CHAPTER FOUR

No Genes for Intelligence in the Fluid Genome

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Abstract

Revolution is brewing belatedly within the heartlands of the genetic determinist establishment still in denial about the fluid genome that makes identifying genes even for common disease well-nigh impossible. The fruitless hunt for intelligence genes serves to expose the poverty of an obsolete paradigm that is obstructing knowledge and preventing fruitful policies from being widely implemented. Genome-wide scans using state-of-the art technologies on extensive databases have failed to find a single gene

Advances in Child Development and Behavior, Volume 45
ISSN 0065-2407, http://dx.doi.org/10.1016/B978-0-12-397946-9.00004-X

for intelligence; instead, environment and maternal effects may account for most, if not all correlation among relatives, while identical twins diverge genetically and epigenetically throughout life. Abundant evidence points to the enormous potential for improving intellectual abilities (and health) through simple environmental and social interventions.

1. THE BELL CURVE ILLUSION

The heritability of intelligence or IQ (intelligence quotient, Table 4.1) has been hotly debated for decades. The most recent round of exchange was provoked by *The Bell Curve* written by Richard Hernstein and Charles Murray, published in 1994. In the book, they argued that IQ tests are an accurate measure of intelligence, that IQ is a strong predictor of academic and career achievement, that it is highly heritable and little influenced by the environment, and most controversially, racial differences in IQ are likely due to genes. Consequently, the authors were skeptical about the ability of public policy initiatives to have much impact on IQ or IQ-related outcomes (Nisbett et al., 2012).

The Bell Curve sold 300,000 copies and attracted a great deal of uncritical media attention. The American Psychological Association commissioned a report from a panel of experts rebutting its main claims published in 1996. Now 16 years later, a second report has been issued to take account of the many new findings, including the following:

- Almost no genetic variants have been discovered that are consistently associated with variation in IQ in the normal range;
- The heritability of IQ varies significantly by the social class;
- The importance of the environment for IQ is established by the 12 point to 18 point increase in IQ when children are adopted from working-class to middle-class homes;
- Even when improvements in IQ produced by the most effective early childhood interventions fail to persist, there can be very marked effects on academic achievements and life outcomes;

Table 4.1 What is IQ?

IQ, intelligence quotient, is a score resulting from one of the several standardized tests designed to assess intelligence. Modern IQ tests were constructed to have a mean score of 100 and SDs of the mean (e.g., between 70 and 130).
Quite apart from the fierce debate over the heritability of IQ or intelligence, the claim that IQ assesses intelligence and the validity of any single measure of intelligence are both strongly contested.

- In most developed countries studied, gains on IQ tests have continued and are beginning in the developing world; and
- The IQ gap between Blacks and Whites has been reduced by 0.33 SD in recent years.

1.1. Revolution in the Heartland of Genetics

The report does not quite capture the revolution breaking out in the heartland of genetics.

Simply put, there are no genes for intelligence in the human genome; however, one chooses to define intelligence; and there has been much contention on that claim alone. For example, recent research shows that nonintellectual factors such as test motivation can increase IQ scores by an average of 0.64 SD, with larger effects for individuals with lower baseline IQ scores (Duckworth, Quinn, Lynam, Loeber, & Stouthamer-Loeber, 2011).

More fundamentally, the heritability of IQ estimated in the conventional model is now widely seen as deeply flawed. Heritability—the component of population variation (variance) attributed to genes—has been inflated by gene interactions, gene–environment interactions, and other nonlinear effects, in the same way that the heritabilities for common diseases have been inflated (Ho, 2012d). Not only that, the heritability estimated from resemblance (correlation, covariance) between twins and siblings could be due to shared environments especially maternal environments.

Even more seriously, the classical Mendelian inheritance on which all estimates of heritability depends has been severely compromised by pervasive epigenetic (and environmental cultural) inheritance. Epigenetic and cultural inheritances often go together, resulting in correlations between relatives that have been erroneously attributed to shared genes. On the other hand, epigenetic variations due to individual experiences, and somatic mutations from a host of DNA marking and changing processes, make even monozygotic twins diverge genetically from each other to substantial degrees. These observations strike at the very core of the conventional genetic determinist paradigm.

I shall start from the problems that emerge in identifying genes for common diseases, which looks much more concrete than genes for intelligence.

2. WHERE ARE ALL THE PROMISED GENES?

When the human genome sequence was announced in 2000, President Clinton said it would "revolutionize the diagnosis, prevention, and

Table 4.2 Genome-wide association studies

Genome-wide association studies (GWAS) involve rapidly scanning markers across the complete genomes of many people to find associations of genetic variants to particular diseases or traits. Typically, thousands or tens of thousands of individuals are scanned, simultaneously for up to 550,000 single nucleotide polymorphisms (SNPs)—common differences in single nucleotides at specific sites across the human genome with frequencies >5%—using DNA microarrays (chips).

treatment of most, if not all human diseases." Ten years on, and *Fortune* magazine called it: "The great DNA letdown". A poll by the science journal *Nature* returned the verdict: "the hoped for revolution against human disease has not arrived."

That is as some of us had predicted in 2000 (Ho, 1998) and before (Ho, 2000). The human genome project has generated reams and reams of data since its inception, but there is little progress even in the apparently simple task of finding the genes responsible for susceptibility to common diseases (Ho, 2012d, 2010b).

Top geneticists recently admitted that human genetics has been haunted by the mystery of "missing heritability" of common traits. Genome-wide association studies (GWAS, Table 4.2)—the current gold standard for the most exhaustive gene hunt that can be performed—have identified approximately 2000 genetic variants associated with 165 common diseases and traits; but these variants appear to explain only a tiny fraction of the heritability in most cases (Visscher, Brown, McCarthy, & Yang, 2012; Zuk, Hechter, Sunyaev, & Lander, 2011).

Heritability is technically the proportion of the variability of the trait in a population due to genes. Variability is measured statistically as *variance*, the sum of the squared individual deviations from the population mean. Heritability is commonly referred to as the "genetic component" of the variance as opposed to the proportion due to the environment, or the "environmental component". Note that heritability refers to the variation, and *not* to the trait itself. Heritability changes according to the environment. It is not uncommon for the heritability of traits such as milk yield or height of a plant from the same genetic strain to change substantially from one year to the next. However, there is a tendency for some scientists as well as the popular media to mistakenly assume that any trait with a large heritability means it is predominantly genetically determined, which is definitely not the case.

2.1. No Genes for Common Diseases?

Nevertheless, the hunt for genes determining susceptibility to common diseases has continued for decades, spurred on over the past 5 years by the availability of DNA chips that allow genome-wide scans for more than 500,000 SNPs simultaneously.

Eric Lander and his team at Board Institute MIT & Harvard, Harvard, Massachusetts are among those suggesting that much of the missing heritability never existed in the first place (Zuk et al., 2011). They base their argument on *biometrical genetics*, a mathematical discipline that deals with continuously varying traits, such as crop yields, height, body mass, IQ scores, or disease states that fall on a continuum, as for example, blood glucose, blood pressure, or some measure of disease severity.

I should point out that one arrives at precisely the same conclusion given the pervasive epigenetic influences of the environment on development (Ho, 1998, 2000, 2010b), which have been abundantly confirmed and extended since the human genome was sequenced, as I have reviewed elsewhere (Ho, 2004, 2009b; ISIS scientific preprint).

This convergence of molecular and biometrical genetic analyses is the most conclusive refutation of the reductionist, genetic determinist paradigm of linear causation from genes to traits that had made the Human Genome Project seem such a compelling undertaking; only to thoroughly discredit it as a result (Ho, 2003), as argued in my book, *Living with the Fluid Genome*, published in 2003.

We now know that much of the variation may come from *individual* experiences of the environment. Furthermore, those experiences can mark and change genes, influencing the development of the individual and in many case, the individual's offspring. Genes and environment operate in enormously complex feed-forward and feed-back networks that straddle generations. This fundamentally *circular causation* between genes and environment means that genetic and environmental contributions are inseparable, and *any attempt at assigning linear effects to single genes is doomed to failure*.

We shall see how genetic determinism is finally unraveling within the heart of the genetics establishment, beginning with the findings of Lander's team with regard to common disease traits (Ho, 2012d) and continuing with the intelligence and IQ debate (Ho, 2012e).

2.2. The Genetic Component Has Been Greatly Overestimated

Specifically, Lander and colleagues show that the missing heritability arises from an overestimate of total heritability (the genetic component of the variation in the trait), which implicitly assumes that no gene interactions

(or gene environment interactions) exist, an assumption clearly unjustified. Including gene interactions gives a much smaller total heritability. In short (Zuk et al., 2011), "missing heritability need not directly correspond to missing variants, because current estimates of total heritability may be significantly inflated by genetic interactions."

Actually, gene interactions do belong to the "genetic component" of heritability. In biometrical genetics, "broad sense heritability" H^2 includes additive genetic effects as well as effects due to gene interactions and any nonadditive, nonlinear effects due to genes. But the broad-sense heritability is very difficult to determine. In practice, only the "narrow sense heritability h^2 (the additive, linear effects due to genes) can be estimated. *Narrow-sense heritability applies strictly to* 'polygenic' *traits due to many genes, each with a small additive effect, and is implicitly assumed to apply to all polygenic traits*, beginning with the pioneers of biometrical genetics" (see later).

Geneticists therefore define the proportion of heritability of a trait explained, $\pi_{\text{explained}}$, as a ratio of phenotypic variance explained by the additive effects of known genetic variants, h^2_{known}, to the phenotypic variance that can be attributed to the additive effects of all variants, including those not yet discovered, h^2_{all} (Eqn (4.1)).

$$\pi_{\text{explained}} = h^2_{\text{known}} / h^2_{\text{all}} \tag{4.1}$$

The nominator h^2_{known} can be calculated directly from the measured effects of the variants, but the denominator h^2_{all} must be inferred indirectly from population data.

The prevailing view among geneticists is that the missing heritability is due to additional variants yet to be discovered, either common alleles with moderate-to-small effects or rare alleles (frequency <1%) with large effects (Visscher et al., 2012; Zuk et al., 2011).

The other possibility, favored by Lander's team, is that the missing heritability does not actually exist, and is an artifact arising from the total heritability h^2_{all} being overestimated in the first place, by ignoring the impacts of gene interactions.

For example, Crohn's disease (inflammatory disease of the bowel) has so far 71 risk-associated loci identified. Under the usual assumption of additive effects, these loci explain 21.5% of the estimated total heritability. Genetic interactions could account for the remaining nearly 80% missing heritability. Why then has genetic interaction never been detected in population analyses? Lander and colleagues point out that to detect gene interactions for Crohn's disease may require sample sizes in the range of 500,000 individuals, which is rarely attained.

Gene interaction, or *epitasis*, is well known and pervasive, even before the human genome was sequenced, as I have stressed in *Genetic Engineering Dream or Nightmare*, which predicted why genetic modification is both dangerous and futile (Ho, 1998). Since the human genome was sequenced, gene interaction takes on a literal dimension, as epitomized in the findings of project ENCODE (Encyclopaedia of DNA elements) organized by the U.S. National Human Genome Research Institute, in which a consortium of 35 research groups went through 1% of the human genome with a fine-tooth comb to find out exactly how genes work (ENCODE Project Consortium, 2007). They discovered that (Caruso, 2007) "genes appear to operate in a complex network, and interact and overlap with one another and with other components in ways not fully understood." Essentially, the "gene" as a well-defined, separate unit of structure or function no longer applies. Instead, genes exist in bits strewn across the genome, structurally *and* functionally intertwined with other genes. The same sequence of DNA can have very different functions and very different sequences can have the same function.

2.3. How Phantom Heritability Arises

Lander and colleagues point out (Zuk et al., 2011) that in calculating the explained heritability (Eqn (4.1)), the numerator h^2_{known} is estimated based on the effects of the individual genetic variants. The problem comes in estimating the denominator h^2_{all}. Because not all the variants are known, their contribution must be inferred based on phenotypic correlations in a population. This gives an *apparent heritability*, h^2_{pop}. And the missing heritability is then estimated by assuming that $h^2_{\text{all}} = h^2_{\text{pop}}$.

However, there is no guarantee that $h^2_{\text{all}} = h^2_{\text{pop}}$, unless the trait is strictly additive, and neither gene–gene interaction nor gene–environment interaction exists. For traits with gene interaction, which would realistically apply to practically all common traits and diseases, h^2_{pop} may significantly exceed h^2_{all}. In that case, even when all the variants for the trait have been identified, the missing heritability π_{missing} will not diminish to zero, instead, it converges to $1—(h^2_{\text{all}}/h^2_{\text{pop}})$, which Lander and colleagues refer to as "phantom heritability", π_{phantom}.

2.4. Simple Model Shows How Genetic Interactions Create Phantom Heritability

To show how genetic interactions create phantom heritability, Lander and colleagues introduced a simple model in which a trait depends on input from more than one processes, Phantom heritability—that which remains

missing even when all genetic variants have been identified—grows quickly with the number of inputs, approaching 100% of the total variation. For Crohn's disease, for example, just three inputs are sufficient to account for 80% of the phantom heritability.

Similarly, gene–environment interactions can produce additional phantom heritability, (as indeed other unaccounted sources such as epigenetic effects).

2.5. Twin Studies Deeply Flawed

The typical framework for analyzing human traits depends on a systematic denial of epistasis, assuming that genes act in a purely additive way, each gene contributing a small amount to the trait, which is summed up depending on how many of those genes are present.

One measure of apparent heritability h^2_{pop} (ACE) assumes additive genetic variance, as well as common environmental and unique environment variance components, and a usual definition for apparent heritability is $h^2_{\text{pop}}(\text{ACE}) = 2(r_{\text{MZ}} - r_{\text{DZ}})$, where r_{MZ} and r_{DZ} are the phenotypic (measured trait) correlations between monozygotic twins (sharing 100% of their genes) and dizygotic twins (sharing 50% of their genes); while the environment they share is assumed to be common, including the maternal environment.

But realistically,

$$h^2_{\text{pop}}(\text{ACE}) = h^2_{\text{all}} + W \tag{4.2}$$

where W represents the sum of variances due to all possible higher order additive and nonadditive interactions between genes. The crucial point is that if there are any gene interactions, then $W > 0$, so h^2_{pop} (ACE) overestimates h^2_{all}.

Unfortunately, there has been no way to estimate W from population data. In most human studies, the solution is to assume there is no gene interactions, in which case $W = 0$. Thus, twin studies systematically overestimate the genetic contribution to disease and other traits, most notably, and controversially IQ (Ho, 2012e).

2.6. Additive Assumption Fundamental to Biometrical Genetics

Lander and colleagues are not the first to expose the fundamentally flawed assumptions of classical biometrical genetics. Helen Wallace of UK-based GeneWatch has published a similar critique 5 years earlier (Wallace, 2006): gene–gene and gene–environment interactions could reduce the calculated

heritability considerably below that predicted by the standard twin-studies method based on pioneering British geneticist Ronald Fisher's 1918 assumption that genes act additively.

2.7. Implications

The major implication is that the hunt for susceptibility genes is practically useless. Indeed, Lander and colleagues (Zuk et al., 2011) and others (Visscher et al., 2012) see the primary purpose of medical genetics as the identification of underlying pathways and processes analogous to the hunt for mutants in model organisms; and not in "explaining heritability" or "predicting personalized patient risk."

But there are much wider implications on health policies. Governments and companies have been keen to set up whole genome biobanks ever since the human genome sequence was announced (Ho & Papadimitriou, 2002 and other articles in the series). The UK government is pushing to let companies gain access to the public health records to drive discovery in the disease genomics (Kohane, 2011). But if the genetic contribution to disease is largely a phantom, what is the point of integrating the whole genome sequences with electronic medical records as most of this information is likely to be clinically useless for most people (Ho & Papadimitriou, 2002; Wallace, 2012)?

There are vested interests that want to keep the genetic myth alive. As Wallace points out, the evidence she presented in 2006, and Lander and colleagues presented in 2011 has had no impact on gene testing companies such as Illumina and 23and Me, which continue to claim that everyone will have that person's genome mapped or sequenced in future, at birth or as a routine part of health care. The Director of the National Institutes of Health Francis Collins has echoed these claims in his populist book *The Language of Life* (Collins, 2010). Wallace is convinced, as I am, that (Wallace, 2012) "whole genome sequencing of everyone, leading to the"prediction and prevention"of disease, is a science fantasy and a massive waste of money."

A fraction of the resources divested into the much needed primary health care and disease prevention through nutritional and other environmental/social interventions will do infinitely more to improve the health (as well as brain power) of the nation, as we shall see.

3. THE ELUSIVE IQ GENES

The hunt for IQ genes has been inspired by the large heritability estimated in conventional biometrical models based on correlations between

twins and other biological relatives (Ho, 2012d). But the results so far have been disappointing to say the least, even more so than the hunt for disease genes.

A GWAS on 7000 subjects published in 2008 found only six genetic markers (SNPs, single-nucleotide polymorphisms) associated with cognitive ability, and only one of those remained statistically significant on further tests. Together, the six markers explained barely 1% of the variance in general cognitive ability (Butcher, Davis, Craig, & Plomin, 2008). Recently, the association between 12 specific SNPs and "general intelligence" factor *g* was put to test in an attempt to replicate the associations found in earlier studies, but only one SNP remained significant. The researchers conclude that (Chabris et al., 2012) "most reported genetic associations with general intelligence are probably false positives."

As in the case of common disease traits (Ho, 2012d), IQ or intelligence is plagued by the problem of "missing heritability". Even the heritability of human height, estimated at approximately 90%, failed to turn up common variants contributing more than 0.5 cm; and the set of 180 height-associated SNPs identified by the most comprehensive meta-analysis (on pooled data from many studies) only explains about 10% of the population variance.

The usual explanation for the missing heritability is that it is difficult to detect genetic variants with a small effect. In the case of intelligence, much is made of the findings in a new study led by researchers at Edinburgh University in the U.K., which claims to (Davies et al., 2011) "establish that human intelligence is highly heritable and polygenic". The group first used data from five different GWAS and failed to identify any individual marker associated with either "crystallized" or "fluid" intelligence. (Crystallized intelligence is the individual's store of knowledge about the nature of the world and learned operations such as arithmetic that can be drawn upon to solve problems; while fluid intelligence is the ability to solve novel problems that depend relatively little on stored knowledge as well as the ability to learn). They then applied a new method that tests the cumulative effects of all the SNPs, essentially by calculating the overall genetic similarity between each pair of individuals in a sample, and correlating this genetic similarity with phenotypic similarity (in IQ) across all the pairs. The result is that *all* the approximately 550,000 SNPs together could jointly explain 40% of the variation in crystallized intelligence and 51% of the variation in fluid intelligence. This exercise sounds more like a counsel of despair than a solution to the problem, and the result certainly does not offer any useful predictive information.

Other researchers are tackling the problem at the more fundamental level of the heritability estimates.

3.1. Maternal Environment Accounts for Much of Heritability

One of the first rebuttals to *The Bell Curve* came from Bernard Devlin and colleagues at University of Pittsburgh in the United States in a paper published in *Nature* in 1997 (Devlin, Daniels, & Roeder, 1997). They showed that covariance (correlation) between relatives may not be due only to genes, but also to shared environment, especially maternal environment, which is not taken into account in conventional models. In a meta-analysis of 212 previous studies supplemented with twin studies published after 1981, Devlin and colleagues showed that an alternative model with two maternal womb environments, one for twins—both monozygotic and (MZ) and dizygotic (DZ)—and another for siblings, fit these data much better.

Maternal effects, often assumed to be negligible, account for 20% of the covariance between twins and 5% between siblings, thereby correspondingly reducing the effects of genes, so the two measures of heritability were both less than 50%: the broad and narrow sense heritability were 48% and 34%, respectively.

The shared maternal environment may explain the striking correlation between the IQs of twins, especially adult twins reared apart. It also accounts for age-effects: an apparent increase in heritability with age. Devlin and colleagues pointed out that cultural inheritance and interaction between genes and environment may also be at work to boost the apparent heritability of intelligence.

There is substantial brain growth in utero, and the brain has 70% of its final mass within a year of birth. IQ is known to be affected by prenatal environment: it is positively correlated with birth weight. Twins usually weigh less than singletons, and score on average 4–7 points lower on IQ tests.

Devlin and colleagues rejected Hernstein and Murray's conclusion; instead, they believed that "Interventions aimed at improving the prenatal environment could lead to a significant increase in the population's IQ."

Devlin and colleagues may well have *under*estimated the shared maternal environment for MZ twins, which in addition to sharing the same womb as for DZ twins, usually share the same placenta, and more importantly, originate from the same egg with common cytoplasmic components, including mitochondrial DNA and transcripts and gene products that control early embryonic development (Charney, 2012). Common cytoplasmic effects will be expected to further reduce heritability estimates.

3.2. Virtual Twin Studies and Rearing Environment

Nancy Segal and colleagues at California State University Fullerton in the United States have pioneered the study of behavior in "virtual twins" (VTs): same age, unrelated siblings reared together since infancy. VTs replicate the rearing environment of twins but without the genetic relatedness, thereby enabling direct assessment of shared environmental effects on behavior. Virtual twins are created in adoption, in which infants were adopted before one year of age; the unrelated sibling differing by less than 9 months in age, attend the same school grade, the pair being free of adverse birth events, and at least 4 years old. The foster homes are predominantly the upper middle class.

In an updated analysis of IQ data based on a sample of 142 VT pairs, the VTs mean IQ score was 105.83 (SD = 13.37) and correlation between VTs is 0.28 ($p < 0.001$), showing a substantial contribution of rearing environment during infancy (Segal, McGuire, & Stohs, 2012).

The mean IQ score of the biological siblings exceeded that of the adopted siblings and when the paired data for members of 49 adopted-biological pairs were examined, biological children scored 113.08 (SD = 14.64), whereas adopted children scored 105.67 (SD 12.53), a difference of 7.41 points.

Significantly, there was greater similarity in IQ scores between adopted-biological than adopted–adopted pairs, resulting in correlations of 0.47 vs 0.10. Similar results have been found by other research groups, suggesting that the environmental stimulation from a high-IQ biological child may also enhance adopted sibling's IQs. (Note that this is my own suggestion, not Segal's (Segal, 2012)).

The IQ correlation of the adopted-biological pairs (0.47, $p < 0.001$) approaches that of DZ twins (0.46) and full siblings (0.47) reported by others.

To me, the research of Segal's group and that of Devlin's group together makes it highly likely that common rearing environment during infancy and maternal effects could account for most, if not all, the heritability in IQ that has been attributed to genes.

3.3. Socioeconomic Status and IQ

The higher IQ scores of the biological children relative to the adopted children observed by Segal's team (Segal et al., 2012) are not surprising in view of the predominance of upper middle-class parents in the study, whereas adopted children are predominantly from parents of lower socioeconomic status (SES). Studies dating to the 1990s have shown that adopted children

typically score 12 points or higher than siblings left with birth parents or children adopted by lower SES parents (Nisbett et al., 2012). A meta-analysis carried out in 2005 found an average effect of adoption of 18 points when extremely deprived institutional settings were included in the comparison (Van Ijzendoorn, Juffer, & Poelhuis, 2005).

What correlates SES with IQ? There are marked differences beginning in infancy, between the environment of higher SES families and lower SES families in factors that are likely to influence intellectual growth, including nutritional status (Ho, 2012b). A study published in 1995 (Hart & Risley, 1995) showed that by the age of three, a child of professional parents would have heard 30 million words spoken, while a child of working-class parents would have heard 20 million words, and a child of unemployed African American mothers would have heard 10 million words. The child of professional parents received six encouragements for every reprimand, the child of working-class parents received two encouragements per reprimand, and the child of unemployed African American mothers received two reprimands for every encouragement. These findings were extended using the HOME technique (Home Observation for Measurement of the Environment) (Nisbett et al., 2012). HOME researchers assess family environments for the amount of intellectual stimulation: how much parents talk to the child; how much access to books, magazines, newspaper, and computers; how much the parents read to the child; how many learning experiences outside the home (trips to museums, visits to friends); degree of warmth of parents vs punitive behavior toward the child, and similar measures. Very substantial association was found between HOME scores and IQ scores: a 1 SD difference in summed HOME scores is associated with a 9-point difference in IQ. These studies do not separate genetic and environmental contributions, but as the authors of the new report of the American Psychological Association commented (Nisbett et al., 2012): "It is almost surely the case, however, that a substantial fraction of the IQ advantage is due to the environments independent of the genes associated with them." That is because of the knowledge that adoption adds 12–18 points to the IQ of unrelated children, who are usually from lower SES backgrounds.

Shared environmental effect on IQ applies not just to children. According to a review of six well-conducted studies, shared environment effect in adulthood is about 0.16 on average.

Consequently, most if not all twin studies, especially studies of adults, overestimate heritability of IQ, especially as lower SES individuals are difficult to recruit to laboratories and testing sites.

4. EPIGENETIC AND CULTURAL INHERITANCE

Human population geneticist Marcus Feldman and his colleagues at Stanford University in the United States and the University of Aarhus in Denmark noted that current models are strictly based on Mendelian genetics, failing to consider non-Mendelian epigenetic modifications of genes in response to environmental states. These epigenetic modifications usually do not involve DNA base sequence alterations and are hence not detected in SNP scans; they are also independent of SNP variations. Instead, they involve chemical markings of DNA or histone proteins that bind to DNA, or other mechanisms that change the state of expression of certain genes. Epigenetic modifications are often passed on to subsequent generations.

Indeed, epigenetic modifications are inherited, both good and bad, as I have reviewed elsewhere (Ho, 2009b) and by other articles in the present volumes. Recent research shows that even what is inherited in the DNA does not determine the amino acid sequences of proteins, as revealed by a widespread mismatch of expressed RNA to the DNA sequences. Somehow, the DNA sequences are profusely edited, possibly to make them fit for purpose and context at any one time and place (Ho, 2012c). And most surprisingly, geneticists have discovered that even the food we eat can affect the expression of our genes via small RNA sequences in the food (Ho, 2012a), giving a literal meaning to "we are what we eat", and incidentally, show up yet another hazard from genetically modified food with unpredictable, uncontrollable changes in the repertoire of new RNAs produced.

Feldman and colleagues addressed the problem at the level of biometrical models by extending the models to include epigenetic and environmental effects (Furrow, Christiansen, & Feldman, 2011).

They found that variation in epigenetic state and environmental state can result in highly heritable phenotypes through a combination of epigenetic and environmental inheritance. These two inheritance processes together can produce familial covariances (correlations) significantly greater than those predicted by models of purely epigenetic inheritance and similar to those expected from genetic effects. The results suggest that epigenetic variation, inherited both directly, and through shared environmental effects, may make a key contribution to the missing heritability.

In other words, epigenetic and environmental effects working together can account for practically all the variation now attributed to the genes.

Chief among environmental effects is cultural inheritance. Feldman and colleagues referred to the aggregation of the disease Kuru in families of the Fore tribe of Papua New Guinea due to the ingestion of a *prion* protein (infectious protein agent) during funeral rituals in which the dead relatives or close acquaintances are consumed. This case of purely cultural inheritance was originally mistaken for a genetic disorder because of high disease correlations between relatives.

A well-studied case of environmental epigenetic inheritance is the mother's licking-grooming of offspring in mice, which induces epigenetic changes in the offspring, influencing its response to stress as adults, and perpetuates the maternal behavior in her female offspring (Ho, 2009a). This results in highly correlated behavior between mother and offspring in both maternal behavior and response to stress as adults, even though the epigenetic modifications are erased during early embryogenesis. Consequently, cross-adoption between mothers with high and low licking-grooming behavior will break the biological mother–offspring correlations in a single generation.

5. IDENTICAL TWINS ARE *NOT* GENETICALLY IDENTICAL

As noted above, biometrical genetics models are based on classical Mendelian inheritance, in which genes are immune to direct or predictable environmental influence and passed on unchanged to the next generation except for rare random mutations. The old paradigm has been discredited at least as far back as the late 1970s (Ho, 1998, 2003), long before the Human Genome Project was conceived.

In the postgenomics era, an increasing number of geneticists have begun to take notice of non-Mendelian inheritance and its invalidation of the basic tenets of biometrical genetics.

In a paper about to be published in *Behavioral and Brain Sciences*, Evan Charney at Duke University speaks of a "paradigm shift" in the science of genetics. He points to recent discoveries of numerous processes that create extensive mutations in genome sequences and structure, as well as epigenetic modifications, which are completely at odds with the Mendelian model of inheritance underpinning heritability estimates (Charney, 2012). Individuals do not have genes that are immutable throughout life, nor do they have the same genes in every cell of the body. He highlights retrotransposons—jumping genes that replicate and integrate themselves into different sites in the genome—that alter the sequence and state of activity of many genes,

copy number variation and chromosomal abnormalities (aneuploidy) similarly, occur frequently in somatic cells as well as germ cells, both as part of normal development and in response to noxious environmental stimuli. Different tissues show distinctly different propensity for change; brain cells being especially prone to such modifications. These add to the already large repertoire of epigenetic modifications that modify genes in response to environmental stimuli (Ho, 1998, 2003, 2009b, 2012a,d), and most notably in the brain, as reviewed elsewhere (Ho, 2009c).

The fundamental assumption of twin studies—that monozygotic twins share 100% of their genes—is demonstrably false. MZ twins differ, to begin with, in the mitochondrial DNA (mtDNA) complement allocated in cell division of the original oocyte that generated the twins. The oocyte may have had different sets of mtDNA, a condition referred to as heteroplasmy. MZ twins diverge substantially in epigenetic modifications as well as retrotransposition, copy number variations, and aneuploidy throughout life. Although the numerous processes that alter genomes occur in normal development, perhaps as part of "natural genetic engineering" (Ho, 1998, 2003), the same processes are known to be involved in many behavioral, psychiatric, and neurodegenerative diseases, leaving us in no doubt that they have phenotypic consequences (Charney, 2012).

In addition, stochastic nonlinear developmental changes account for substantial divergence in the activities of different brain regions between twins (Molenaar, Boomsma, Smit, & Nesselroade, 2012).

To summarize, no genes for intelligence can be found in the human genome. Instead, common environments, including maternal and rearing environments, along with epigenetic and cultural inheritance create substantial correlations between genetically unrelated individuals, while even "identical twins" diverge genetically and epigenetically throughout life.

The fundamentally *circular causation* between genes and environment makes it futile to separate genetic from environmental contributions to development (Ho, 2010a). Consequently, we must redouble all efforts at appropriate interventions to improve the mental and physical well-being of the nation, for which there is already a great deal of evidence (Ho, 2012b).

6. ENVIRONMENTAL INTERVENTIONS CAN IMPROVE IQ AND ACADEMIC ACHIEVEMENT

The 2012 report on intelligence from the American Psychological Association (APA) states (Nisbett et al., 2012): "A large number of

interventions have been shown to have substantial effects on IQ and academic achievement."

The collapse of the genetic paradigm should convince us to spare no effort at interventions that can improve the intellectual prowess of the nation and deliver substantial health bonuses. Let's look at some of the options.

6.1. Education and Enrichment Programmes

There is clear evidence that schooling affects intelligence as reviewed in the APA report (Nisbett et al., 2012). Children deprived of school for an extended period of time show IQ deficits as much as 2 SDs (standard deviations). A child entering fifth grade approximately a year earlier than one nearly the same age (who enters fourth grade) will have a verbal IQ more than 5 points higher at the end of the school year and as much as 9% higher by the eighth grade.

Children lose IQ and academic skills over the summer and the loss is much greater for children of lower SES. The knowledge and skills of children in the upper fifth of family SES, however, actually *increase* over the summer. This effect is so marked that by late elementary school, much of the difference in academic skills between lower and higher SES children may be due to the loss of skills over the summer for the lower SES children as opposed to the gains for the higher SES children. Intervention over the summer months targeted at low SES children should narrow this gap. The beneficial effects of schooling apparently continue at least through the junior high school.

The best prekindergarten interventions for lower SES children have substantial effects on IQ, but this typically fades by late elementary school, perhaps because the environments of the children do not remain enriched. Two examples in which the early gains from prekindergarten intervention remained both placed children in average or above-average elementary schools. Children in the Milwaukee Project had an average IQ 10 points above controls at adolescence; and children in the intensive Abecedarian program had IQs 4.5 points higher than controls at 21 years of age. Regardless of whether the high-quality interventions have sustained IQ effects, the effects on academic achievement and life outcomes can be very substantial. The gains are particularly marked for intensive interventions such as the Perry School Project and Abecedarian program. By adulthood, individuals who had participated were about half as likely to have repeated a grade in school or to have been assigned to special education classes, and were far more likely to have completed high school, attended college, and to own

their own home. This suggests that some of the effects are produced by gains in attention, self-control, and perseverance than IQ.

Self-control and discipline, along with creativity and flexibility, are considered the key qualities to success in life, and can be targeted by specific interventions as described in a recent review (Diamond & Lee, 2011). For example, martial arts that emphasize self-control, discipline, and character development such as *tae-kwon-do* gave children substantial gains in those cognitive functions (referred to as "executive functions"), much more so than the standard physical education. The children participating in *tae-kwon-do* also improved more when tested on the mental mathematics. Other effective interventions include "mindfulness" practices that focus one's complete attention on present experience, and *Tools of the Mind* that develop social and socializing skills through play.

The quality of teaching in kindergarten has a measurable impact on academic success and life outcomes (Nisbett et al., 2012). Data from Project STAR in Tennessee showed that students randomly assigned to small kindergarten classrooms were more likely to subsequently attend college, attend a high ranked college, and have better life outcomes in a number of respects. Students who had more experienced teachers had higher earnings as adults, as did students for whom the quality of teaching—as measured by test scores—was higher.

6.2. Memory Training for Fluid Intelligence

It is perhaps not surprising that training people in working memory skills can enhance fluid intelligence, while having no effect on crystallized intelligence (Nisbett et al., 2012). This applies to both adults and children with attention deficit hyperactivity disorder. Working memory training of low SES children using a variety of computer and noncomputer games resulted in IQ gains of 10 points on a matrix reasoning task.

Similar memory training over an 8-month period was effective for elderly participants (Nisbett et al., 2012). Training older adults in memory, speed in processing, and particular narrow-reasoning skills produces substantial improvements that remain over a period of years. A study in the U.K. showed that an extra year of work was associated with a delay in the onset of Alzheimer's disease on average by 6 weeks (Belleville et al., 2011).

6.3. The Overriding Importance of Early Nutrition

The overriding importance of early nutrition for learning is highlighted in a comprehensive resource list for professionals provided by the Food

and Nutrition Information Center of the U.S. Department of Agriculture's National Agricultural Library (USDA, 2011). It gives clear evidence that nutritional intervention in elementary school can improve both health and academic performance.

Retrospective analyses were conducted on school-performance indicators associated with the implementation of the Healthy Kids, Smart Kids program, a grass-roots effort to enhance school food and physical activity environment in Browns Mill Elementary School, Georgia. Data from 1995 to 2006 showed that the number of nurse, counseling, and disciplinary referrals per 100 students followed a downward trend, while standardized test scores followed an upward trend beginning in the year of the program implementation.

A second study demonstrated the effect of a two-year obesity prevention program on body mass index (BMI) and academic performance in low-income elementary school children. There were four intervention schools and one control school totaling 4588 school children, 48% Hispanic. These data were presented for the subset (1197) of the children (68% Hispanic) who qualified for free or reduced-price school lunches. The results showed that significantly more intervention than control children stayed within normal BMI range for both years. Although not significantly so, more obese children in the intervention than in the control decreased their BMI. Overall, children who received the intervention had significantly higher math scores in both years, and Hispanic and White children who received the intervention were significantly more likely to have higher math scores. Although not significantly so, children who received the intervention had higher reading scores in both years.

The association between intelligence and diet at 3.5 and 7 years of age was examined in more than 500 children of European descent in Auckland, New Zealand—approximately half of them with low birth weight (≤10th percentile) (Theodore et al., 2009). The relationship between IQ and diet measured by food frequency was investigated using multiple regression analysis. There was no significant difference in IQ between children with low birth weight and normal birth weight at 3.5 and 7 years of age, and no differences in food frequencies (i.e., how often they ate different foods).

Eating margarine at least daily was associated with significantly lower IQ scores at 3.5 years in the total sample, and at 7 years in children with low birth weight. After controlling for potential confounds, children who ate margarine daily scored 2.81 points lower than children who did not. In all children, eating the recommended daily number of breads and cereals—4 or more

times—was associated with significantly higher IQ scores at 3.5 years; the gain was 3.96 points after controlling for potential confounds. Children who ate fish at least weekly had significantly higher IQ scores at 7 years than those who did not, a gain of 3.64 points after controlling for confounds.

Eating fish does make you smart, it appears, precisely as we have been told in the traditional folklore of many cultures. A large study was carried out in Sweden to evaluate the association between fish intake and academic grades of 9488 adolescents using multiple linear regression models and adjusting for potential confounds such as parents' education (Kim et al., 2010). The results showed that grades were higher by 14.5 points in adolescents who ate fish once a week compared with those eating fish less than once a week. Adolescents who ate fish more than once a week scored even higher by 19.9 points. In the model stratified for parents' education, there were still higher grades among children with frequent fish intake in all educational strata.

A review published in 2008 (Cook & Frank, 2008) summarized evidence indicating that food insecurity is a prevalent risk to the growth, health, cognitive ability, and behavior of poor children in the United States. Infants and toddlers in particular are at risk even at the lowest level of food insecurity. The data indicate an "invisible epidemic" of a serious condition.

The effect of nutritional status on the brain development and scholastic achievement was examined in 96 high-school graduates selected from the public and private schools in the richest and poorest counties of Chile's metropolitan region (Ivanovic et al., 2002). These graduates had no history of alcoholism, or symptoms of brain damage, epilepsy or heart disease, and whose mothers had no history of smoking, alcoholism or drug intake before and during pregnancy (all known to affect fetal development). The object was to have a healthy balanced sample in terms of low and high IQ, sex, and SES. The results showed that, independent of SES, high school graduates with similar IQ have similar nutritional, brain development and scholastic achievement. Multiple regression analysis revealed that maternal IQ ($p < 0.0001$), brain volume ($p < 0.0387$), and severe undernutrition during the first year of life ($p < 0.0486$) were the independent variables with the greatest explanatory power for the IQ variance, without interaction with age, sex or SES. IQ ($p < 0.0001$) was the only independent variable that explained both scholastic achievement variance and academic aptitude test variance, without interaction with age, sex or SES.

Studies by the Institute of Nutrition of Central America and Panama (INCAP) showed that supplementary feeding of infants and young

children—with drinks that provide energy only or with added protein, both containing micronutrients—resulted in significant increases in cognitive development and school performance through to adolescence (Engle & Fernández, 2010). The research also suggested that the link of malnutrition to the later development is not only through the neurological system, but also through changes in behavior that affect the kinds of care the individual child receives.

A longitudinal two-year study on school children in rural Kenya found significant relationships on regression analyses between available Fe, available Zn, vitamin B12, and riboflavin with improved cognitive test scores, after controlling for confounds such as energy intake, school, socioeconomic status, and illness (Gewa et al., 2009).

Interventions aimed at eliminating food insecurity and micronutrient deficiencies are easily within the means of all developed nations and should be given top priority in both developed and developing nations.

6.4. Exercise Increases Brain Power by Making More Neurons

A sedentary lifestyle is associated with increased risk for cardiovascular and metabolic diseases as well as cancer, and it is well known that exercise can reduce the incidence of diabetes, cancers, and heart disease. Less well-known is the beneficial effects of exercise for the brain, described in a comprehensive review (Van Praag, 2008). In humans and rodents, physical activity enhances cognitive functions and counteracts age-related decline of memory, delays the onset of neurodegenerative diseases, and enhances recovery from brain injury and depression.

A meta-analysis of a large number of studies on older adults has shown that aerobic exercise, at least for the elderly, is very important for maintaining IQ, especially for executive functions such as planning, inhibition, and scheduling of mental procedures (Colcombe & Kramer, 2003). The effect of aerobic exercise is more than 0.5 SD for the elderly, more for those past age 65 than those younger. It is possible to begin cardiovascular exercise as late as the seventh decade of life and substantially reduce the likelihood of Alzheimer's disease.

But exactly how does exercise work to increase brain power and help prevent degeneration? The most likely answer appears to be through neurogenesis, the ability of the brain to repair and renew itself by making new neurons (Pereira et al., 2007).

Not long ago, neurobiologists and the general public believed that we were born with the neurons we would have in life, and no new neurons would ever be generated in the brain. That dogma was overturned in the

1990s. New neurons are continually generated throughout adulthood, mainly in two regions of the brain: the dentate gyrus in the hippocampus, a paired brain structure involved in memory, learning, and emotion, and the subventricular zone, a layer of cells found along the brain's lateral ventricles. The newly generated neurons form synapses and integrate into existing neuronal circuits.

Laboratory experiments have revealed that exercise not only significantly increases the number of new neurons in rats and mice, it also influences the morphology of individual newly generated cells and enhances their maturation, and is associated with increased plasticity in the hippocampus in forming synapses, thereby influencing learning and memory. In rodents, both voluntary wheel running and forced treadmill training have been shown to improve spatial learning with different types of mazes and training.

In rodents as well as nonhuman primates, aging is associated with a decline in neurogenesis and cognitive functions. The age-dependent reduction in neurogenesis can be partially prevented when animals are housed with a running wheel over a 6-month period. Furthermore, the decline in neurogenesis and cognitive functions associated with normal aging can be reversed in part by wheel running. Mice that had been sedentary for 18 months were started on the running wheel for one month, after which they showed significant improvements in spatial memory in learning the water maize, and the survival of newly generated neurons was also increased to the level of young sedentary controls.

Correlation between neurogenesis and exercise was first established in mice through MRI measurements of angiogenesis (blood volume) (Cotman & Berchtold, 2002). Among all hippocampus subregions, exercise was found to have a primary effect on the dentate gyrus cerebral blood volume (CBV), the dentate gyrus was only subregion known to support adult neurogenesis. Moreover, exercise-induced increases in dentate gyrus CBV were found to correlate with postmortem measurements of neurogenesis. Using similar MRI technologies, CBV maps were generated over time in the hippocampus of exercising humans. As in mice, exercise was found to have a primary effect on dentate gyrus CBV, and the CBV changes were found to selectively correlate with cardiopulmonary and cognitive functions.

Another significant effect of exercise is an increase of brain-derived neurotropic factor (BDNF) in the hippocampus, which supports the survival of existing neurons and encourages the growth and differentiation of new neurons and synapses (Charney, 2012; Muotri, Marchetto, Zhao, & Gage, 2009). The levels of hippocampal BDNF are significantly higher in wheel

running as opposed to sedentary rodents after 5 days, and correlates with the level of activity. There is also 3.1 fold as many new neurons in the dentate gyrus of running compared to sedentary mice.

Most intriguingly, running also increases retrotransposon activity, reflected in the number of new insertions of long interspersed nucleotide elements (LINEs-1, of L1) in the hippocampus, and also activates silenced L1 insertions in other non-neurogenic brain regions (Belleville et al., 2011). Such regulated "natural genetic engineering" processes are now found to be particularly active in the brain, and are strongly associated with normal brain function (Charney, 2012) (see also Ho, 2009c).

The correlations between BDNF, neurogenesis, and L1 insertions are presented in Fig. 4.1 (Charney, 2012).

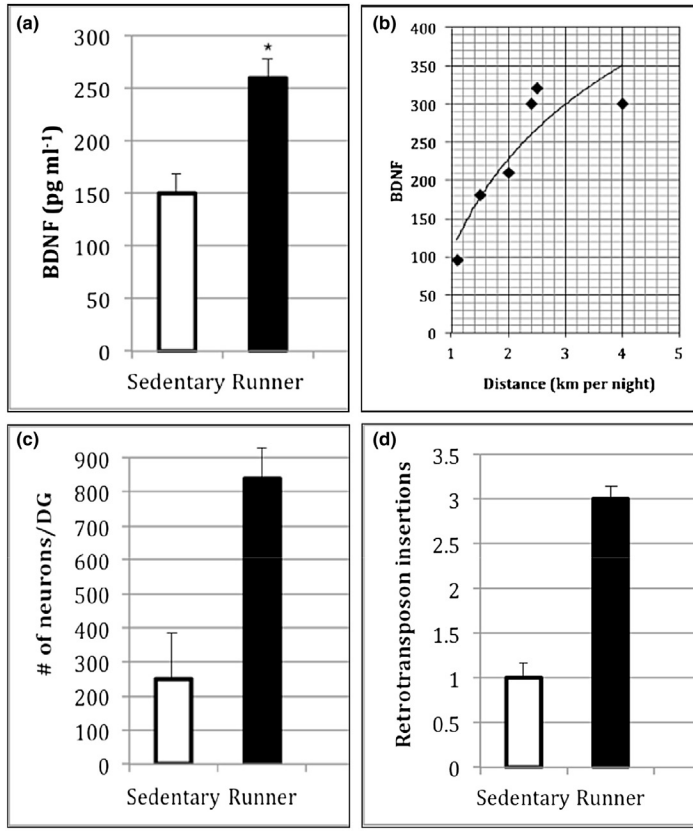

Figure 4.1 Correlations between physical exercise and increase in BDNF neuronal growth factor (A, B), number of new neurons generated (C), and retrotransposon insertions (D). *(Redrawn after Charney (2011), Charney (2012)).*

7. TO CONCLUDE

There is now an overwhelming evidence that perinatal nutrition, education and enrichment programs, and physical exercise are all highly effective in improving the brain function, as well as health and well-being, and for all age groups. For far too long, our policy makers have been misled and misinformed into believing that intellectual ability and health are largely determined by the genes, and hence social and environmental interventions would have little or no effect. This pernicious genetic determinist ideology has now been definitively and thoroughly refuted by a convergence of findings in molecular genomics and biometrical genetics. It is our responsibility to take immediate action in all the appropriate remedial and proactive interventions to safeguard the physical and mental health and well-being of the nation for the present and future generations.

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