Commentary: The Human Genome: philosopher’s stone or magic wand?

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The commentary by Buchanan et al. in this issue provides a candid assessment of our progress in the search for genetic determinants of complex diseases. Geneticists, physicians, and especially epidemiologists should take note. In the authors’ evaluation, human genome research has been disappointing, yielding few results with a positive impact on public health. Are the authors correct in their assessment? We need to critically evaluate the points raised by Buchanan et al. and consider the practical suggestions that they offer.

One useful framework for exploring the themes presented by Buchanan et al. would be to identify two separate goals (among many others) for research in human genomics. First, there is the search for genetic causes of complex diseases. This immense effort serves as the flagship project for discovery science, an exciting and ever-expanding research programme ‘in which one generates large resources of information on biologic molecules in aggregate without necessarily knowing in advance which pieces of information and which correlations will prove most important’ [p. 34 in Ref. (2)]. Epidemiologists have embraced the search for genetic risk factors and are devoting enormous time, effort, and money to the enterprise. Detailed haplotype structures and tag SNPs now make it possible for epidemiologists to conduct genome-wide association studies using DNA collected from persons with and without disease. Although many researchers recommend caution, there is no doubt that the epidemiology community is moving ‘full speed ahead’ in a comprehensive search for genetic risk factors in human populations. A second, closely related goal for human genome research is to develop individual-level applications for genomics and related technologies. Clinicians wish to use genomic information to predict the future occurrence of disease for patients and their families, design interventions, and tailor therapeutic strategies to individual patients. Proponents of this approach hold that genomics, proteomics, and related ‘omics’ technologies offer the promise of early detection of disease and development of more effective therapies, and will usher in an era of ‘personalized medicine’.

In the sections that follow, the authors’ comments are evaluated in relation to the two afore-mentioned goals: identifying risk factors in populations as part of the broad mission of public health and developing applications for individual patients in clinical settings. Buchanan et al. state that our search for genetic causes of complex diseases is a ‘vain quest for the philosopher’s stone’, and our time would be better spent promoting changes in diet and physical activity. In my view, we should continue the search for genetic risk factors because it has yielded some reproducible, positive findings. But at the same time, we should apply what we already know about the causes of disease, and in order to improve our study designs, we should incorporate the practical suggestions offered by the authors. It is with regard to the second goal that the critical comments by Buchanan et al. seem to be the most relevant. The push to develop ‘personalized medicine’ has all the earmarks of an attempt ‘to turn base metals into gold’ and it is here that we need to focus a more critical eye.

Discovering genetic risk factors in populations

Buchanan et al. refer to the ‘alchemist’s vain quest for the philosopher’s stone . . . a substance that would turn base metals into gold’ [p. * in Ref. (1)]. The authors imply that the alchemical quest was conducted for financial gain only, and ‘proper advice . . . would have been to stop that approach and seek riches elsewhere’ [p. * in Ref. (1)]. In fact, the quest for the *lapis philosophorum* was much more profound. The alchemist’s quest was philosophical as well as technological, and involved intensive discussions about meaning and values. Discovery science does share some features with the alchemical quest: there is certainly a large measure of enthusiasm, devotion, and commitment to developing new technologies. Often missing is the philosophical component, asking the important questions before trying to find the answer. In an earlier paper, one of the authors states, ‘It is at least fair to ask whether scaling up current genetic approaches . . . would be the wisest investment when a major justification is that nothing else has worked so far’ [p. 155 in Ref. (6)]. We are reminded in the same article that ‘SNPs . . . cannot rescue a question not properly posed’ [p. 154 in Ref. (6)]. Likewise, as stated in a famous alchemical text, ‘All error in the art arises because men do not begin with the proper substance’ [p. 127 in Ref. (7)].

What should we anticipate at the outset when exploring genetic causes for human disease? First, as emphasized by Buchanan et al., we must expect that common alleles will exhibit weak associations with disease. As pointed out by Wang et al., ‘most irrefutable disease-susceptibility variants that have been identified so far—mainly from functional-candidate association studies—have allelic odds ratios that are in the order
of 1.1–1.5…Thus, it would be unwise to undertake genome-wide association studies that do not have sufficient power to detect…effects of this magnitude’ [p. 112 in Ref. (4)]. The weak effects of common alleles are a product of physiology and selection, with the result that common alleles are neither necessary nor sufficient for disease. Most genetic risk factors may simply be ‘contributory’, and operate in multiple causal pathways to disease, as pointed out by Buchanan et al.1 Second, chronic diseases are often the result of ‘decades-long processes’, multi-stage pathways that develop over time and include many contributory factors. Thus, two immediate threats to discovering genetic risk factors for human disease are aetiologic heterogeneity and a protracted course for disease causation. An insightful metaphor developed by the authors is particularly useful in addressing these issues.

As depicted in Figure 1 of their paper,1 the authors present disease causation as a ‘many-to-many causal fabric’ in the shape of an hourglass. The neck of the hourglass represents precursor states ‘that may be arrived at via many alternative genetic and/or environmental paths’ [p. * in Ref. (1)]. The authors rightly point out that evaluation of genetic determinants of precursor states is a worthwhile goal and is more likely to yield stronger, more reproducible associations than relying upon more distal disease end points. As stated by Morrison in the context of cancer, ‘The time required for an exposure to result in a precursor lesion may be much less than that necessary for the ultimate development of a cancer. As a result, the relationship between such a factor and a precursor lesion might be much easier to evaluate than the association between the same factor and cancer’ [p. 714 in Ref. (8)]. Morrison also points out that the mathematical attenuation of effects across stages of a multi-step pathway often makes it impossible to detect associations for more distal disease end points. Recent success in identifying genetic determinants of HDL cholesterol levels9 is an example of the gains to be made by focusing on intermediate end points. The hourglass metaphor also helps to address the issue of aetiologic heterogeneity. By focusing on more narrowly-defined phenotypes, the search for risk factors is pared down to exposures that are most relevant to causation. As stated by Weiss and Lif: ‘Our ability to detect an exposure that is a component of one causal pathway to disease is diminished by the presence of other causal pathways in which the exposure plays no role’ [p. 14 in Ref. (10)]. Recent studies of age-related macular degeneration used narrowly-defined phenotypes to yield reproducible results across three separate genome-wide association studies.11–14

Cancer researchers have begun to address the issue of disease heterogeneity using expression profiling and tissue microarrays.15–16 The most recent effort to identify sources of tumour heterogeneity is the Cancer Genome Project (CGP), another example of discovery science. Researchers are using the human genome sequence to catalogue somatically acquired DNA sequence variations in a variety of human cancers (http://www.sanger.ac.uk/genetics/CGP). The approach has met with some success. For example, Futreal et al.,17 recently showed that the genes most commonly altered in human cancer encode protein kinases and proteins involved in DNA binding and transcriptional regulation. Information from CGP could yield greater understanding of pathogenesis and may provide clues to cancer causation. Cancer epidemiologists have yet to fully incorporate knowledge of disease subtypes and mechanisms for causation into the search for new risk factors. The approach suggested by Buchanan et al.,1 for addressing phenotypic heterogeneity—incorporating more narrowly defined phenotypes and precursor states—could yield important information concerning inherited genetic as well as environmental risk factors for cancer and other chronic diseases.

Developing clinical applications for individual patients

A second goal for genomics and related sciences is to develop specialized applications for patients in clinical settings. The human genome is invoked as a sort of ‘Magic Wand’, a tool that identifies the underlying cause of illness (one’s genes), determines what diseases are on the horizon, and summons up an array of effective therapies tailored to the individual patient.18 One is reminded of the television and movie series, Star Trek, in which the ship physician waves a scanner over ailing crew members to diagnose and treat illness. Although ‘personalized medicine’ may open the door to more effective therapies, especially for cancer patients, the benefits are less clear in the areas of individualized risk assessment. Predicting disease occurrence many years in the future for persons who appear outwardly healthy is fraught with difficulty. As the authors point out, making inferences about individuals based upon group-level data is ‘a well-known source of error in epidemiology’[p. * in Ref. (1)]. Here, the analogy of trying to turn ‘base metals into gold’ appears more apt. Risk factors are identified for populations, and population-level associations often have limited discriminatory power at the individual level.19 We can anticipate that the discriminatory power of common genetic risk factors will be quite low owing to the previously described problems of weak associations, aetiologic heterogeneity, and a protracted time course for human disease onset. Once again, the hourglass metaphor is useful: ‘Why is individual risk essentially impossible to predict? The reasons have to do with the fact that, because they are generally due to both endogenous genetic and exogenous environmental components, complex diseases represent a many-to-many causal universe’ [p. * in Ref. (1)]. Translating group-level results to individual patients is also a problem when developing screening tests, as shown by the recent controversy surrounding the use of proteomic patterns to screen for ovarian cancer.20–23 Here, the issues include use of appropriate statistics, sampling, publication bias, and the potential ‘gold’ of commercial profit.

Where do we go from here?

As a research community, we would appear to be on firmer ground in the search for genetic causes of complex diseases in populations (the ‘philosopher’s stone’) than we are when attempting to use genomics to predict disease occurrence in individual patients (the ‘magic wand’). However, as Buchanan et al.1 suggest, the ‘secret’ to securing the health of populations may ultimately lie in more ‘ordinary’ things: modification of behaviour, preventing environmental degradation, and reducing disparities in access to treatment. One of the principal lessons
of the alchemical quest was that the answer was often present all along, but had gone unnoticed. As stated by Jung, ‘Simple things hold the secret, not complicated ones’. The authors quite rightly point out the necessity of applying what we already know about the causes of disease: for example, addressing the rise in obesity in developed countries, and the scourge of AIDS and other infectious diseases in the developing world. In a recent commentary in the Lancet, the editors forcefully state that to ignore such problems and their obvious solutions would be ‘catastrophic’ and ask, ‘Where are the zealous physicians and public health advocates of the 19th and early 20th centuries? Public health has become complacent. It is failing’ [p. 745 in Ref. (25)]. One might also ask, where are the devoted scientists of the Middle Ages, for example, the astute physician–philosopher (and alchemist) Paracelsus? We already know about the causes of disease: for example, environmental, social, behavioural, and socioeconomic risk factors for disease. The enduring capacity for imagination, insight, and scientific inspiration is one of the most important forces driving progress in human health. However, like the alchemists of old, we need to do two things: we must foster enthusiasm, creative energy, and devotion to discovery, but we must also commit ourselves to critical discussion, collaboration, and applying existing knowledge. A newly formed network of investigators in human genome epidemiology represents an important collaborative effort to share data and resources. But as Buchanan et al. 1 remind us, we need to do more. We must constantly reappraise what we do, think critically about the methods we use, and offer research paradigms that can lead us towards genuine improvements in public health.

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References