Genomics, epidemiology, and common complex diseases: let’s not throw out the baby with the bathwater!

From MUIN J KHOURY and MARTA GWINN

As public health professionals working to translate advances of genome-based research into population health benefits,1,2 we found the article by Buchanan et al.3 and associated commentaries4–10 fascinating and informative. We too are sceptical of ‘genohype’ and we are critical of the specious ‘people are not born with complex, exogenous experience rather than endogenous genetic susceptibility’.11 Obviously, ‘people are not born with complex, late-onset disease’; on the other hand, people who continue to promote a healthy diet, adequate physical activity, and smoking cessation, it makes no sense to assert that ‘the preponderance of cases of complex chronic disease are owing to exogenous experience rather than endogenous genetic susceptibility’.10

Although we agree that public health programmes should continue to promote a healthy diet, adequate physical activity, and smoking cessation, it makes no sense to assert that ‘the preponderance of cases of complex chronic disease are owing to exogenous experience rather than endogenous genetic susceptibility’.10

(Despite vigorous public health education campaigns) do not always develop heart disease. Clearly, there is much more to learn about gene–environment interactions underlying these diseases and to use this knowledge in intervention efforts.

As we have argued elsewhere, 14 the public health significance of genomic research on common complex diseases with strong environmental determinants lies not in finding new genetic ‘causes’ of these diseases but in helping us to better recognize and modify interacting environmental risk factors. Each investigation that increases our understanding of gene–environment interaction, etiological heterogeneity, pathogenesis, and natural history of common diseases adds to a knowledge base for estimating risks and guiding interventions to improve population health. Epidemiology is unique in offering a set of evolving tools and methods that are explicitly designed to observe disease variation in populations and reveal the joint effects of individual biology and behaviour in the context of social and physical environment. In an already complex world, human genetic variation is another dimension that is just now opening for exploration.15 For epidemiologists to retreat now would be to abandon the field just when they are needed most.

The concerns enumerated by Buchanan et al.3—including phenotypic and genotypic heterogeneity, the interplay between individual and ecological variables, the dynamic nature of environmental risk, chance, and bias—are all important and well-recognized challenges in epidemiological research. Nevertheless, we take issue with their assessment that ‘the lack of an obvious alternative does not justify continuing to invest in what does not work’. Indeed, there is no obvious alternative to epidemiology for translating genetic information from basic science to population health benefits but the assertion that it

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From ANNE BUCHANAN1, KENNETH M WEISS1,* and STEPHANIE M FULLERTON2

Drs Khoury and Gwinn1 write in support of the future of genetic epidemiology. They express disappointment with the conclusions of our paper, but they present no new arguments nor do they refute our specific points. Instead, they simply urge that we must stay the course because genetic epidemiology holds such promise, especially now that the Human Genome Project (HGP) is complete. We do not question the potential that genetic knowledge has for making important contributions to medicine and public health nor was our paper in any way a ‘summary dismissal of genetic epidemiology’. However, we are clearly much less sanguine than they about the field’s future, until that future includes conceptual rethinking.

Contrary to the impression they give, genetics is by no means a formal theory of exposure that is much more powerful than environmental epidemiology (the theory of Mendelian inheritance). To express a belief that we could now make inference by current conceptual methodologies are misleading. The epistemological problems of making inference by current conceptual methodologies are greatly more complicated than they about the field’s future, until that future includes conceptual rethinking.

Genomics research, and that, by implication, having the complete genome sequence will obviate the many basic issues we discussed in our paper. Powerful computing and molecular technologies have provided greater specificity, and the potential for new kinds of intervention, once the role of genes in a problem is understood, is clearly greater than before. But the basic causal nature of complex traits has been known for the better part of a century, since work of Sewall Wright, RA Fisher, and others. Most of the long-standing core concepts in genetics are still valid. The HGP has not occasioned a conceptual ‘paradigm’ shift that will somehow permit a rosy future if we but carry on as usual, as Khoury and Gwinn seem to imply, a view that essentially rests on faith not on evidence or a new theory of disease.

Likewise, environmental epidemiology has been a major and well-supported component of the health industry roughly since World War II, when the (supposed) conquest of infectious disease turned attention to the causation of chronic late-onset disease. There has been no fundamental shift in epidemiological thinking that would occasion new optimism about its role in interpreting genetic data. The epistemological problems of making inference by current conceptual methodologies are widely shared and long-standing, a fact that was a basic motivation for our paper.

Indeed, even with all the advances of the HGP, and with a formal theory of exposure that is much more powerful than environmental epidemiology (the theory of Mendelian

References


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