Not in Your Genes—Time to Accept the Null Hypothesis of the Human Genome Project?

Oliver James

Introduction

The hypothesis of the Human Genome Project (HGP) was that differences in genetic material contribute significantly to explaining why one individual is more likely to possess a trait than another. This would be tested by comparing groups. For example, when 10,000 people suffering from major depressive disorder are compared with 10,000 who do not qualify for this diagnosis, the HGP hypothesises that there will be differences between the two groups in a single gene*, or groups of genes, or in numerous tiny variations in genetic material, that explain a significant (usually regarded as greater than 20%) amount of the reason (known as variance) why one group is depressed and not the other. Replicated in other samples, the HGP expected to establish reliable genetic causes of traits like depression: specific differences in genetic material that were proven to directly contribute to such traits to a significant extent.

The null hypothesis of the HGP is that differences in genetic material play little or no role in explaining why one individual is more likely to possess a trait than another.

It is a little known fact outside the world of those directly concerned with molecular genetics, that, so far, the HGP has been unable to identify genes, groups of genes, or small variations in genetic material, that explain more than a tiny proportion of why two groups differ in any psychological respect at all. This applies whether it be depression, schizophrenia, anxiety disorders, or any other mental illness. The same is true of mental abilities and of personality. In all cases, genes explain only about 1–5% of the variation (Plomin &Simpson, 2013). As Robert Plomin, one of the leading figures in the field, put it during an interview

*A brief glossary of basic molecular genetic terms is included at the end of this article, asterisks are used to indicate when a term is defined in it.

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with Peter Wilby (the respected ex-editor of *The Independent* newspaper) in the *Guardian* newspaper in 2014, "I've been looking for these genes for 15 years and I don't have any" (Wilby, 2014).

Although the reader might find it hard to believe, it is completely uncontroversial—an established and oft-repeated fact within the scientific literature—that, so far, genes identified by the HGP explain only 1–5% of the variance between groups for psychological traits of all kinds. This assertion is not an interpretation of the evidence, it is accepted as fact by virtually all scientists working in this field.

The debate concerns whether the HGP will discover genetic differences explaining more of the variance in the future. So far, to put it bluntly, the HGP has proved that genes play virtually no role in explaining our psychological differences. Precisely at what point the principal scientists in the HGP will accept its null hypothesis is an interesting issue.

The main empirical evidence upon which the HGP hypothesis was based were familial studies of twins and to a lesser extent, adoptees. For example, twin studies find heritabilities of 50% or more for many major mental illnesses, like schizophrenia and bipolar disorder (Kendler, 2001). They also do so for scores on tests of intelligence (Deary, Johnson, & Houlihan, 2009).

Because there is such a yawning gulf between twin study findings and those of the HGP, rather than simply accepting the null hypothesis, researchers have dubbed the absence of significant findings "missing heritability". Ignoring the many strong reasons to doubt the scientific validity of twin studies (James, 2005; Joseph, 2013), the researchers obtained grants to examine larger samples in order to identify this putative absence. When study after study (and there have been hundreds) continued to find virtually no genes explaining significant amounts of variance in traits, hardly any of the researchers even considered the possibility that the heritability was not missing, it simply does not exist—although there have been a handful of exceptions (e.g., Sonuga-Barke, 2010).

As methods for studying differences in genetic material became faster and cheaper, they were able to test for differences at greater and greater numbers of genetic locations. The latest technology can search millions of different locations on each individual's genome, in samples of many thousand. On top of that, scientists started to pool their findings, to create larger samples.

While they have managed to find some differences in sequencing of DNA* between groups for some illnesses, these differences are unable to explain more than a tiny amount of the variance in illnesses. For example, a recent study examined the genes of 150,000 people, of whom 36,989 had been diagnosed with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). This is a huge sample. The study identified 108 genetic locations where the DNA sequence in people with schizophrenia tended to be different from those without the disease. Yet, taken together, the total variance

which these differences in DNA sequence explained was a paltry 3.4%. An important proviso about this study is that a considerable number of the genetic locations in the study had not been replicated: again and again, studies have purported to find new locations that subsequently turn out not to replicate.

Remarkably, this study was heralded on the BBC *Today* programme as "a huge breakthrough" (BBC *Today* Programme, 2014). Taken at face value, it could be suggested that the study proved that 96.6% of the difference between schizophrenics and non-schizophrenics is non-genetic. If the study was indeed a huge breakthrough, it was because it proved that schizophrenia is almost completely not caused by genes, the exact opposite of the way in which it was portrayed by the BBC.

In this paper, I shall first provide a brief survey of the findings of the HGP regarding mental illness to date. I will then summarise the areas of research that are still held to be promising in establishing a role for genetics in causing mental illness. I will briefly consider the implications of the HGP findings for twin studies and offer an alternative interpretation of their supposed findings of high heritabilities. I will end by considering what will be accepted as evidence for the null hypothesis of the HGP.

The findings of the Human Genome Project for mental illness

Only a few years after the announcement of the mapping of the human genome in 2000, leading figures in the field stated emphatically that they had already established that single "genes for" psychological traits did not exist. With the HGP results about to be published, in 2000 Robert Plomin had predicted that "within a few years, psychology will be awash with genes associated with behavioral disorders" (Plomin & Crabbe, 2000). For decades Plomin had been predicting genes, or groups thereof, for specific mental illnesses (and for intelligence) in highly influential scientific papers and textbooks for students (Plomin, 1990). His colleague at the Institute of Psychiatry, Peter Mcguffin, had been equally emphatic about genes for schizophrenia (e.g., Plomin, Owen, & Mcguffin, 1994).

By 2003, based on the complete absence of any such genes having emerged from early HGP studies, both had admitted they were wrong in expecting groups of "genes for" common traits and that the truth was there would be a very large number of tiny variants, each contributing small effects. Only extremely rare disorders would be caused by monogenic, Mendelian genes. For example, in 2005, Plomin and colleagues pronounced that "Common disorders of the sort seen in child psychology and psychiatry . . . are likely to be caused by multiple genes of varying but small effect size" (Harter et al., 2005).

The hunt was on for large numbers of tiny parts of genes, rather than groups of genes, associated with specific mental illnesses. The small effects of each little

difference would, together, amount to similar heritabilities to those found in twin studies, it was believed. The method for finding them was called Genome Wide Association (GWA) studies, an atheoretical genetic fishing trip. Instead of starting from the assumption that specific candidate genes would explain differences, researchers started looking for any kind of difference across massive numbers of locations in large samples of people. In 2009, Robert Plomin was bullish about the prospects for GWA studies: "Conceptual advances . . . have led to a revolution in molecular genetic research: genome-wide association . . . In just a year's time, GWA studies have come to dominate the gene-hunting literature" (Plomin & Davis, 2009).

There are some three billion base pairs* on the double helix of the DNA of each individual, of which 99% are the same from person to person. The 1% difference is the focus of GWAs. One source of gene variance of particular interest was single-nucleotide polymorphisms (SNP*), entailing an inherited mutation in one nucleotide. At first GWAs targeted hundreds of thousands, and subsequently millions, of gene locations to see if they could find SNPs that correlated with particular mental illnesses.

An alternative target for the fishing trip was copy number variants (CNV*). A CNV is where there has been duplication, insertion, or deletion of stretches of DNA base pairs. These CNVs are mostly not inherited, developing independently of the genes that were passed on from parents. In fact, all of us have CNVs spread around our DNA, up to and including the absence of whole genes, usually without any discernible consequence. CNVs could not be a major way of identifying genetic inheritance of mental illness, but they might be locations of genetic material differing between the ill and the well.

As techniques became more sophisticated and cheaper, and researchers increasingly pooled their results, larger and larger samples became available, especially in the last five years. In due course, numbers of both SNPs and CNVs were found to be associated with many mental illnesses (Plomin & Simpson, 2013). But individually, the variants explained only miniscule amounts of heritability. When their effects were added all together they continued to explain very little. This cannot be stressed enough: added together, the polygenic findings of GWAs studying SNPs and CNVs continue to be able explain no more than 1–5% of differences in psychological traits, despite the major investment in large samples (Plomin & Simpson, 2013).

Psychiatrists were excited to find that most SNPs and CNVs that were associated with schizophrenia were also associated with bipolar disorder. Some of those clusters of both SNPs and CNVs have further been found to overlap in people with major depression, autism, and attention deficit hyperactivity disorder (ADHD). Leaving aside the crucial fact that these clusters provide tiny heritability estimates for any of these mental illnesses, even if the clusters were proven to be more than merely "noise" from a large fishing trip, it has been pointed out that they seem to

undermine the notion of discrete, biologically based illnesses that underpins the *Diagnostic and Statistical Manual* of mental illnesses. If all people with numerous major mental illnesses share the same genetic variants, where does that leave the idea of discrete diagnoses of biologically based particular "illnesses"?

In fact, recent formulations by leading psychiatric scientists suggest that there are no genes that are unique to people with mental illnesses. For example, Kenneth Kendler, perhaps the most highly regarded such psychiatrist, states that

> The efforts to ground a categorical model of schizophrenia in Mendelian genetics have failed. The genetic risk for schizophrenia is widely distributed in human populations *so that we all carry some degree of risk*. (Kendler, 2014, my emphasis)

If that is true, it is difficult to see in what sense particular genes are the cause of schizophrenia in one person but not in another.

The scientists continue to argue that they need ever-larger samples in order to identify what they assume to be hundreds or thousands of tiny differences in nucleotide sequences that will eventually make up the missing heritability. Because whole-genome sequencing will become feasible and affordable for each individual before long, it should be possible to establish definitively what combinations of sequences are associated with which traits, and what contribution they make to them, if any. The scientists believe that when cheap enough technology is available to scan all of the three billion nucleotide base pairs in large samples of people, the genetic truth will out. They now tend to believe that, rather than there being clusters of genetic profiles for specific traits, the profiles will be for a variety of interrelated psychologies—a proneness to a variety of mental illnesses overlapping with a variety of mental capacities and personality traits. In this Brave New World, the geneticists continue to dream of the day when all newborns are routinely given a genome-wide scan in order to help advise parents on which kind of environment to provide, physically and emotionally (Plomin, & Simpson, 2013, p. 1274).

So far, the HGP has proved the extreme improbability of such a scenario, because it has been wholly incapable of demonstrating a significant relationship (explaining beyond 1–5% of the variance) between any patterns of specific DNA variants and any particular psychological traits in the parts of the genome that would be at all likely to prove this, or any other. They have already searched in most of the places that significant effects would be expected to be found (the 2% of the genome that codes for the proteins that cause amino acid metabolisation). They are now beginning to clutch at straws.

The only way in which scientists have managed to extract significant heritability estimates from the data has been to give up altogether on the idea that any particular genes are linked to any particular outcomes. Genome Wide Complex Trait Analysis (GTCA) was developed when it became increasingly clear that significant effects were not going to emerge from the conventional model, where

specific gene variants should have direct effects. GTCA looks for the average impact of genes in a group of people on a trait, without identifying any specific DNA variants that explain it. Using elaborate mathematical formulae, it compares how different the variants are in one sample, overall, with the overall pattern in another. By this means, it has been possible to extract significant heritability estimates for mental illnesses (and other traits, like personality, political beliefs, and economic behaviour), although these are rarely more than half those found in twin studies (Plomin & Simpson, 2013). These findings often remain to be replicated—repeated in studies using the same method—and have already drawn a blank in a large and telling study of psychopathology in children (Trzaskowski, Dale, & Plomin, 2013). There are also suspicions that the results will not stand up when they are done on different populations.

Because the GTCA method does not demonstrate that specific genetic variants reliably cause differences it is of no practical use and it is not a test of the main HGP hypothesis. That its heritabilities are half or less of those of twin studies is suspicious, although attempts have been made to explain this (Plomin & Simpson, 2013). It is interesting that GTCAs are rarely used in the introductory or discussion sections of scientific papers to support the contention that genes are a significant cause of mental illness. Perhaps this is because the scientific community knows that GTCA studies will prove to be a red herring.

A final area which some geneticists hold out hope for is the "dark matter" that makes up 98% of the genome. Only 2% of DNA is in a gene's "coding region", the portions of gene that code for proteins. Until the HGP, it was believed that the "junk DNA" of dark matter played no role in affecting what we are like. Since then, studies in mice and other mammals have suggested that the dark matter may affect the transcription* of DNA into RNA (Pennisi, 2012). In doing so, they could have an effect on how DNA is expressed, including, in theory, vulnerability to mental illness. To date, there is no solid evidence that this is so, it is primarily a hypothesis.

It may be seen from this brief review that the HGP findings might lead a truly independent scientist to incline towards acceptance of the null hypothesis: that genetic variations play little or no part in explaining individual differences in human psychology. If the whole-genome sequencing studies continue to find only 1–5%, it is hard to see where the scientists will be able to turn in order to avoid that conclusion. However, there are two areas that some scientists still hold out hope for.

Remaining areas of research that some believe could identity missing heritability: gene-environment interactions

Although GWAs have been the main method for finding missing heritability, there have also been attempts to look for gene-environment interactions where

candidate genes have been identified. These are specific genes, or parts thereof, associated with particular traits, in which the genetic variant is supposed to create a vulnerability whose fulfilment depends on environmental factors.

The most promising of these seemed to demonstrate that certain variants of the 5-HTT gene created vulnerability to depression when combined with childhood maltreatment (Caspi et al., 2003). People with a functional polymorphism in the promoter region of the serotonin transporter gene (5HTT) possess one or two short alleles associated with lower transcriptional efficiency of the promoter than those with one or two long alleles. The study found that those with one or two copies of the short version who were maltreated as children, or who had suffered stressful life events, were more likely to be depressed. The relationship between the possession of the short alleles and depression was linear: having one short allele increased the risk, having two increased it even more, having one long allele reduced it, having two did so even more. Most startlingly of all, people with two long alleles who were severely maltreated were at no greater risk of depression than those with two long alleles who were not maltreated: two long alleles meant degree of maltreatment made no difference to risk of depression, for depression to occur you needed to possess one or two short alleles. One short allele combined with severe maltreatment increased the risk by half, and two short alleles doubled it.

These dramatic findings inspired a flurry of further studies, some of them epidemiological.

At the simplest level, it might be assumed from the theory that groups of depressed people would be more likely to have more of the (depression-conferring) short alleles than the undepressed. This was quickly shown not to be so in large samples (Lasky-Su, 2005; Mendlewicz et al, 2004). An international study compared presence of the short alleles in nations with high and low prevalence of depression, finding that, if anything, there was more likelihood of short alleles in the relatively *undepressed* nations (Chiao & Blizinsky, 2009). Interestingly, while the short allele did not predict depression, degrees of individualism or collectivism of the society did.

However, it can be objected that such epidemiological studies do not directly address the gene-environment interaction that was proposed by Caspi and colleagues (2003). This was examined in a review of the fourteen best studies to date. It found that the short allele combined with stress did not increase risk for depression (Risch et al., 2009). An attempt was made to re-evaluate the evidence for several gene-environment interactions, not just the 5-HTT serotonin transporter (Belsky et al., 2009). It maintained that genetic variants should be understood as making people both more likely to be upset by adversity and to benefit from supportive experience. This made better sense of the existing evidence, it was argued. However, in 2011, a study was published reviewing the 103 gene-environment studies published between 2000 and 2009 (Duncan &

Keller, 2011). This found that only 27% of attempts to replicate initial findings proved positive.

Overall, the case for gene-environment interactions is weak in the light of so many studies that do not replicate original findings. What is more, for all kinds of illness, physical as well as mental, when candidate genes are tested in GWAs, they mostly do not emerge as significant (Siontis, Patsopoulos, & Ioannidis, 2010). This study reviewed them in 100 GWA studies and came up with very little.

A final area that has attracted a great deal of interest is that of epigenetics. This is the theory that environmental experiences cause the release of chemicals that either activate or suppress certain genes. There is some evidence that this pattern of chemicals can be passed down the germline to the next generation, although most of the evidence for this is in experiments performed on non-human mammals (Roth, 2014).

It should be stressed that epigenetics cannot solve the missing heritability problem. It is essentially a mechanism by which the environment causes outcomes through activation or suppression of genes. For example, there is considerable evidence for hypermethylation* of key genes in adults who were abused as children and have developed psychiatric conditions (Roth, 2014, p. 1281). Methyl is a chemical group that can inactivate genes.

Contrary to some of the claims made for epigenetics, it is not evidence for the argument that psychiatric outcomes are caused by both genes and environment, the "bit of both" theory. In the epigenetic studies, it is primarily the presence of childhood maltreatment or adult stress that is the causal factor, not variations in genes. As such, it is an account of how maltreatment or stress can affect outcomes, a mechanism no different in kind from the considerable evidence that these adversities can cause changes in key neurotransmitters or hormones. For example, cortisol regulation is strongly affected by adversities, resulting in psychiatric problems (e.g., reviewed by Hunter, Minnis, & Wilson, 2011).

Taken overall, gene-environment theories are highly unlikely to solve the missing heritability problem. No candidate genes have been unequivocally shown to interact with childhood maltreatment or stress to be a major cause of mental illness. Epigenetics is not a theory that could explain missing heritability.

A reinterpretation of the results of twin studies in the event of acceptance of the null hypothesis of the HGP: twin studies' "heritability" is shared environment (THISE)

Molecular geneticists continue to believe that the HGP may discover significant effects of genetic variation on mental illness through whole-genome sequencing studies. Within a very few years we shall find out if they are right. Given the findings of GWAs so far, there is good reason to doubt that they will be.

Let us suppose that no further significance is revealed and the null hypothesis of the HGP is accepted. In that eventuality, how would we interpret the findings of high heritabilities in twin studies?

Numerous studies of twins have concluded that half or more of important traits, like intelligence, major depression, schizophrenia, and bipolar disorder, are heritable (James, 2005; Plomin, 1990). Lower heritabilities are found for minor depression, anxiety disorders, and personality traits, in the range of 10–30% (James, 2005; Plomin, 1990). These twin studies are the primary scientific foundation for the belief that genes are a major cause of individual differences. The positing of a missing heritability is based on them (Plomin & Davis, 2009).

If the HGP null hypothesis were to be accepted, then it would be necessary to re-evaluate the findings of twin studies. All scientists accept that direct evidence from measurement of the genome is much more reliable than the indirect evidence of twin studies. Writing in 2009, Robert Plomin stated that "The future of genetics belongs to molecular genetics . . ." (Plomin & Davis, 2009). If the HGP null hypothesis were accepted, it would have to be further accepted that the heritabilities of twin studies are suspect at best, or more likely, simply incorrect.

For example, the much-publicised results of the Thomas Bouchard's study of twins reared apart would begin to look highly suspect (Bouchard et al., 1990). Indeed, grave doubts have been cast on the reliability of Bouchard's methods and of his findings (see James, 2005, Appendix 1). He and his colleagues would have to permit independent scrutiny of their data, something Bouchard has refused (Wright, 1997), an unfortunate refusal in the light of the history of deception in this area of research (Macintosh, 1995).

That twin studies turn out to be incorrect in their assessment of heritability would come as no surprise to longstanding critics of the method (James, 2005; Joseph, 2004, 2006). They maintain that flaws in the method exaggerate the role of genes, or that it is simply impossible to estimate heritability using this method. What is more, closer inspection of the twin method offers an intriguing alternative view of what their results demonstrate, one other than heritability.

The twin study method compares the degree of concordance (similarity) for a trait between samples of identical twins and same-sexed, non-identical twins. Whereas identical twins have identical genomes, non-identical twins have only half their segregating genes in common. If the identical twins are more concordant than the non-identical twins, it could be that this difference is caused by the differing degrees of genetic concordance. However, this requires an assumption, known as the equal environments assumption (EEA): that identical and non-identical twins are as likely to be treated similarly by parents, carers, and other significant people in their environment. If the identical twins are treated more similarly, then greater similarities in traits could be caused by that environmental influence, rather than genes. Breaching of the EEA would make it impossible to disentangle shared environmental effects and those of genes.

As Joseph (2013) has fully documented, from the 1960s onwards most scientists accepted that the EEA was, indeed, false: identical twins *are* treated more similarly than non-identical twins. This is unsurprising, given that they look the same, are often dressed similarly, have the same haircut, and so on. However, twin researchers maintained that this breach of the EEA did not disqualify the method, for two reasons (discussed by Joseph, 2004, 2006, 2013).

First, they maintained that genetic similarities in the psychology of identical twin psychology cause parents and others to respond to them more similarly; it is not just a matter of their physical similarity causing the more similar treatment. For example, children born with a sunny or grouchy disposition might cause positive or negative responses to them. It is held that their, allegedly genetical caused, more similar psychology causes them to choose more similar environments, which in turn creates greater concordance. Children both born with high or low aptitude to sport, for example, would consequently be more or less likely to be engaged with sporting environments, with all the feedbacks that would entail.

Second, it was maintained that, although the identical twins do have more similar treatment, that treatment is not necessarily more similar for environmental factors relevant to outcomes of particular traits being studied. For example, persons diagnosed with schizophrenia are three times more likely to have suffered childhood maltreatment (Varese et al., 2012) but that does not mean identical twins are necessarily equally likely to be subjected to it, so genes could still be the primary cause of that illness.

Joseph (2013) provides compelling evidence and arguments for rejecting these propositions.

A particularly telling study suggested that when identical twins are concordant for psychotic experience, they are also significantly more likely to have suffered childhood adversity (Alemany et al., 2013). If twins were discordant, the one who had not suffered adversity was significantly less likely to have psychotic symptoms. The study was able to show that adversity was directly causing psychotic symptoms, independent of genes. There are other studies with related findings. For example, Ball and colleagues (2008) found that being bullied before the age of five correlated at r=0.77 in identical twin boys but only at 0.41 in fraternal twin boys; there were similar findings for girls.

This is by no means the whole of the evidence relating to this issue, and there are studies that support defenders of the EEA, beyond the scope of this paper. But if the EEA is false as an assumption and if the ancillary arguments to protect it are also false, it suggests that a great deal of what has previously been ascribed to the role of genes is in fact due to shared environment.

The causes of variance in outcome in twin studies are partitioned into three factors (Plomin, 1990): *shared environment*, the role of shared experiences in the environment; *non-shared environment*, the role of experiences that are different

between the pair; and *heritability*, the role of genes. Using this partitioning of variance, twin studies find very little role for shared factors, much higher estimates of the effect of non-shared ones (Plomin & Daniels, 1987).

However, this method for apportioning variance requires the EEA to be valid, or for its protective arguments to be so. If they are false, it is very possible that a great deal of what has up until now been assumed to be caused by genes, currently partitioned as heritability, is in fact caused by shared environment. That leads to a fascinating alternative interpretation of twin study findings: where high "heritabilities" have been found in twin studies, rather than the role of genes, they are actually demonstrating that there is greater similarity of treatment for that trait. Equally, where "heritability" is low, it suggests a large non-shared environment contribution. I characterise this re-analysis as THISE (twin studies' "heritability" is shared environment).

Given a null hypothesis for the HGP, a THISE analysis can make the assumption that much of what was previously regarded as heritability in twin studies is shared environment. While it is impossible to use twin studies to identify the small role genes may play, given that the HGP does find 1–5% heritability, it is reasonable to assume that the great majority of supposed heritability is shared environment.

If we take schizophrenia, heritabilities of at least 50% are frequently found in twin studies. In the THISE interpretation, this would be taken to show that the adverse childhood environmental factors that cause "heritability" are more likely to be shared than for less "heritable" traits, like minor depression. For example, maltreatment is three times commoner in schizophrenics compared with controls (Varese et al., 2012). Of the various kinds of maltreatment, emotional abuse was shown to be the largest cause in Varese and colleagues (2012) review. THISE analysis would suggest that where there are twins and where there is emotional abuse in the family, it is more likely to be shared than other kinds of maltreatment, like emotional neglect, for which the review found less of an effect. That would be in accord with a finding by Bornovalvova and colleagues (2013) that emotional abuse was more shared by identical (any gender, $r = 0.53$) than fraternal twins ($r = 0.36$).

Where there is relatively low twin study "heritability" for a trait, a THISE analysis suggests low concordance in environmental influence—a large non-shared environmental contribution. The case of the causes of attachment is particularly interesting in the light of THISE because there is substantial evidence that attachment patterns have little or no heritability during childhood, if one interprets twin studies as measuring genetic factors (see *Introduction* in Fearon et al., 2014). But rather than heritability, THISE re-analysis of those findings would indicate that parents do not treat children similarly in regard to the environmental factor known to affect attachment pattern, namely, availability (divided into responsiveness and accessibility) (Bowlby, 1978). In other words,

what twin studies may prove about childhood attachment patterns is that they are very largely the product of non-shared environmental availability.

A recent report of a twin study suggested relatively high heritability for attachment patterns in adolescence, around the 40% mark (Fearon et al., 2014). THISE reanalysis of these findings would suggest that environmental factors affecting attachment in adolescence are more shared by siblings, compared with in childhood. Fearon and colleagues (2014) present their findings as proof of heritability, yet they make no acknowledgement anywhere in their paper of the tiny heritability findings of the HGP. With an HGP null hypothesis accepted, a THISE analysis seems much more probable—the study by Fearon and colleagues (2014) has raised the possibility (subject to replication) that shared environment becomes a more significant cause of attachment patterns in adolescence compared with childhood.

An interesting more general implication of a THISE analysis is that shared environment plays a greater role in causing major mental illness than minor mental illness, which would seem to be more caused by non-shared environment: twin studies find much higher heritability for major, rather than minor, mental illness. It could be that the adversities that cause major mental illness are more likely to be shared than those that cause minor mental illness.

Conclusion

What evidence will molecular geneticists accept as a basis for accepting the null hypothesis of the HGP? It seems probable that even if whole-genome sequencing studies produce similar findings to those of existing GWAs, and studies of SNPs and CNVs, there will be continued attempts to find genetic alternatives.

In the newspaper article in which Robert Plomin acknowledged that "I've been looking for these genes for 15 years and I don't have any", Peter Wilby, his interviewer, ended with a further question. Wilby wrote that, in answer to the question "What if the genes he's looking for are never found?" Plomin replied "I will still believe that heritability is true" (Wilby, 2014).

This response by Plomin may be an indication of how hard it will be to persuade behavioural geneticists (who conduct twin studies) or molecular geneticists to accept the null hypothesis of the HGP. Robert Plomin is rightly regarded as a man of integrity and as a major scientist in this field. Yet he states that he will continue to believe that "heritability is true" even if no genetic material can be found to explain significant amounts of variance. It would be interesting to know what Plomin would regard as evidence that, on the balance of probabilities, the null hypothesis of the HGP should be accepted.

For, while it is impossible to prove a negative, balances of probability can be used to evaluate the likelihood of a null hypothesis. If the whole-genome studies

of sequencing in large samples are unable to find greater significance than existing GWAs and other methods, that will surely be the point at which the null hypothesis must be seriously considered, if not provisionally accepted.

In the meantime, papers reporting studies of twins continue to ignore the HGP null evidence when introducing their studies, or in discussing them. Equally, reports of HGP findings continue to flatly state at their outset that the traits under investigation "are" highly heritable, citing twin studies. Neither of these practices should continue.

Equally, students at all stages of education continue to be taught that traits are highly heritable, with little or no reference to either the flaws of twin studies or to the null findings of the HGP. At the very least, it is time for teachers in secondary and higher education, and in clinical trainings, to begin teaching that there are strong reasons to doubt that traits are highly heritable.

If the whole-genome sequencing studies are as null as previous HGP investigations, it will be time for the next generation of students to be taught that the HGP is probably proving that genes play very little role in causing differences in traits. In this eventuality, students should also be taught that the findings of twin studies can no longer be regarded as safe and that a THISE interpretation is what a parsimonious *Occam's Razor* would lead us to.

More generally, there are momentous implications for parents, society, and psychotherapists if the null hypothesis of the HGP is accepted. Not the least of these is that no psychopathologies should be treated as immutable genetic destinies. For those of us engaged in the task of using an attachment informed relational therapy to help people troubled by past maltreatment, it is a highly optimistic spur to promote ever more emotional health. And also a spur for us as psychotherapists knowing the possibilities for therapeutic change.

Brief glossary of basic molecular genetic terms

Allette: an alternative form that a gene may have from other versions of it that may be associated with a particular behavioural or other phenotypic outcome.

Base pair: the double helix of DNA is like a staircase each of whose steps is a base pair made up of various bonded chemicals.

Copy number variants (*CNV*): a CNV is where there has been duplication, insertion, or deletion of stretches of DNA base pairs. These CNVs are mostly not inherited, developing independently of the genes that were passed on from parents. In fact, all of us have CNVs spread around our DNA, up to and including the absence of whole genes, usually without any discernible consequence. CNVs could not be a major way of identifying genetic inheritance of mental illness, but they might be locations of genetic material differing between the ill and the well.

Deoxyribonucleic acid (*DNA*): the double-stranded molecule that contains information.

Gene: a sequence of DNA that codes for particular outcomes.

hypermethylation:

Single-nucleotide polymorphism (*SNP*): a polymorphism has more than one allele. An SNP has a mutation in a single nucleotide in a base pair.

Transcription: occurs in the cell nucleus when DNA becomes synthesised into the RNA that instructs specific bodily change.

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