Beyond susceptibility

Behavioural genetics can advance our understanding of psychiatric disorders, but might not meet the expectations for new cures

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Understanding how genes influence behaviour is a pressing question in biology that fosters vivid interest and inevitable controversy. Perhaps the thorniest challenge for behavioural geneticists in the past three decades has been the gradual acceptance by the public of the power of genetics to explain human biology, including the ways in which we think and act. This, in turn, has created expectations that genetic research will not only help to diagnose psychological disorders and disease, but also point to new therapeutic approaches. Here, we discuss the validity of behavioural genetics and its capacity to advance our understanding of behaviour, especially with regard to psychiatric disorders, although we also highlight its limitations in meeting expectations for new diagnostics and cures.

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The conceptual framework and the technical tools used to study behaviour have undergone considerable changes, especially in the past 50 years. For a long time, quantitative behavioural genetics tried to dissect genetic and environmental contributions to individual differences in behavioural traits and disorders. In the 1980s and 1990s, advances in molecular genetics drastically simplified the search for the mechanisms of

behaviour by examining the effects of specific gene variations within the larger genetic pool. The combination of association studies, in which a known genetic variant is statistically linked to a phenotype in a heterogeneous population sample, and linkage studies, in which chromosome markers spaced along the genome are statistically associated with a phenotype, was a highly successful strategy to link genetic variation causally with behavioural phenotypes.

The enthusiasm for this reductive approach triggered the rise of what has been called 'neurogenetic determinism', which, driven in part by a fundamentalist ultra-Darwinism, seeks to explain every aspect of human conduct and mental state in evolutionary terms (Rose, 1995). This reached a peak with the completion of the Human Genome Project in 2000, when scientists claimed that the identity or essence of each individual resides in his or her genome (Kay, 2000; Keller, 2000). This was followed by a long list of gene-association

studies that linked single nucleotide polymorphisms (SNPs) with features of human conduct as diverse as sexual orientation, alcoholism and risk-taking. In most cases, such claims were subsequently retracted, criticized or found to be nonreplicable.

At the same time, association and linkage studies of mental disorders accompanied by overt neurophysiological defects, such as Huntington disease or Tay-Sachs disease, have been extraordinarily successful. However, when considering behavioural traits and mental disorders without consistent neurological findings, it has been much more difficult—if not impossible—to identify specific genetic risk factors (Kendler, 2005). Furthermore, it is clear that each gene can cause several phenotypes and that each phenotype is caused by several genes, which makes matters more complicated. Therefore, although researchers correctly refer to the gene for Huntington disease, it is unlikely that there is a gene for impulsivity or depression.

One strategy to resolve the link between genes and behavioural and psychiatric phenotypes was to study endophenotypes. These subcategories of phenotypes—usually physiological, anatomical or biochemical measures, such as heart rate, neural activity or synaptic structure—bear a closer relationship to the underlying biological processes than do phenotypes and are therefore crucial tools with which to analyse the influence of genetic variation (Gottesman & Gould, 2003). Although there are examples in which endophenotypes seem to link genes with behaviour, there is still considerable scepticism about their general usefulness.

Another strategy to resolve the poor predictive power of traditional association studies came from the growing importance of stratifying subjects by environmental exposure (Moffitt *et al*, 2005; Rutter, 2007). This gene–environment approach assumes that specific environmental pathogens, the risks of which are stipulated or restricted by genetic variation, influence psychopathology. This conceptual framework was adopted, for example, to explain how genetic variation modifies the activity of catechol-O-methyltransferase, which in turn moderates the influence of adolescent cannabis use on adult psychosis (Caspi *et al*, 2005). The ability of such studies to find genetic risk factors for psychopathology, an area in which earlier association studies had failed, attracted considerable attention and much behavioural genetic research today has adopted the gene–environment approach.

At the same time, the technology used for measuring human genetic variation has grown considerably more sophisticated. Today, researchers routinely sequence millions of SNPs in hundreds or even thousands of individuals, and the extensive sequencing of human genomes has generated a repository of common natural variations. The International HapMap Project has collected series of consecutive sequence variants that are commonly found together in the human population. These ‘haplotypes’ have made it possible to rapidly identify sequence variants between individuals by sequencing only a subset of all genetic variations across a group (International HapMap Consortium, 2005; Goldstein & Cavalleri, 2005).

Moreover, new forms of genetic variations have been discovered, the most notable being individual differences in the

copy numbers of genes (Redon *et al*, 2006). Large segments of chromosomes contain genes that are multiplied or deleted, and the resulting changes in their copy numbers are emerging as an important source of phenotypic variation. Undoubtedly, vast areas of variation in the genetic landscape are still awaiting discovery. Areas that are now attracting much interest include the epigenetic control of viral and other parasitic DNAs that constitute more than 50% of the human genome (Goll & Bestor, 2005), variations that affect the expression of non-coding RNA transcripts (Bartel, 2004), and variations that are induced by somatic mutations such as transposons and other mobile or unstable DNA elements (Whitelaw & Martin, 2001). Clearly, our ability to catalogue genetic variations is rapidly outpacing our ability to link such changes with behavioural phenotypes.

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The era of direct gene–phenotype association studies based on a ‘one gene, one phenotype’ hypothesis has evolved into a more complex framework of interacting genetic, environmental, stochastic and emergent phenomena. The erroneous presumption of a causative link between a gene variant and a behavioural phenotype or mental illness, and the underlying genetic essentialism behind this view (Nelkin & Lindee, 1995), have been replaced by a language of probability and susceptibility (Rose, 2006). However, statements such as “X is a susceptibility gene for Y” remain simplistic and problematic. In our view, the web of contingencies between the environment and genes calls for an aetiological description that goes beyond susceptibility. A more sophisticated model posits that genes restrict or channel behavioural outcomes by producing the structural building blocks of the underlying mental apparatus, and at the same time moderate the impact of past and present environmental experiences on fundamental behaviour. To this view we must also add emergent and stochastic events, which we have few scientific tools to help us understand.

Clearly, the relationship between genes and behaviour can no longer be considered straightforward. However, there are compelling reasons for using genetics to study behaviour. First, genes are amenable to quantification and manipulation, which are essential prerequisites for scientific analysis. Second, gene products can be subjected to pharmacological manipulation and, hence, are avenues for the development of pharmacotherapy. Third, genetics is a powerful tool with which to identify the molecular mechanisms underlying a phenotype; no other scientific technique is able to link phenotypes and molecules as quickly and definitively. Fourth and finally, genetics allows conclusions to be drawn about cause and effect.

One recent study in mice illustrates the power of genetics to uncover new and obscure mechanisms underlying behavioural phenotypes. In this case, a null mutation in a transmembrane receptor called CD38, which was previously known to be involved in controlling immune cell responses, was found to induce a deficit in maternal nurturing behaviour (Jin *et al*, 2007). Further investigation revealed that CD38 has a crucial, but unsuspected, role in moderating the release of the maternal peptide hormone oxytocin from the brain. Nurturing behaviour could be restored by treatment with oxytocin, which implies that CD38-dependent oxytocin release is a direct moderator of maternal behaviour, including offspring retrieval and grooming. As a result of this research, CD38 has become a new candidate therapeutic target for disorders involving deficits in social communication and attachment, such as autism.

It should be borne in mind when considering the results of behavioural genetic studies that, even if an association between a gene and a phenotype is significant and reproducible among independent studies, it still might not have predictive value. In most cases, knowing whether a person carries a genetic risk factor is useless in predicting whether he or she will develop the phenotype; the predictive value of a genetic variant is proportional to its

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effect size. Scientists must take considerable care when they present such data to the lay public, who are eager to see the direct diagnostic value of genetic studies. However, small effect sizes do not detract from the ability of association studies to uncover new molecular mechanisms and, hence, potentially new therapeutic avenues for behaviour-related diseases. But some aspects of complex human behaviour will probably remain forever inaccessible to genetic investigation owing to the lack of either appropriate tools or a measurable genetic influence. Behavioural genetic studies should not regard genes as fixed determinants of psychological characteristics, or mental disorders as things in themselves, but instead should view them as restricting factors operating on the complex mix of direct and indirect effects at different points in a causal chain.

Current approaches to behavioural genetics must also be aware of the social context and its influence on this type of research. Without a proper appreciation of the impact of cultural influences, behavioural geneticists will probably find themselves faced with results that are of questionable medical and scientific utility. Two areas of intense social and cultural controversy have had an important influence on current thinking in behavioural genetics: medicalization and social constructionism (Press, 2005). In this context, medicalization refers to the process by which an increasing number of non-pathological behavioural traits are being brought under the scrutiny of medicine. Geneticization refers to the extension of medicalization into the realm of genetics (Lippman, 1992). According to social constructionism, concepts or facts that seem to be a product of nature are considered to be an artefact of culture developed in a given social context.

Increasingly, Western societies create new 'disorders' and 'diseases' by extracting normal phenomena from their context, and labelling them as pathologies, thereby rendering them subject to the attention of medicine (Foucault, 1994). In turn, this process provides genetic analysis with new traits and behaviours, particularly psychiatric disorders. Hence, traits and phenotypes that are in reality fluid and continuous concepts become reified in psychiatric categories.

The number of conditions now regarded as mental illnesses and the number of affected individuals are continuously growing

(DSM-IV, 2000; Lenzenweger *et al*, 2007). For example, the number of people diagnosed with anxiety disorders—generalized anxiety disorder, panic disorder, social and specific phobia, post-traumatic stress disorder and obsessive-compulsive disorder—has increased notably. On their website, the Anxiety Disorders Association of America (Silver Spring, MD, USA) estimates that about 18.1% of the adult US population are affected at some point during their lives (www.adaa.org).

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However, anxiety and distress are a normal and intrinsic part of human behaviour in response to threatening or conflicting social stimuli. They are categorized as pathological only if they become excessive or severely disrupt routine activities, such as work, sleep or socializing. In Western society—with its emphasis on self-sufficiency, productivity and an efficient division of labour—anxiety disorders are likely to become more frequent, if only because social demands are less tolerant of disruptive stressful or anxious states. People suffering distress and unhappiness from circumstances that are intrinsic to social life—such as romantic disturbances, physical illness, problems at work or a failure to achieve aspirations—become medicalized more easily according to the symptom-based logic of diagnostic classification. At the same time, the availability of pharmacological interventions to treat non-pathological anxiety and stress has further accelerated the trend towards medicalization.

The knowledge that a condition is the result of a chemical imbalance that can be restored with a drug or blamed on heredity helps many people to cope

A representative example is provided by the case of shyness. The term shyness commonly refers to an emotional state of behavioural inhibition and discomfort in the presence of unfamiliar people or situations,

and there is some evidence that shyness is a risk factor for anxiety disorders, especially social phobia (Schmidt *et al*, 1999). As a result, shyness has been proposed as an endophenotype of anxiety disorders and has been subjected to genetic analysis (Arbelle *et al*, 2003). This approach seems to follow sound reasoning, and several studies have found significant genetic components to shyness (Fyer, 1993; Hudson & Rapee, 2000; Melke *et al*, 2003; Roberts *et al*, 2004). However, shyness is hard to categorize and includes definitions of anxiety disorders, physical disability and social deviance, which depend on social judgements about appropriate forms of behaviour. Extensive research on the medicalization of shyness has pointed to this behaviour as an 'unhealthy' state of mind in contemporary Western societies because shy individuals fail to comply with certain cultural values such as assertiveness, self-expression and talkativeness (Scott, 2006). Behavioural geneticists must therefore be aware of how social norms can define the objects of study. Such an approach would dictate that shyness should be studied only if it can tell us something important and new about the neural control of full-fledged anxiety and depression.

Finally, behavioural geneticists must be aware that biological, and particularly genetic, explanations of psychological phenomena have a growing cultural credence in contemporary Western societies. The knowledge that a condition is the result of a chemical imbalance that can be restored with a drug or blamed on heredity helps many people to cope (McHugh, 1999). In the light of this, behavioural genetics must accept that under certain circumstances, other non-genetic approaches might be more efficient in relieving the suffering associated with pathological behaviour.

We have underlined the existence of a dynamic feedback loop between genetic research and a medicalizing society. Social contingencies and medicalization provide behavioural genetics with new objects for investigation, and, in turn, behavioural genetics contributes to the growing expansion of the medical realm. This intricate relationship artificially accentuates the view of psychiatric conditions as firm categories, and leads to an emphasis on genetic and neurochemical components rather than social factors. For scientists, understanding

the genetic underpinnings of anxiety means initially defining this trait and dissecting it into multiple components. However, this also means that behavioural phenomena are abstracted from their social realities and that crucial contextual influences are neglected.

In conclusion, searching for genetic factors that influence behaviour is a powerful way in which to develop new diagnostic and therapeutic avenues for treating mental illness. However, scientists must recognize the limitations of the genetic approach and the influence of social norms on the selection of traits and behaviours. An integrative operational framework that recognizes the complexity of the behavioural phenomena under investigation, and the consideration of genes as influencing a complex mix of direct and indirect effects, can legitimize this research approach. The rapid growth in genomic information is uncovering new terrains of genetic variation; at the same time, the growing trend towards medicalization is expanding the repertoire of behaviours that are considered to be amenable to genetic study. Under these circumstances, behavioural geneticists must steer a clear course toward addressing the molecular mechanisms of behavioural risk factors for mental illness without becoming sidetracked by the study of spurious traits.

REFERENCES

- Arbelle S, Benjamin J, Golin M, Kremer I, Belmaker RH, Ebstein RP (2003) Relation of shyness in grade school children to the genotype for the long form of the serotonin transporter promoter region polymorphism. *Am J Psychiatry* **160**: 671–676
- Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* **116**: 281–297
- Caspi A *et al* (2005) Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene $\times$ environment interaction. *Biol Psychiatry* **57**: 1117–1127
- DSM-IV (2000) *Diagnostic and Statistical Manual of Mental Disorders*, 4th Ed. Washington, DC, USA: American Psychiatric Association
- Foucault M (1994) *The Birth of the Clinic: An Archaeology of Medical Perception*. New York, NY, USA: Vintage
- Fyer AJ (1993) Heritability of social anxiety: a brief review. *J Clin Psychiatry* **54**: S10–S12
- Goldstein DB, Cavalleri GL (2005) Genomics: understanding human diversity. *Nature* **437**: 1241–1242
- Goll MG, Bestor TH (2005) Eukaryotic cytosine methyltransferases. *Annu Rev Biochem* **74**: 481–514
- Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* **160**: 636–645
- Hudson JL, Rapee RM (2000) The origins of social phobia. *Behav Modif* **24**: 102–129
- International HapMap Consortium (2005) A haplotype map of the human genome. *Nature* **437**: 1299–1320
- Jin D *et al* (2007) CD38 is critical for social behaviour by regulating oxytocin secretion. *Nature* **446**: 41–45
- Kay LE (2000) *Who Wrote the Book of Life? A History of the Genetic Code*. Stanford, CA, USA: Stanford University Press
- Keller EF (2000) *The Century of the Gene*. Cambridge, MA, USA: Harvard University Press
- Kendler KS (2005) “A gene for...”: the nature of gene action in psychiatric disorders. *Am J Psychiatry* **162**: 1243–1252
- Lenzenweger MF, Lane MC, Loranger AW, Kessler RC (2007) DSM-IV personality disorders in the national comorbidity survey replication. *Biol Psychiatry* doi:10.1016/j.biopsych.2006.09.019
- Lippman A (1992) Led (astray) by genetic maps: the cartography of the human genome and health care. *Soc Sci Med* **35**: 1469–1476
- McHugh PR (1999) How psychiatry lost its way. *Commentary Magazine* **108**: 32–38
- Melke J *et al* (2003) A polymorphism in the serotonin receptor 3A (*HTR3A*) gene and its association with harm avoidance in women. *Arch Gen Psychiatry* **60**: 1017–1023
- Moffitt TE, Caspi A, Rutter M (2005) Strategy for investigating interactions between measured genes and measured environments. *Arch Gen Psychiatry* **62**: 473–481
- Nelkin D, Lindee MS (1995) *The DNA Mystique*. New York, NY, USA: Freeman
- Press N (2005) Social construction and medicalization: behavioral genetics in context. In Parens E, Chapman AR, Press N (eds), *Wrestling with Behavioural Genetics: Science, Ethics, and Public Conversation*. Baltimore, MD, USA: Johns Hopkins University Press
- Redon R *et al* (2006) Global variation in copy number in the human genome. *Nature* **444**: 444–454
- Roberts RL, Luty SE, Mulder RT, Joyce PR, Kennedy MA (2004) Association between cytochrome P450 2D6 genotype and harm avoidance. *Am J Med Genet B Neuropsychiatr Genet* **127**: 90–93
- Rose N (2006) *The Politics of Life Itself*. Princeton, NJ, USA: Princeton University Press
- Rose S (1995) The rise of neurogenetic determinism. *Nature* **373**: 380–382
- Rutter M (2007) *Genes and Behaviour*. Oxford, UK: Blackwell
- Schmidt LA, Fox NA, Schulkin J, Gold PW (1999) Behavioral and psychophysiological correlates of self-presentation in temperamentally shy children. *Dev Psychobiol* **35**: 119–135
- Scott S (2006) The medicalisation of shyness: from social misfits to social fitness. *Sociol Health Ill* **28**: 133–153
- Whitelaw E, Martin DI (2001) Retrotransposons as epigenetic mediators of phenotypic variation in mammals. *Nat Genet* **27**: 361–365

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