exposure occurs.

As Schulte points out in his editorial, “it remains unclear to what extent identifying susceptibles can be applied in occupational safety and health”.⁴ Unlike most occupational exposures, which can be reduced or eliminated if proven to cause harm, inherited gene variants cannot be changed and can be passed on to subsequent generations. Given the number of metabolising enzymes and the wide variation in their expression, it would be too simplistic to propose that one gene at a time be examined in relation to disease risk. Therefore, methods and techniques have been developed for examining whole pathways, containing tens to hundreds of genes, and their expression patterns in relation to disease risk. In a shifting strategy, researchers are using whole-genome scanning to search for disease genes. This technique casts a wide net over the genome, allowing researchers to

evaluate thousands of genes simultaneously without prior assumptions about the underlying mechanisms. Although this whole-genome scanning might reveal new disease pathways, it has key limitations, such as the exclusion of the important post-translational epigenetic phenomena. Until these powerful new techniques have shown their full potential, it will be difficult to use genetic characteristics or risks in subgroups when setting exposure limits.

Successful disease prevention programmes at the worksite should ideally be based on an understanding of the natural history of the disease or injury. Many of the factors in gene-environment interactions are modifiable, and these would provide a good starting point for primary prevention in the occupational setting. The number of genes that contribute to susceptibility to disease is likely to be large, and the effects of each gene on a disease will be weak. For example, if a dozen or more genes contribute to myocardial infarct or to lung cancer, attempts to identify susceptible occupational subgroups for intervention would be too complex to be of practical value. Thus, in the case of these and many other chronic diseases, it is likely that more

people would benefit from changes in their work conditions or other modifiable factors than from knowledge about their genes. For complex diseases such as cancer, for which there are a number of underlying critical genes, the likelihood that gene-environment studies will provide answers with practical applicability is decreasing.⁵

If scientists conduct a comprehensive search for the genetic basis of every health outcome and ignore occupational exposures and other work-related factors and attributable risks, we are likely to miss opportunities to prevent disease and injury. Over-optimistic expectations about the ability of genomics to address chronic diseases (stemming partly from a lack of understanding of the complexity of disease causation and partly from a tendency by some scientists to overemphasise the immediate medical significance of their work to the media and granting agencies) emerged in the wake of the Human Genome Project. While occupational health and safety professionals should keep abreast of this rapidly advancing field, use of genomics in the surveillance, monitoring or screening of workers is not practicable at present. The obstacles range from inadequacies in the

scientific database to ethical, legal and social implications. This view is in line with the considerations of the European Group on Ethics in Science and New Technologies.⁶

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