Horses for courses: The need for pragmatism and realism as well as balance and caution. A commentary on Angel

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One of the major impediments to translating scientific advances into benefits for human populations is the different, sometimes conflicting, explanatory models and terminologies used in different fields of endeavour and the fundamental differences in the goals and the values placed upon different goals. For example, the article I will be commenting on, “Agency versus Structure: Genetics, Group Membership, and a New Twist on an Old Debate” (Angel, 2011) is framed in sociology-speak in terms of “agency” versus “structure”. Most non-sociological readers will not be familiar with these terms (and the definitions are, perhaps, not entirely simple and straightforward (Scott & Marshall 2009)) and the author acknowledges that there is dispute about the usefulness of this distinction (Angel, 2011).

The current commentary article is written from my own perspective as a clinical psychiatrist. I have been involved in molecular genetic investigation of major psychiatric disorders for the last 20 years. I regard genetics as a scientific tool capable of improving understanding of the causes and triggers of illness. Medical practitioners have to be pragmatists (Craddock, Kerr, & Thapar, 2010). Medical training and practice requires willingness to adopt different models in different situations with the single over-riding aim of trying to get the best possible outcome for the patient seeking help (Craddock et al., 2008; Craddock et al., 2010). Angel’s (2011) article is an interesting and stimulating article that makes several important points. Many of the key views expressed are shared by myself and, I expect, by most clinical and non-clinical scientists involved in molecular genetic research on human diseases and normal traits. For example, the succinct statements in the abstract are excellent summaries of the state of genetic research and potential opportunities as well as the need to address important ethical and social issues and to be realistic about the often very limited degree of correlation of particular genetic and environmental variations with specific behavioural and social outcomes. It is, of course, important to remember that the caveats and cautions about over-interpreting the “causality” of genetic variation apply equally to the many important non-genetic (environmental, social...) variables that contribute to variation in human traits, including illnesses.

An issue of terminology that is worthy of consideration is the validity and usefulness of the supposed distinction between “biological” and “social” (and the same arguments extend also to “psychological”). If social theory relates to interactions amongst groups of humans (or other organisms) then, at some level, this can surely be thought of as an important and specialized branch of the broad field of biology — in much the same way that chemistry can be thought of as a specialized branch of physics (Craddock et al., 2010). If this is accepted, then it may be more helpful to avoid setting up simplistic distinctions that can be a barrier to discourse and understanding and move towards accepting that there is an inter-twined relationship between the ways different factors influence human traits. Some will be best understood using basic (perhaps molecular) biological approaches and models; others will be best understood by thinking about the properties of social groups; some, perhaps many, will ultimately be amenable to some...
degree of useful understanding at multiple levels. Thus, the traditional distinction between “biological” and “social” (and “psychological”) is likely to become less useful as knowledge accumulates and it may be helpful to start thinking more broadly as soon as possible. Thinking in silos is a barrier to progress.

Angel (2011) rightly acknowledges the fundamental importance of both genes and environment — this is surely the correct starting point for sensible debate. The earlier polarized, often heated arguments about “nature” or “nurture” are completely outdated, naive and unhelpful. Undoubtedly, all human behaviour is the product of the genetic inheritance of an individual, expressed in the context of the environmental variables to which the individual has been exposed at all stages from conception, through foetal life, childhood, adolescence and adulthood. Furthermore, both theoretical considerations as well as the developing research evidence support the proposition that there will be limitations on the extent to which complex behaviours and social outcomes are correlated with (and, thus, predictable from) any individual specific genetic variant (Cradock & Sklar, 2009; Khoury, Beaty, & Cohen, 1993). We can expect a spectrum of genetic correlations for behaviours: some will be completely unpredictable, but others may be highly predictable. We need to embrace this truth that there will be no single, simple model. Many readers will be aware that a relatively short length of DNA (a few hundred base pairs) at one particular gene can be a crucial determinant of whether a vole (a small rodent) is monogamous or promiscuous. The species with one variant of the sequence displays lifelong monogamous mating/pairing behaviours whereas a species without this variant is polygamous (Young, Nilsen, Waymire, MacGregor, & Insel, 1999).

Moreover, it has been shown that changing the sequence experimentally can alter the mating/pairing pattern. This is a level of evidence that is difficult to achieve in humans, for obvious ethical reasons. Moreover, the gene variant mentioned is but one part of a complex biological system that influences the mating/pairing behaviours. However, it demonstrates that even complex behaviour patterns may, under some circumstances, be predictable from information about a surprisingly restricted piece of the human genome. Thus, whilst we must be cautious, realistic and humble about the predictive utility of genetic information for complex traits including behaviours, we need to embrace the fact that sometimes it may be possible to make strong predictions — and in a subset of such cases the predictions may be useful. An example relevant to humans is the greatly increased risk of developing psychosis in adult individuals with a deletion of part of chromosome 22, causing so-called “Velo-cardiofacial syndrome” (Murphy, Jones, & Owen, 1999). Adults with this chromosome deletion have a 25% risk of developing a severe psychotic illness (compared with about 1% in the general population). Being able to predict this high risk allows the possibility of targeted reduction of any other known person-specific risk factors and monitoring mental state so that appropriate social, psychological and medical treatments can be offered as early as possible if illness develops.

Whilst Angel's (2011) article is generally factually accurate, there are two important statements by the authors that are incorrect and likely to mislead the reader. The first of these relates to the basic principles of screening tests in clinical medicine and public health: “It is doubtful that one would evolve group-specific screening procedures” (Angel, 2011). In fact, this is exactly what is usually desired for screening tests (Farmer & Lawson, 2004; Khoury et al., 1993). Tests are more effective when screening is undertaken in a high-risk group. In such a group, the test is potentially more useful because there is a favourable ratio of true positives to false positives. In a low risk population, the ratio of true positives to false positives will always be much lower and the overall benefits of screening will be much lower. Consider for example, breast cancer screening. In the UK this is used for women above a certain age because that group has a high risk of developing breast cancer. Young women have much lower risk, as do men of all ages. These latter groups are not usually screened. This is an example of selecting on the basis of genetics (carrying two X chromosomes) and age. At the end of the article, the authors make the (incorrect) point (Angel, 2011): “If someone identifies him or herself as a member of a social group with high rates of diabetes a physician would no doubt test glucose levels and look for other markers of the disease. But the doctor should do that anyway regardless of the patient’s group membership.” Although this sounds plausible to those without knowledge of the properties of diagnostic tests, it is incorrect. All tests have some non-zero probability of being wrong and giving a “positive” result in a person who actually does not have illness — this is a “false positive”. (Of course, there is also a finite risk of false negatives but I will not discuss that here). Unselected application of testing for (say) diabetes in situations where the risk of the illness is very low subjects the patient to a high probability that a “positive” test is actually a false positive and that they will then be given un-needed interventions. It is, therefore, good medical practice to minimize the number of tests that are not based on an increased suspicion of clinical risk. It must be emphasized that as we understand more about genetic susceptibility there will be increasing opportunities for clinically and practically useful screening/testing. It can be further expected that we will learn more about the particular situations and patient/population groups in which the benefits of such tests will outweigh potential disadvantages.

The second factually incorrect statement is: “We have decoded the entire human genome…” (Angel, 2011). In fact, what has been achieved is that (almost) the entire human genome has been sequenced. This means we know the usual (“consensus”) order of nucleotide base pairs in the DNA comprising the 23 human chromosomes. However, there is an enormous amount of work still required to catalogue the extent of variation of the usual sequence (including systematic differences between population groups) and make biological sense out of knowledge of the usual sequence and its variants. In other words “decoding” or annotating the human genome will take some decades to come. Only then will we have a clear idea of the extent to which genetic variation can predict complex biological processes, including social behaviours and outcomes — and this includes the extent to which systematic genetic differences between population groups might influence these processes, behaviours and outcomes.

It is understandable that the authors make the point that “How genetics can inform social policy remains unclear” (Angel, 2011). It is certainly right to be cautious about this. However, genetics and biology may be helpful, in some situations, in providing a context and setting some constraints for the development of effective social policy. In other words, social policy will need to be aware of findings in genetics. It seems technically unlikely - and morally undesirable - that it would be driven by genetic findings.

In summary, there is much in this article that is useful and thought provoking. There are undoubtedly limitations on the extent to which genetic knowledge can predict complex social behaviours. As with all scientific developments there are important ethical and practical issues that need to be considered to prevent the misuse of genetic knowledge. Genetics offers great potential for improving human health — particularly mental health - over the coming decades (Cradock & Owen, 2010 Feb; Craddock, Kendler et al., 2009). Much of this will relate to better understanding of the biological mechanisms involved in illness and the way in which genetic variation and environmental variation combine to affect outcomes (Cradock, O'Donovan, & Owen, 2009 May). Some benefits will relate to predictive testing and some of this will
involves targeting particular “high risk” groups. Life, illness and
behaviour are inherently messy and not easily accommodated
within simple one-size-fits-all models. We need to let the data tell
their story. As Angel points out, ultimately particular approaches or
tests will stand or fall according to their practical utility in
benefiting individuals and the wider population. That is how it
should be.

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