

Genetics and behaviour

ADY COUSINS

ASK any psychologist to complete the following phrase: 'nature–nurture _____'. The answer will no doubt be 'debate' or 'controversy'. But the controversy that swirled around behavioural genetics research in psychology during the 1970s has largely faded. During the 1980s and, especially, the 1990s, psychology became much more accepting of genetic influence, as can be seen in the increasing number of behavioural genetic articles in mainstream psychology journals and in research grants. One symbol of this change was the 1992 centennial conference of the American Psychological Association. In preparation for the conference, a committee selected two themes that best represented the past, present, and future of psychology. One of the two themes chosen was behavioural genetics (Plomin & McClearn, 1993).



ROBERT PLOMIN argues that psychologists should prepare to maximise the benefits and minimise the risks that will emerge from DNA research.

In my view, this choice represents one of the most dramatic shifts in the modern history of psychology. Indeed, the wave of acceptance of genetic influence in psychology is growing into a tidal wave that threatens to engulf key messages coming from behavioural genetic research.

The first message is that genes play a surprisingly important role throughout psychology. But the second message is just as important: individual differences in complex psychological traits are due at least as much to environmental influences

as they are to genetic influences. In fact, behavioural genetic research provides the strongest available evidence for the importance of environmental factors. But in some areas of psychology, especially psychopathology, the pendulum representing the accepted view may be swinging too far from environmental determinism to genetic determinism.

Perspectives

Behavioural genetics focuses on questions of why individuals within a species differ

in behaviour (e.g. why children differ in rates of language acquisition), whereas much research in psychology investigates species-typical behaviour (e.g. the average age at which children use two-word sentences). Descriptions and explanations of species-typical behaviour bear no necessary relationship to descriptions and explanations of individual differences within a species. For example, the fact that our species begins to use two-word sentences at the average age of 18 months is an evolutionary adaptation ultimately due to selection of genes, but this does not mean that genetics is responsible for the delayed use of two-word sentences by some children.

The fundamental accomplishment of genetic research in psychology to date has been to demonstrate the ubiquitous importance of genetics throughout psychology. As described later, this evidence consists of twin studies that compare the similarity of identical and non-identical twins; and adoption studies that consider the resemblance of adopted-away children to their biological parents. These methods and the theory that underlies them are called quantitative genetics, in contrast to molecular genetic research, which attempts to identify specific genes. Behavioural genetics includes both quantitative genetic research and, increasingly, molecular genetic research. Although this brief target article is limited to human behavioural genetics, more powerful quantitative genetic and molecular genetic methods are available for analysing animal behaviour (Plomin *et al.*, 2001).

We can see this focus on species-typical behaviour in several key areas of psychology. For example, experimental psychology implicitly studies species-typical behaviour, comparing an experimental group with a control group representing typical behaviour, with individual differences considered as an error term in an analysis of variance. Similarly, much molecular genetic research consists of experimentally mutating a gene so that it is no longer expressed, and comparing these mutated animals with normal animals; whereas behavioural genetics has focused on naturally occurring genetic variation. Finally, evolutionary psychology also focuses on species-typical behaviour using comparisons between species as evidence for evolutionary adaptations. Although this is a type of genetic analysis of behaviour, the perspectives and empirical foundations for

behavioural genetics and evolutionary psychology are so different that I think it causes confusion to conflate the two fields. I should emphasise that perspectives are not right or wrong, just more or less useful to address particular questions.

Autism as an example

As recently as the 1970s autism was thought to be caused by cold, rejecting parents. Certainly, parents whose children are autistic behave differently towards their children compared with parents of non-autistic children, but the direction-of-effects question looms large: Are the differences in parenting cause or effect? The accident of nature that results in identical (monozygotic) twins or non-identical (fraternal or dizygotic) twins provides one way to address this question. Identical twins are like clones, genetically identical to each other because they came from the same fertilised egg. Non-identical twins, on the other hand, developed from two eggs that happened to be fertilised at the same time. Like other siblings, they are only half as similar genetically as identical twins.

At the Institute of Psychiatry Michael Rutter and his colleague Susan Folstein were the first to use the twin method to investigate the causes of autism (Folstein & Rutter, 1977). They reasoned that if autism is caused by parental treatment, then non-identical twins ought to be as similar (concordant) for autism as are identical twins, because both types of twins are reared by the same parents in the same place and the same time and presumably get similar treatment. But if autism is influenced by genes, then non-identical twins ought to be less concordant. Folstein and Rutter located 10 autistic children in Britain who were non-identical twins. In none of these cases was the other twin also autistic. This result was not surprising, because autism is rare (an incidence of about one in a thousand) and it was already known that only about 3 per cent of the non-twin siblings of autistic children are autistic. The surprise came in the result for identical twins. Folstein and Rutter found 15 children diagnosed as autistic who were identical twins. Eight of these children were in four concordant pairs of twins in which both identical twins were diagnosed as autistic. The incidence of autism in children who have an autistic sibling, though low in absolute terms, represents a risk that is 30 times higher than that for children whose siblings are unaffected; the incidence in children who have an autistic identical twin represents a 500-fold

increase in risk over the general population. The results of this small study have been replicated in other twin studies (as reviewed by Bailey *et al.*, 1996).

The twin method Why are identical twins so much more concordant for autism than non-identical twins? The most parsimonious explanation is that identical twins are much more alike genetically. Another hypothesis puts the blame on prenatal factors. Identical twins often share the same chorion (the outermost membrane surrounding the foetus during prenatal development), which might make them more similar than non-identical twins (who never share the same chorion). So far the scanty evidence relevant to this issue is mixed (Sokol *et al.*, 1995). Another possibility is that twins may not be representative of the non-twin population because of adverse intra-uterine environments caused by sharing a womb (Phillips, 1993). However, the statistical distributions for most psychological dimensions and disorders for twins and non-twins are generally similar (e.g. Christensen *et al.*, 1995).

A subtle but important factor is that identical twins might have more similar experiences than do non-identical twins *after* they are born. The use of the twin method is based on the assumption that the environments of non-identical twins reared in the same family are approximately as similar as the environments of identical twins reared in the same family. This assumption has been tested in several ways and appears reasonable for most traits, although it has not been tested specifically in regard to autism (Bouchard & Propping, 1993). Although the possibility remains that identical twins may be treated more alike by their parents because they are more similar in appearance and behaviour, the twin method provides a rough but useful screen to unpack the 'bottom-line' effects of genes and environment (Martin *et al.*, 1997).

The adoption method Although there are no adoption studies of autism, the adoption method is another quasi-experimental design that has a different set of assumptions and potential problems. Family members normally share both heredity (first-degree relatives correlate .50 genetically) and environment (they share the same family). Thus, familial correlations cannot tell us about the relative extent to which genetic and environmental factors contribute to observed resemblance

between family members. The adoption method separates the effects of nature and nurture by studying adopted-apart genetic relatives (to assess the role of genetics) and by studying genetically unrelated individuals brought together by adoption (to assess the role of family environment).

For example, for most psychological traits parents and offspring resemble each other. Because these are genetic-plus-environmental parents, parent-offspring resemblance could be due to nature or nurture. 'Genetic' parents and their adopted-away offspring do not share postnatal environment and thus their resemblance can be attributed to genetics and (in the case of birth mothers but not fathers) prenatal environment. 'Environmental' parents and their adopted children do not share heredity and thus

I found that adoptive families are reasonably representative of the population and that selective placement was negligible (Plomin *et al.*, 1997).

Twin and adoption studies can be used not only to demonstrate the statistical significance of genetic influence but also to estimate its effect size, called heritability. Heritability is that proportion of the variance of a particular trait in a population that can be accounted for by genetic factors.

Beyond heritability For autism, the twin research without the additional weight of confirming adoption data was responsible for the shift from thinking about autism as a disorder caused entirely by environmental factors to its current status as one of the most heritable mental disorders. Genetic

Another direction for research concerns the effects of the environment. Because identical twins are not 100 per cent concordant for autism even though they are identical genetically, twin studies also provide strong support for the importance of environmental factors (though no support for theories that place the blame on the parents' behaviour). Environmental factors must contribute to differences in autism for two children – even identical twins – growing up in the same family. Such environmental influences are called 'non-shared' to distinguish them from shared environmental influences that make children growing up in the same family similar. What are the specific non-shared environmental factors that make identical twins growing up in the same family different and that widen the differences between other sibling pairs? Much remains to be learned about this important issue, for autism and for other psychological characteristics (Harris, 1998).

Another example of the use of genetic research to help us understand the environment has been called 'the nature of nurture' (Plomin, 1994). Twin and adoption studies have shown that genetic factors can have effects on the environment itself and that such effects can be found on aspects of the environment measured in psychological research. Such effects, known as 'genotype-environment correlations', could operate in various ways. Genetic factors could affect the reactions we evoke in others and the experiences that we select, construct and re-construct in memory. For example, autistic children evoke distancing responses in others and select non-social experiences that reinforce their genetic tendency towards social and communication abnormalities. Environmental influences need to be examined in genetically sensitive designs, and genetic influences need to be examined in environmentally sensitive designs that incorporate specific measures of the environment (Rutter *et al.*, 1997).

A new direction for research is to attempt to identify some of the specific genes responsible for the genetic

their resemblance can be attributed to family environment. The adoption method also includes siblings or twins reared apart. Because the twin and adoption methods are so different, greater confidence is warranted when results from these two methods converge on the same conclusion – as they usually do.

One issue for adoption studies is that adoptees and their adoptive families might not be representative of the population as a whole, either because they have distinctive characteristics or because they span a narrower range. There is also the possibility that adopted children might be selectively placed with adoptive parents matched to the birth parents. These issues can be examined empirically. For example, in a longitudinal prospective adoption study of normal behavioural development that began in 1975, my colleagues and

research has now moved on to other issues. One direction is to examine, using multivariate statistics, the genetic links between autism and other problems. The genetic vulnerability to autism has been shown to extend well beyond classic diagnostic symptoms: it includes milder social and communication difficulties that are found to be more common in the biological relatives of autistic people (Rutter *et al.*, 1999).

HYPERACTIVITY

Several twin studies of attention deficit hyperactivity disorder (ADHD) have been carried out in recent years. These studies have consistently pointed to high heritability for hyperactive symptoms and for the ADHD diagnosis itself. Again, genetic links between the normal and abnormal have been found. Several molecular genetic studies have indicated a role for dopamine genes in the aetiology of hyperactivity (Thapar *et al.*, 1999).

READING DISABILITY

Reading disability shows moderate heritability – concordances for non-identical and identical twins are about 40 per cent and 70 per cent respectively. As with autism and many other disorders, the genetic liability for reading disability extends beyond the dichotomy imposed by a yes-or-no diagnostic procedure. On average, the non-identical twins of reading-disabled probands (index cases) are much better readers than the probands themselves, but they are significantly worse readers than the rest of the population. In contrast, the identical twins of reading-disabled probands read almost as poorly as the probands. As with autism, these results suggest a genetically influenced continuum between normal and abnormal. That is, genetic factors that affect diagnosed reading disability may be the same genetic factors that contribute to the quantitative dimension of reading ability (DeFries & Alarcón, 1996).

Results that demonstrate a continuum between the normal and abnormal have major implications for molecular genetic research, because they imply that many different genes contribute to the heritability of common disorders (Plomin *et al.*, 1994). Unlike the relatively rare disorders in which a single gene is necessary and sufficient for the development of the disorder, common disorders like reading disability are complex traits influenced by environmental factors and by many genes of varying but relatively small effect size (called quantitative trait loci or QTLs). Multiple-gene systems require more powerful genetic designs that can detect genes of small effect. Reading disability is the first common behavioural disorder to which a QTL approach was applied. A linkage between reading disability and DNA markers on the short arm of chromosome 6 (Cardon *et al.*, 1994) has been consistently replicated (e.g. Gayán *et al.*, 1999). This QTL appears to be broad in its effect, involving both phonological (auditory) and orthographic (visual) aspects of reading disability.

contribution to various disorders, even though it seems likely that the target is many genes of small effect size rather than one or two genes of major effect. An international team initially led by Rutter and Monaco has identified a region on chromosome 7 that may be linked with vulnerability to autism (International Molecular Genetic Study of Autism Consortium, 1998). Finding specific genes that contribute to vulnerability to autism and other behavioural disorders and dimensions will provide the strongest evidence for genetic influence and will make it easier to explore the developmental interplay between nature and nurture (Plomin & Rutter, 1998).

Other examples

For milder psychological disorders too, a more balanced view that accepts the role of nature as well as nurture is beginning to prevail, and researchers are making progress in identifying specific genes. Two further examples are reading disability and hyperactivity (see boxes).

Other behavioural disorders and dimensions Moderate genetic influence has been found for most behavioural disorders that have been studied to date, including schizophrenia, mood disorders and anxiety (Plomin *et al.*, 2001). Indeed, behavioural disorders tend to show greater

genetic influence than common medical disorders such as breast cancer or heart disease (Plomin *et al.*, 1994). The reason for the greater genetic influence for behavioural disorders may be that many different biological pathways can affect behaviour. Behaviour can be seen as the downstream outcome of many different biological systems; thus, genetic influences can operate on behaviour via all of the upstream systems.

Genetic influences are not limited to disorders, they also contribute to normal variation in personality (Loehlin, 1992) and in cognitive abilities (Plomin & DeFries, 1998), as well as to psychopathology. For self-report questionnaires, most personality traits show moderate genetic influence, with twin correlations of about 0.50 for identical twins and 0.20 for non-identical twins. In the case of self-report personality questionnaires, the far fewer adoption studies appear to suggest only about half as much genetic influence as twin studies, perhaps because twin studies capture different types of genetic variance than adoption studies (Plomin & Caspi, 1998). Genetic factors even appear to be involved in social and political attitudes and occupational interests (Plomin *et al.*, 2001). Genes responsible for the heritability of personality are beginning to be identified (Hamer & Copeland, 1998).

One of the best documented cases in all

of science for genetic influence is general cognitive ability (*g*), although it remains controversial in psychology (Plomin *et al.*, 2001). Dozens of studies including more than 8000 parent–offspring pairs, 25,000 pairs of siblings, 10,000 twin pairs, and hundreds of adoptive families all converge on the conclusion that genetic factors contribute substantially to *g*. Estimates of the effect size, called heritability, vary from 40 to 80 per cent; but estimates based on the entire body of data are about 50 per cent, indicating that genes account for about half of the variance in *g*. Sorting the results by age indicates that heritability increases from about .20 in infancy to about .40 in childhood to .60 or higher later in life (McGue *et al.*, 1993), even for individuals 80+ years old (McClearn *et al.*, 1997).

This increase in the heritability of *g* throughout the lifespan is interesting because it is counterintuitive in relation to the accumulation of life's experiences. It may be that heritability increases because individuals seek and create environments correlated with their genetic propensities. That is, genetic propensities might be best considered as appetites rather than aptitudes, making some children hungrier for knowledge and more able to digest it. Molecular genetic studies are also beginning to identify genes associated with *g* (Fisher *et al.*, 1999).

New avenues Genetic research to date has only scratched the surface of possible applications in psychology, even within the best-studied domains of psychopathology, personality, and cognitive disabilities and abilities. For psychopathology, genetic research has just begun to consider disorders other than schizophrenia and the major mood disorders. Developmental psychopathology has recently become an active area of genetic research (Rutter *et al.*, 1999). Personality is so complex that it can keep researchers busy for decades, especially as they go beyond self-report questionnaires to use other measures such as observations and ratings by others (Riemann *et al.*, 1997). A rich territory for future exploration is the links between psychopathology and personality (Nigg & Goldsmith, 1994). New directions for genetic research on cognitive abilities and disabilities includes the systematic analysis of psychological theories of cognition (Mackintosh, 1998), the use of information-processing measures of reaction times (e.g. Neubauer *et al.*, 2000), and brain-imaging measures (Kosslyn & Plomin, 2001).

The vast majority of human genetic research in psychology has centred on psychopathology, personality, and cognitive disabilities and abilities because these areas have long been the focus of research on individual differences. Three new areas of psychology that are beginning to be explored genetically are psychology and aging, health psychology, and evolutionary psychology (Plomin *et al.*, 2001). Some of the oldest areas of psychology – perception and learning, for example – have not emphasised individual differences and as a result have yet to be explored systematically from a genetic perspective. Entire disciplines within the social and behavioural sciences, such as economics, education, and sociology, are still essentially untouched by genetic research.

Genetic research in psychology is moving beyond heritability, as illustrated by the examples of autism, reading disability and hyperactivity. Asking whether and how much genetic factors affect psychological dimensions and disorders are important first steps in understanding the origins of individual differences, but these questions are only a beginning. The next step involves the question ‘how’ – that is, the study of the mechanisms by which genes have their effects. Avenues for genetic research in psychology include developmental change and continuity, links between the normal and abnormal, multivariate genetic analysis of heterogeneity and comorbidity, and the interplay between genes and environment. An especially exciting direction for research is identification of some of the specific genes responsible for the heritability of psychological disorders and dimensions.

DNA

Although attention is now focused on finding specific genes associated with complex traits, the greatest impact on psychology will come after genes have been identified.

Using DNA Few psychologists are likely to join the hunt for genes because it is difficult and expensive, but once genes are found, it is relatively easy and inexpensive to use them (Plomin & Rutter, 1998). DNA can be obtained from cheek swabs, rather than blood, at a cost of less than £10 per individual. One cheek swab yields enough DNA to genotype thousands of genes, and several genes can be genotyped for less than £5 per individual. Microarrays the size of a postage stamp, called DNA chips, are

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becoming available that can genotype thousands of genes in a few minutes at costs that will eventually be very low per individual.

Although some psychology departments already have DNA laboratories, it is likely that most psychological research with DNA will be accomplished through collaborations with molecular geneticists or through commercial arrangements. It is critical for the future of psychology as a science that we be prepared to use DNA in our research and eventually in our clinics. What has happened in the area of dementia in the elderly will be played out in many areas of psychology. The only known risk factor for late-onset Alzheimer’s disease (LOAD) is a gene, apolipoprotein E (ApoE), involved in cholesterol transport. A form of the gene called allele 4 quadruples the risk for LOAD but is neither necessary nor sufficient to produce the disorder; hence it is a QTL. The association between allele 4 and LOAD was first reported only in 1993, but it has already become *de rigueur* in research on dementia to genotype subjects for ApoE to ascertain whether the results differ for individuals with and without this genetic risk factor. Genotyping ApoE will become clinically routine if this genetic risk factor is found to predict differential response to interventions or treatments.

Scientific implications Among geneticists it is generally believed that we will be awash in genes associated with complex traits including behaviour in the next few years. This is especially likely as the Human Genome Project completes sequencing all 3.5 billion DNA bases (the four-letter alphabet of the genome that forms the steps in the spiral staircase of DNA) and identifies all genes and the

several million DNA bases that differ among us. The future of genetic research lies in moving from finding genes (genomics) to finding out how genes work (functional genomics). Functional genomics is usually considered in terms of bottom-up molecular biology at the cellular level of analysis. However, a top-down psychological level of analysis may be even more valuable in understanding how genes work at the level of the intact organism, in understanding interactions and correlations between genes and environment, and in leading to new treatments and interventions. For example, top-down approaches for genes associated with learning and memory could trace the effects of genes through cognitive processes as outlined by theories of cognitive psychology (e.g. Mackintosh, 1998), in contrast to a bottom-up approach that begins with the cellular functioning of neuroreceptors. The phrase ‘behavioural genomics’ has been suggested to emphasise the importance of top-down levels of analysis in understanding how genes work (Plomin & Crabbe, in press). Bottom-up and top-down levels of analysis of gene-behaviour pathways will eventually meet in the brain. The grandest implication for science is that DNA will serve as an integrating force across diverse disciplines.

Clinical implications Geneticists need clinical psychology to define phenotypes, to design treatment, intervention and prevention programmes, and to evaluate these programmes. For clinical psychology, DNA may eventually lead to gene-based diagnoses and treatment programmes. The most exciting potential is secondary prevention. Because DNA analysis can be used to predict genetic risk for an

individual, it offers the hope for intervention before disorders create cascades of complications.

Interventions for complex psychological traits, and even for single-gene disorders, are likely to involve environmental rather than genetic engineering. For example, phenylketonuria (PKU), a metabolic disorder that can cause severe mental retardation, is caused by a single gene on chromosome 12. A particular form of the gene, found in 1 in 10,000 babies, damages the developing brain postnatally. This form of mental retardation has been largely prevented, not by high-tech solutions such as correcting the mutant DNA or by eugenic programmes or by drugs, but rather by a change in diet that prevents the mutant DNA from having its damaging effects. For this reason newborns have been screened for decades for PKU to identify those with the disorder so their diet can be changed. The example of PKU serves as an antidote to the mistaken notion that

genetics implies therapeutic nihilism, even for a single-gene disorder. This point is even more important in relation to complex disorders that are influenced by many genes and by many environmental factors as well.

Social implications Psychologists should participate constructively in the discussion of scientific, clinical and social implications of the advances brought about by DNA research. The search for genes involved in behaviour has led to a number of ethical concerns: there is fear that the results will be used to justify social inequality, to select individuals for education or employment, or to enable parents to pick and choose among their foetuses. These concerns are largely based on misunderstandings about how genes affect complex traits such as the mistaken implication of therapeutic nihilism mentioned earlier, the assumption that genetic factors imply determinism, or that

genetics justifies the status quo (Rutter & Plomin, 1997).

'DNA' For these reasons, it is crucial that psychologists be prepared to maximise the benefits and minimise the risks that will emerge from DNA research. Students in psychology must be taught about genetics to prepare them for this future. Otherwise this opportunity for psychology will slip away by default to geneticists, and genetics is much too important a topic to be left to geneticists! Clinical psychologists use the acronym 'DNA' to note that their clients 'did not attend.' It is critical to the future of psychology as a science that, for all psychologists, DNA denotes deoxyribonucleic acid rather than 'did not attend'.

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Pushing at an open door?

ROBERT Plomin is a great enthusiast for genetic approaches to psychology, and he has done much to bring research in the area to the attention of his colleagues. But at times, like other enthusiasts, he overstates his case. Much of his brief review reads as if he is still trying to convince us that nature as well as nurture is involved in the development of human behaviour. Why is it necessary to push so strongly against an open door?

The controversy around behaviour genetics in the 1970s was not about any general claim that nature is involved as well as nurture. Rather it questioned the specific conclusion drawn by Arthur Jensen (1969) and others that the relatively high heritability claimed for IQ meant that compensatory education for children was bound to fail, as well as some statements they made about the origin of black/white IQ score differences. More fundamental issues about the validity of the heritability approach were also raised (Feldman & Lewontin, 1975; Kempthorne, 1978).

The general point is that heritability is a very rough and ready statistic with specific and limited application. The real puzzle is that psychologists have put so much effort into its calculation. Heritability partitions variance into two rather ill-defined categories – genetic and environment, or nature and nurture (as well as error and interaction terms). Fundamental simplifying assumptions need to be made. The values you derive depend on the assumptions you make. What studies show is that for almost all behavioural and social traits examined, the proportion of inherited variance is in the mid to low range. Towards the upper range of the cluster there are studies of, for example, reading disorder and religious interest (Waller *et al.*, 1990), and towards the lower end schizophrenia and divorce (McGue & Lykken, 1992).

But it seems to me that almost nothing



Peer commentary by **MARTIN RICHARDS**.

follows from the position in this league table of heritability. Despite Plomin's statement that 'behavioural disorders tend to show greater genetic influence than common medical disorders such as breast cancer or heart disease', we must realise that in the broad sense heritabilities do not, and cannot, measure the strength of genetic influence. We know that while for the majority of the population of women who develop breast cancer familial effects seem relatively small, there is a subgroup revealed by family pedigree and DNA linkage studies who carry a very significant inherited risk. Research has identified the

involvement of at least two genes, BRCA1 and BRCA2, with strongly predisposing germline mutations.

The identification of these genes allows the possibility of predictive genetic testing and, crucially, provides a whole new approach to the dissection of the tumour genesis process. But we should note that this understanding owes nothing to the calculation of heritabilities and represents a level of molecular genetic knowledge far ahead of that we have for any behavioural disorder. Cancer, after all, is a genetic disease.

In principle, taking statistical behaviour genetics into the DNA era is no different from work on any other kind of disorders. However, attempts at this – well illustrated by the work on schizophrenia – have been characterised by numerous claims followed by refutations (Moldin, 1997). The difficulties seem to stem from the use of poor definitions of the condition and ascertainment, small sample sizes, and premature publication. And there are doubts that the techniques that have been used can accurately detect genetic variants associated with very small genotype-relative risks that are typical for behavioural disorders.

Plomin suggests that in the next few years we will be 'awash in genes associated with complex traits including behaviour'. That may be over-optimistic. Nevertheless, common genetic variants associated with psychiatric and behavioural disorders will be found sooner or later. The likelihood is that there will be many associated genetic variants each

contributing small degrees of risk. But genetic variants associated with the level of risk predicted by ApoE4 may be very rare. However, such factors, though of too small predictor power to provide useful tests at the individual level, may provide important new entry points into developmental pathways when their functions come to be understood.

But such approaches may be much less helpful in the study of variation in normal range (Flint, 1996). Here it is likely that many of the associated genetic variants found may play very peripheral roles in the

complex networks of interacting pathways involved in the development of the characteristic. I certainly support Plomin's suggestion that psychologists may have a great deal to gain from building collaborations with geneticists and developmental biologists, but they will have to think very carefully about the strategies of where to place their efforts. Simply fishing for DNA variation between groups known to differ in behavioural characteristics may simply prove to be a very expensive waste of time and resources.

Plomin briefly touches on the social and ethical implication of genetic research. Here are fields where psychologists have already contributed much research on such topics as genetic counselling, genetic testing, family communication about disorders that may run in the family, and knowledge and understanding of inheritance (Marteau & Richards, 1996; Richards, 1998). This is a rapidly growing field of research and it is very encouraging to see increasing numbers of psychologists entering it. In the ethics field the Nuffield Council on Bioethics (1998) has reviewed research on mental disorders and has recently begun an inquiry into research on genes and behaviour.

The new molecular genetics does open some exciting new doors for psychologists. It is not going to provide any instant solutions to old problems. But it does offer new avenues to explore for the analysis of the extraordinarily complex processes of behavioural development.

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Not all behaviour can be mapped

ABOUT 25 years ago proposing that there were significant genetic influences on behaviour would, at the very least, have invited controversy; and, at the worst, have provoked verbal (if not physical) assault. More recently the climate of opinion has changed and 'finding genes for behaviour' is now a respectable, if not very successful, occupation.

This is not to say that the older debates about the heritability of IQ are dead. A recent paper argued that shared maternal environment may explain the striking correlation between the IQs of twins, with a consequent reduction in the effect of genes (Devlin *et al.*, 1997). But the view that genetic effects are unimportant is now rarely voiced: even taking into account 'maternal effects', genes accounted for 50 per cent of the variation in IQ.

Plomin has been a champion of the



Peer commentary by **JONATHAN FLINT**.

cause of behaviour genetics for many years and his work has been influential in bringing about a change in opinion. He is now in the curious position of warning that the pendulum may have swung too far, that genetic determinism may have become too popular in some areas of psychology. He points out the striking finding from twin studies about the importance of unique environmental effects on individual differences in behaviour. He doesn't dwell on this point, but I think it's worth stressing with an example.

Many studies of personality and intelligence, as well as other measures of individual differences, show correlations between monozygotic (MZ) twins of about 0.5, and values of about 0.3 for correlations between dizygotic twins (Loehlin, 1992). Calculate twice the difference and you have a quick measure of the heritability, in this case 0.4 or 40 per cent. In the excited controversy about the validity of such a calculation, it was not noticed that this figure is very close to the MZ correlation of 0.5 (50 per cent). What makes MZ twins similar is not just their genes, but their common life experiences, for example the school they went to, their parents, their social status. Most people, including sociologists and psychologists, work under the reasonable assumption that some of the variation in personality and intelligence is explained by differences in such factors.

But we now suspect that such shared environmental factors are not so relevant. The fact the genetic effect accounts for almost all of the similarity between the MZ twins means that these common life experiences are relatively unimportant in explaining why some people are more intelligent, more moody, more outgoing, more prone to depression than others. Instead, individual differences are due to person specific events, the nature of which has still to be fully worked out. This is an important message for anyone studying the environmental determinants of behaviour and, as Plomin points out, it comes from genetic studies.

Once the debates about heritability have settled down, where does the field move? Plomin suggests that attention is fixed on finding specific genes. The technology of molecular genetics has a habit of confounding those who doubt its power. For example, few people would have

predicted that the genome of an entire multicellular organism (the fruit fly) could be sequenced within a year and that human genome project would be complete within the following 18 months. So perhaps I should be careful in criticising the view that specific genes influencing behaviour will soon be found. The trouble is that so many studies have now been published with so little agreement between them that it is easy to be cynical. For instance, one example quoted here, a region on chromosome 7 that may be linked to vulnerability to autism, was not found in a separate US study (Risch *et al.*, 1999).

Perhaps the more important issue here is that we still do not know which behaviours should be studied using genetic mapping techniques. The assumption behind the search for genes that influence behaviour is that if we knew about the genes then we'd know something about the biology of behaviour. However, in many cases, genetic effects may be mediated through other factors, so that finding the genes will not be helpful (at least not directly). For example, the efficacy of cognitive therapy on altering self-esteem

and alleviating depression can be interpreted as evidence that low self-esteem has a causal role in predisposing to depression.

Self-esteem is heritable (the heritability in women is 32 per cent and in men 29 per cent (Kendler *et al.*, 1998), so we could argue that understanding the genetic determinants of self-esteem would be a way of accessing the biological basis of susceptibility to depression. Yet our approach would be flawed: it turns out that the personality construct of neuroticism is a better genetic predictor of a woman's underlying vulnerability to major depression than self-esteem. Kendler and colleagues report that the genetic correlation between depression and self-esteem is almost entirely mediated by neuroticism (Roberts & Kendler, 1999).

So not all behaviours are appropriate for genetic mapping, and we cannot rely on heritabilities alone to guide us. Plomin points out that genetics could be used to explore many areas of psychology and sociology, but I find it difficult to see how 'economics, education and sociology' would benefit from the application of gene

mapping studies without a much better understanding of what mediates the genetic effects. I agree that psychologists cannot afford to ignore genetics and should consider the approaches it affords. Just how far they can apply them remains to be seen.

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DNA is important – But only in its proper place

PSYCHOLOGISTS, Robert Plomin tells us, need to recognise that genetics is important. Well, yes.

To ignore the fact that minds are embodied, that people construct themselves out of the raw materials of their evolutionary, genetic, developmental and social histories, would be absurd. It is hard indeed to imagine many psychologists ignoring this self-evident truth. And for neuroscientists like me, understanding just how living organisms do so construct themselves is a day-to-day laboratory concern.

What is, I suppose, at stake, is to understand where and how such genetics becomes relevant, and here is where Plomin oversells – as when he reflects sadly on the fact that to date sociology is relatively untouched by genetics. But this is no more surprising than to point out that genetics is untouched by quantum physics: the discourses and concerns of the two sciences have no common ground.

The workings of the stock exchange, and the rules of football, would both be very different if humans were not broadly between 1.5 and 2.5 metres tall, lived for 70+ years, had opposable thumbs and worked primarily with visual rather than olfactory senses. All these are the consequences in part of our genetic and evolutionary history, yet that history gives us no useful explanatory purchase on understanding the specificities of either capitalism or sport. To what extent does genetics do better for psychology?

As Plomin points out, geneticists make two types of claim to explain the human condition. On the one hand, the group calling themselves evolutionary psychologists argue that it is possible to describe human universals, laid down as ‘human nature’ in the Pleistocene – for instance as supposed innate mental modules for everything from language to ‘cheat detection’ and love of green gardens. On the other, behaviour geneticists like Plomin are concerned with the putative genetic origins of individual differences, largely within the domains of cognition, personality and psychopathology. The general problem with this approach is its



Peer commentary by **STEVEN ROSE.**

naive belief first that such characteristics can be quantified, and second that their origins can be partitioned into dichotomous ‘genetic’ and ‘environmental’ components. It is on these assumptions that the calculation of heritability is then based.

The (widely misunderstood) heritability estimate is supposed to indicate the extent to which the variance of a trait in a

learn about the pleiotropic and contingent expression of real genes during development – a single gene having several different effects, or those effects being dependent on other genes for their expression – the more the assumption that their expression is simply an additive one becomes implausible. Gene expression changes depend both on the internal environment (including the other genes present in the organism) and the external one in which the organism develops. Nowhere are such complexities more clearly observed than in the huge proliferation of studies of transgenic animals that occupy so much current literature space in the world of real as opposed to paper genetics.

Finally of course, it is necessary to have some phenotype one can measure relatively unambiguously – like milk yield. In my view, heritability estimates are simply meaningless when applied to complex human behavioural traits, where none of these conditions apply (Rose, 1998; Rose *et al.*, 1984). This is why one gets implausible claims such as a significant heritability for ‘religiosity’ or ‘job satisfaction.’

Plomin’s own example, of ‘general cognitive ability’ – Spearman’s famous (or infamous) *g* – makes my point for me. Psychologists themselves are deeply divided over whether there is such a unitary character. According to a meta-analysis of twin studies of IQ stretching back to the 1960s, which my colleagues and I are currently conducting, even different IQ tests give widely different heritability estimates, which casts some doubt on the validity of *g* as a universal measure.

In any event, neuroscientists have little time for such a universalising measure. However difficult it may be to define

ADY COUSINS

It is necessary to have a phenotype that one can measure relatively unambiguously

population is a product of genetic rather than environmental effects. However, the mathematics on which it is based, worked out originally by Fisher in the 1930s, assumes that the two factors, genetic and environmental, are almost entirely additive, with little interaction between them. It was originally employed in agriculture to study traits such as crop or milk yield, in which different genotypes could be distributed experimentally across standard environments, and the equations are such that the estimate itself changes when the environment changes.

Human environments are of course very far from standard, and are continually changing in complex ways we scarcely begin to understand. Further, the more we

intelligent behaviour (and still more to make it context independent: see Richardson, 1999), such behaviour, even when reduced to answering IQ type questionnaires, must be a product of a multitude of processes, which we try to study independently in our labs. These may include attention, arousal, perception, affective and cognitive memory, learned skills and many others. All of these neurobiological and physiological attributes are of course in turn dependent on the developmental expression of a multitude of genes and biochemical processes, some of which have been identified. To bundle the whole lot together into a single index on which it is believed the entire population can be ranked arithmetically, as if intelligent behaviour were as straightforward even as height (which is complex enough), is a fallacy of psychometrics that it is high time we grew out of.

Plomin's article concludes with an expression of hope that psychologists will come to recognise that DNA stands for deoxyribonucleic acid and not for 'did not arrive'. I share that hope (and also that *g* will also take its proper place as the

physicists' abbreviation for the gravitational constant and not for a statistical text artefact within psychometrics). But it is also important – and not just for psychologists – that we recognise the need to locate DNA's proper biological place in the scheme of living systems. It is not the be-all and end-all of biology. It is indeed difficult to imagine any context in which knowing the heritability of IQ will be of the slightest use to a psychologist engaged in either clinical practice or meaningful scientific research.

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Genes really do matter

GIVEN the wealth of evidence that 'genes really do matter', Plomin is right that psychologists must consider the role that genes play in the complex development of human behaviour. We fully endorse Plomin's argument that genes influence both normal and abnormal behaviour, and that for some behaviour there is evidence of a genetically influenced continuum between normal and abnormal. An example of this is childhood hyperactivity, where twin research has shown that the contribution of genetic influences on extreme symptom scores is highly similar to that for normal scores (Thapar *et al.*, 1999).

Genes and the environment

Many psychologists may assume that family risk factors, such as parental psychopathology, represent environmental risks alone. However, twin and family studies have shown that although many traits and disorders cluster in families, much of this can be accounted for by genetic risk factors. For instance, parental criminality is known to be a significant risk factor for the development of childhood conduct disorder. Early research assumed the familial transmission of antisocial behaviour was primarily due to shared environmental adversity; twin and adoption research now suggests that genetic factors also play an important role (Rutter *et al.*, 1999).

Nevertheless, equal consideration must be given to the role of environmental factors when genetic influences are found. Plomin emphasises that genetic studies of psychopathology have consistently shown the important contribution of non-heritable influences, and of gene-environment interactions. Adoption studies provide a powerful methodological design to detect such interactions. For instance, an adoption study of criminality by Bohman (1996) found that when both a genetic risk factor (biological parent with a criminal history) and environmental risk factors were present, they accounted for a higher rate of criminality amongst adoptees (40 per cent) than the combination of these two factors acting independently (12.1 per cent and 6.7 per cent rate of criminality for adoptees at genetic and environmental risk respectively). Psychologists should note



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THAPAR and JANE HOLMES.

that adoption findings also suggest that environmental risks (e.g. adverse parenting) may exert minimal influence on the development and persistence of problem behaviours, unless they are accompanied by a genetic vulnerability (Rutter *et al.*, 1999).

Clinical implications

Plomin draws attention to the potential impact that genetic findings may have for clinical practice. There is already a need for clinical psychologists to provide clients with accurate, up-to-date information about the likely aetiological factors for specific disorders. Moreover, for highly heritable disorders such as autism, psychologists may be required to advise families on the likelihood of having additional children affected with the same disorder (i.e. risk to relatives). It is equally important to convey that even for highly heritable conditions such as schizophrenia and autism, genetically identical twins do not show 100 per cent concordance for these disorders (McGuffin *et al.*, 1994). Thus, genes must be regarded as risk factors that increase the probability of psychopathology, rather than acting in a deterministic fashion.

The potential impact of genetic research on the development of treatment methods is undoubtedly an exciting topic. Plomin successfully conveys optimism for genetics paving the way for new interventions. A more specific question concerns how quickly the identification of specific susceptibility genes will lead to the development of new and effective gene-based treatment strategies.

We need to be cautious in predicting the speed of this process. For example, for many single-gene disorders, such as Huntington's disease, specific genes have been successfully located for some time. However, genetic success has not yet led to the development of novel and effective treatments. Instead, the identification of specific genes has represented an initial

step on a long path to understanding aetiology and developing effective interventions.

Thus, for most psychopathology, there may be a time lag before the identification of specific susceptibility genes has an impact on the development of new, potent treatments. Clinicians need to be confident in communicating new genetic findings and explaining the implications to clients, some of whom may have unrealistic expectations of what the identification of a susceptibility gene means, in terms of treatment.

Importantly, Plomin highlights that a genetic basis to a condition does not necessarily mean that therapeutic interventions must be biologically based. It is essential that psychologists recognise that genetic methods provide powerful tools for unravelling genetic and non-genetic risk mechanisms, as well as protective factors. This is an important point for clinicians, given that the identification of risk and protective mechanisms for psychopathology is critical in providing an empirical base for designing effective intervention and prevention programmes. In short, optimism about the benefits of genetic research is warranted, particularly in the field of psychology, where interventions may be informed by an understanding of external risk processes rather than underlying pathophysiology.

Research challenges

All research encounters challenges to progress, and genetics is no exception. Nevertheless, the need for an increased integration of genetics with other research disciplines can only be of benefit in surmounting these challenges. Plomin points out that geneticists need to use carefully defined phenotypes. This is particularly important for genetic research in psychology, where phenotypes are primarily defined on the basis of reported symptoms, and thus likely to be more distal

from gene products, compared to some medical conditions (e.g. diabetes) that are defined on the basis of physiological measures (e.g. blood glucose levels).

A second challenge lies in the consideration and measurement of environmental influences. As Plomin has stated, it is essential that geneticists appreciate the role of environmental factors and that non-geneticists consider the importance of genetic influences. This is particularly important in the field of psychology, where relevant environmental influences are likely to be correlated with genotype (gene–environment correlation), and where genes and the environment may have an interactive effect (Bohman, 1996).

Finally, it is becoming increasingly apparent from molecular genetic studies that individual effect sizes for susceptibility loci or genes are small (Rutter *et al.*, 1999). This is the case for even highly heritable disorders such as schizophrenia and autism. Thus it seems most plausible that many complex, multifactorial disorders will be explained by the interactive effect of several genes together. Nevertheless, it is heartening that genetic findings have now been independently replicated for disorders

such as autism (Rutter *et al.*, 1999), schizophrenia (Williams *et al.*, 1996) and attention deficit hyperactivity disorder (Faraone *et al.*, 2000).

Conclusion

Plomin's article is important because it attempts to bridge the gap between genetics and psychology. Plomin emphasises the important contribution that genetic research makes to understanding human behaviour and highlights the potential impact that genetics may have on the future of psychology. Thus it is essential for psychology researchers and clinicians to

keep abreast of these research developments. We agree that genetics should increasingly be considered in mainstream psychological research and clinical work. Although, as for all research, we must strive to retain a critical attitude to interpreting and communicating research findings.

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Genotype or genohype?

WHILE controversy surrounds how useful gene identification and manipulation will prove to be in managing and preventing a significant number of behavioural disorders (Holtzman & Marteau, 2000), few psychologists would deny the role of genes in influencing behaviour. One application in clinical practice is likely to involve the use of DNA analyses to estimate vulnerability to a disorder. Individuals may therefore be given personalised information, based on analysis of their DNA and other risk factors, about the chances of developing a condition such as dementia or depression. But as Plomin points out, interventions to avoid or manage such complex psychological traits are likely to involve environmental rather than gene manipulation.

Providing risk information in order to motivate individuals to reduce their risks of health problems is not new, although the type of information given will be novel, namely based on DNA. There is now a large literature showing that the provision of risk information alone can be distressing (Shaw *et al.*, 1999) and is rarely sufficient to achieve behaviour change (Croyle, 1995).

Theoretically based studies in health psychology point to the importance of three key variables in motivating and achieving behaviour change: feeling personally vulnerable to a threat; belief that a behaviour will reduce that threat; and feeling confident that performing the behaviour is within the individual's control (Conner & Norman, 1996). There is now a small but growing body of evidence showing how these and other cognitions can be altered to achieve behaviour change (see e.g. Orbell *et al.*, 1997). Combining these with established behavioural techniques could lead to powerful methods of facilitating behaviour change following the provision of risk information. The first step in this is to understand the likely impact of DNA-based risk assessments on salient cognitions.

How individuals combine risk information from different sources seems to be key in influencing their perceptions of vulnerability. Motivation to change behaviour is also influenced by the representations of individual risk factors, in particular how controllable they are



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perceived to be. These points are illustrated below using examples from studies of physical health, where much of the work to date has been done.

Representations of gene-environment interactions

Envisage a future in which individuals are told their risk of developing schizophrenia, a risk estimate that is based on information derived from DNA testing and their environment. How will they integrate risk information from more than one source?

Do they, for example, combine them multiplicatively or additively? Recent studies suggest a sub-additive model is more common: that is, in the presence of a high level of one risk factor, information about another risk factor is to a large extent discounted (e.g. French *et al.*, 2000; Hermand *et al.*, 1995). For example, smoking amongst heavy drinkers was erroneously seen to be no more harmful than either being a heavy smoker or being a heavy drinker. In another study, a hypothetical individual was perceived as being at similar high risk for a heart attack either with a family history of heart disease or as a smoker or with both risk factors (French *et al.*, 2000).

These results may reflect how

judgements about risk are made, namely with reference to only one strong risk factor. Alternatively, they may be an artefact of the methods used to elicit such judgments. Further work is needed on methods of eliciting representations of multiple causes of conditions in order to develop effective ways of communicating such information.

How are different risk factors weighted? Is a genetic risk given greater weight than risks derived from other sources or vice versa? Some have argued that learning of a genetic risk should increase motivation to alter the environment to reduce the risk. Recent evidence suggests that it does not have this effect. For example, smokers informed that they had a genetic susceptibility to lung cancer were no more likely to quit smoking than those not so informed (Audrain *et al.*, 1997).

Not only may genetic risk information not motivate behaviour change, it may indeed have the opposite effect of discouraging behaviour change. In an analogue study, participants who imagined they had an increased risk of arthritis or heart disease following a DNA-based risk assessment perceived the condition as less preventable than those who had undergone an unspecified blood test to assess risk (Senior *et al.*, 1999b). Reasons for this may lie in the representation many people have of genes.

Representations of genes

There is a strong representation in Western cultures that the term genetic in relation to health and illness is synonymous with something fixed or unchanging (Marteau & Senior, 1997). For example, when a screening test for inherited risk of heart disease was seen as detecting a genetic problem, the condition was perceived as less controllable. By contrast, those who perceived the test as detecting raised cholesterol perceived the condition as dietary in origin and hence more controllable (Senior *et al.*, 1999a).

DAVE ROBERTS

Smoking amongst heavy drinkers was erroneously seen to be no more harmful than either being a heavy smoker or being a heavy drinker

Plomin expresses frustration at the apparent determinism that people associate with genes, suggesting that this is largely based on misunderstanding. Such apparent determinism may reflect a prototype for 'genes' or 'genetic traits' based on traits that largely defy environmental influence, such as the physical characteristics of eye and hair colour. Behavioural genetics challenges this meaning. A challenge for health psychology is to determine how such a prototype can be revised to incorporate mutability.

Plomin rightly calls for psychologists to be prepared to maximise the benefits and minimise the risks that will emerge from DNA research. Health and clinical psychologists, however, are most likely to achieve this not by studying genetics, as Plomin suggests, rather by developing further their traditional strengths of describing, predicting and changing behaviour, albeit in the context of risks defined by DNA. Science policy, with its emphasis on genetics, needs a corresponding emphasis on psychological research into risk presentation and behaviour change

to realise the clinical benefits of genetic investments.

Plomin argues that it is critical to the future of psychology that for all psychologists DNA denotes deoxyribonucleic acid rather than 'did not attend'. DNA should of course hold a double meaning for psychologists and until such time as social inequalities and other

environmental risk factors become trivial forces, psychologists would do well not to forgo the behavioural meaning of the term.

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How will we actually use this map to find our way?

AS a geneticist myself, I wholeheartedly endorse Plomin's closing sentence about DNA. Geneticists are in gung-ho mood at the moment. With the recent publication of the complete DNA sequence of two human chromosomes (Dunham *et al.*, 1999; Hattori *et al.*, 2000) and the entire human sequence just around the corner, we are indeed the cartographers of the new millennium. The human gene map will provide major new opportunities in psychological research, as in every aspect of biological science. But what will be the *practical* benefits of this deluge of genetic information?

Over the past 20 years, geneticists have been astonishingly successful at pinning down the molecular lesions (mutations) that underlie many monogenic diseases, for example thalassaemia, cystic fibrosis, Duchenne's muscular dystrophy and Huntington's disease. Many of these diseases result from simple deficiency of



Peer commentary by **ANDREW WILKIE**.

a single protein. They are inherited in a mathematically predictable fashion and are essentially deterministic – if you inherit the mutation, you get the disease. Finding the causative mutations has transformed diagnosis and provided new options for prenatal and pre-implantation genetic testing.

Yet these discoveries have had remarkably little impact on treatment. Despite the fact that many of the deficiency diseases would be cured if only a small amount of the correctly functioning protein could be put back into the appropriate cells, it has generally proved extremely difficult to achieve this using either protein or gene therapy. The human body contains far more cells (some 100,000 billion) than a cell contains nucleotides of DNA (a mere 6 billion); the problem of delivering the correct protein to the correct cells without harmful side-effects is a correspondingly formidable one. Sadly, Plomin's counter-example of the successful dietary treatment of PKU (which long pre-dates identification of the mutant gene) really is the exception rather than the rule.

Spurred on by their success in identifying the causes of monogenic disorders, geneticists have for the past 10 years increasingly turned their attention to the polygenic/multifactorial conditions, which involve a complex interplay between multiple genetic and environmental determinants. The initial focus has been on many of the common killers in developed countries (heart disease, diabetes, dementia, etc.), but the same approach is applicable to any aspect of normal human variation, including behaviour.

Plomin mentions the two approaches that can be used to identify the genetic determinants. The 'bottom-up' approach is best exemplified by cardiovascular

research, which has led to a rather sophisticated appreciation of the tremendously complex interplay of multiple genetic factors (influencing lipid levels, blood pressure, pharmacological response) and environmental factors (diet, smoking, exercise) leading to heart disease. This field of research provides many cautionary lessons that merit wider appreciation (Ellsworth *et al.*, 1999).

Unfortunately, the geneticists themselves have consistently underestimated the difficulties of applying the alternative 'top-down' approach to complex traits (advocated by Plomin). As stated in a recent review, 'genetics has yet to make a significant impact on the disorders that fill hospital beds and clinics' (Wright *et al.*, 1999, p.397).

Of course, there have been some successes (association of ApoE with late-onset Alzheimer's disease, genetic linkage in reading disability), which Plomin naturally focuses on. The ApoE/Alzheimer association (discussed below) in particular has spawned an entire research industry, and is certainly contributing new ideas on the pathogenesis of dementia. But it must be emphasised that these positive findings represent the tip of a very large iceberg of negative, dubious or unreproducible results. Some of Plomin's other examples are still very contentious. Genetic associations with aspects of behaviour such as novelty-seeking and homosexuality have been questioned (Paterson *et al.*, 1999; Wickelgren 1999); and the suggested association of *g* with loci on chromosome 4 is at this stage simply a statistical finding of uncertain biological significance.

Let us take a closer look at the ApoE/Alzheimer association, which provides the best concrete example for thinking about the strengths and limitations

of identifying susceptibility loci. The robustness of this association, in contrast to most others reported to date, implies that the contribution of this locus to overall disease variability (around 10 per cent) will prove to be greater than is usually the case for complex traits. Yet despite these relatively large statistical effects, the ApoE genotype currently has little or no medical application: the sensitivity and specificity for predicting future risk in healthy individuals is simply not high enough.

It has been calculated by Seshadri *et al.* (1995) that the high-risk allele 4 variant is only present in 56 per cent of people with Alzheimer's disease; and that 71 per cent of people with one allele 4 never develop Alzheimer's disease. Even when applied to people with overt dementia, the added value of ApoE genotyping for discriminating those cases caused by Alzheimer's disease is relatively modest (Mayeux *et al.*, 1998).

The discovery of effective preventive measures would increase the attractiveness of ApoE genotyping to identify those at higher risk. But such prevention, possibly requiring decades of compliance, would have to be extraordinarily safe to justify the fact that about 70 per cent of individuals undergoing the preventive regime would never even develop the disease.

Although it is argued that the identification of additional susceptibility loci in Alzheimer's and other diseases will increase the power of predictive tests, this will require an understanding of how the loci interact. In other words, is the combined risk multiplicative, additive, unchanged or even reduced? Huge sample sizes (tens of thousands) will be required to obtain the various combinations of genotypes in sufficient numbers to answer these questions: expensive, but in theory ultimately feasible. But as the monozygotic twin concordances (generally approximately 50 per cent, as stated by Plomin) confirm, even the complete

understanding of all genetic factors and their interactions would still yield a predictive power well below 100 per cent.

It follows that even a complete description of the genetic variation affecting a complex disease or behaviour will not usually be deterministic. But this is not to say that the information would not be misinterpreted or misused. One example is the widespread shorthand reference to genes 'for' a condition, subliminally implying determinism, when the locus actually contributes only a small percentage of variance (if at all). Another is the potential use of genetic testing by insurance companies or unscrupulous political powers to discriminate groups of individuals at differing average risk.

To conclude, Plomin is correct that we are on the cusp of a research revolution. This will open up many new avenues for psychological enquiry and many academics will make their names based on it. But please, let's try to be a bit less sanguine about where this will lead us in terms of practical benefit. In psychology, one can envisage huge tables charting the statistical associations of specific gene variants with particular behaviours; in medicine, some modest improvements in diagnosis, treatment and prevention. Concurrently, we need to be constantly sensitive to the potential adverse consequences of generating this information.

Finally, I have some practical advice for anyone contemplating this kind of work: don't rely on cheek swabs as your source of genetic material! The complexity of the undertaking is such that your DNA bank will run dry long before you have solved the research questions that interest you.

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Genetics

Response to peer commentaries

ROBERT PLOMIN *replies and invites your comments.*

I AGREE completely with the commentaries by Jonathan Flint, Theresa Marteau, and Anita Thapar and Jane Holmes.

Andrew Wilkie urges caution in expecting too much too soon in terms of the practical benefits of DNA research. Martin Richards says that DNA research is not going to provide any instant solutions to old problems. Who said it would? All I was trying to say was that psychologists should be prepared to use DNA in their research when genes associated with behaviour are identified. In terms of clinical psychology, I said that DNA may eventually lead to gene-based diagnoses and treatment programmes, that the most exciting potential for DNA research is secondary prevention, and that interventions are likely to involve environmental engineering rather than genetic engineering.

A minor point is that I disagree with Wilkie's closing remark that you should not rely on cheek swabs as a source of DNA. If you study patients in hospitals where blood is easily obtained, by all means use blood because it yields more DNA than cheek swabs. However, if blood is not easily available, cheek swabs are so much less invasive than drawing blood and

provide enough DNA for thousands of DNA markers.

Richards and Steven Rose still have trouble with heritability. Heritability is merely an effect size indicator. In psychology, genetic effects are not merely statistically significant—they are often substantial. Genetic effects sometimes account for as much as 50 per cent of the variance of psychological traits.

Richards uses breast cancer to argue that heritability estimates can mislead. His argument is that two genes have been found that are associated with breast cancer even though the heritability of breast cancer is low. My view is that breast cancer is a good example of why heritability estimates are important as a first step in understanding a disorder.

Breast cancer is talked about these days as if it were a genetic disease, yet it yields one of the lowest identical twin concordances in the medical literature. Concordance is only about 10 per cent for identical twin females and only slightly lower for non-identical twins, indicating very low heritability. The identical-twin concordance of about 10 per cent means that for 90 per cent of cases in which one identical twin has breast cancer, her twin clone does not. There can be no genetic

explanation for this 90 per cent discordance for identical twins. The rare type of early-onset and severe breast cancer associated with the BRCA1 and BRCA2 genes probably accounts for most of the meagre heritable influence found for breast cancer. The critically important message from finding such a low heritability for breast cancer is that the vast majority of breast cancer is caused by non-genetic factors.

In contrast, autism is an example of a disorder that had been thought to be environmental in origin. However, twin studies consistently showed that autism is very highly heritable. This finding of high heritability has had a major impact on research in this area and has led to several large-scale efforts to identify some of the genes that contribute to susceptibility to autism.

Rose also tries to argue that estimating genetic effect sizes fails because psychologists cannot measure behaviour, whereas biological phenotypes such as milk yield can be measured 'relatively unambiguously'. In contrast, I would argue that because behaviour is so difficult and complex, psychologists have paid much more attention to measurement issues than biologists. Nearly every time I have tried to use biological measures in my research – such as cortisol assays and blood alcohol curves – I have been struck by their questionable reliability and validity. Rose singles out general cognitive ability for his scorn; but in my view its reliability, validity and heritability are beyond reasonable doubt.

As I indicated in my article, asking whether and how much genetic factors affect behavioural traits are important first steps in understanding the origins of individual differences, even for areas such as economics, education, and sociology that are still essentially untouched by genetic research. However, these questions are only a beginning – genetic research strategies can take us far beyond heritability. This was my major theme, and I mentioned several examples, such as the distinction between shared and non-shared environment, the aetiological links between the normal and abnormal, developmental change and continuity (developmental genetics), the relationship between disorders (multivariate genetics) and the interplay between nature and nurture (genotype–environment interaction and correlation). Identification of specific genes associated with behavioural traits will increase the precision of our research on each of these issues.

WHAT DO YOU THINK?

Professor Robert Plomin would appreciate hearing from the wider psychological community with their views on such issues as:

- What do you think about using the twin and adoption methods as a rough screen for genetic influence on individual differences in behavioural traits?
- In the domains of psychopathology, personality and cognitive abilities, what do you think about the twin and adoption study evidence for significant and substantial genetic influence?
- What do you think about twin and adoption evidence for the importance of non-shared environmental influence?
- What do you think about the evidence for the 'nature of nurture'?
- What do you think about attempts to identify specific genes associated with behavioural traits?
- If specific genes are found that are associated with behavioural traits, do you think that they will be useful in psychological research ('behavioural genomics')?
- What are your concerns in relation to the clinical and social implications of quantitative genetic and molecular genetic research?

Please write to Robert Plomin at r.plomin@iop.kcl.ac.uk. *The Psychologist* would also be interested to hear your comments through the letters pages.