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Intelligence: Genetics, Genes, and Genomics

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More is known about the genetics of intelligence than about any other trait, behavioral or biological, which is selectively reviewed in this article. Two of the most interesting genetic findings are that heritability of intelligence increases throughout the life span and that the same genes affect diverse cognitive abilities. The most exciting direction for genetic research on intelligence is to harness the power of the Human Genome Project to identify some of the specific genes responsible for the heritability of intelligence. The next research direction will be functional genomics—for example, understanding the brain pathways between genes and intelligence. Deoxyribonucleic acid (DNA) will integrate life sciences research on intelligence; bottom-up molecular biological research will meet top-down psychological research in the brain.

As indicated in the preface to this special section on intelligence, the centenary of Spearman's seminal article on intelligence (Spearman, 1904) is an appropriate moment to take stock of what we know about this oldest of personological constructs at diverse levels of analysis—genes, physiology, psychology, and sociology—throughout the life span. More is known about the genetics of individual differences in intelligence than any other behavioral trait. This research is reviewed briefly in the first section of the present article—Genetics. The second section—Genes—describes current attempts to harness the power of the Human Genome Project in order to identify some of the presumably many genes responsible for the heritability of intelligence. The third section—Genomics—discusses the next step, functional genomics, which attempts to chart pathways between genes and intelligence.

To be able to address these issues, this article needs to assume basic understanding of the psychometric construct of intelligence, which is described in the preface and in other articles in this special section (see also books by Bock, Goode, & Webb, 2000; Brody, 1992; Deary, 2000). The problem with the word *intelligence* is that it means different things to different people. The present article uses the psychometric definition of intelligence as general cognitive ability—Spearman's *g*, which was discovered at the same time that Mendel's laws of inheritance were rediscovered (Spearman, 1904). That is, the word *intelligence* will be used to refer to the substantial covariation among diverse measures of cognitive ability as indexed by an unrotated first principal-component score, which typically accounts for about 40% of the total variance of diverse cognitive tests, or by a total score across diverse tests as is done in intelligence tests (Jensen, 1998). We also forgo a discussion of the relationship between intelligence and personality, which is discussed in the preface to this special section. In terms of genetics, reviews have been written about traditional personality traits such as the five-factor model (Loehlin, 1992; Plomin, DeFries, McClearn, & McGuffin, 2001); intelligence is especially related to Openness to Experience (McCrae & Costa, 1997). Personality and its relationship to psychopathology has also increasingly become a target for molecular genetic research aimed at identifying specific genes responsible for the ubiquitous heritability of personality traits (Benjamin, Ebstein, & Belmaker, 2002).

It is also necessary to assume at least some passing familiarity with quantitative genetics and molecular genetics. Quantitative genetics is a theory of familial resemblance for complex traits that leads to methods like the twin method and adoption method, which decompose phenotypic variance into genetic and environmental components of variance. Molecular genetics identifies variations in deoxyribonucleic acid (DNA) sequence that are associated with phenotypic variance. Basic descriptions of quantitative genetics and molecular genetics in relation to behavioral research are available elsewhere (Plomin, DeFries, et al., 2001).

Genetics

Intelligence was one of the first human traits to be the target of genetic research even before psychology emerged as a scientific field. A year before the publication of Mendel's seminal article on the laws of heredity, Galton (1865) published a two-article series on high intelligence and other abilities, which he later expanded into the first book on heredity and intelligence (Galton, 1869). Galton (1883) provoked a needless battle that raged through the 20th century by arguing that "there is no escape from the conclusion that nature prevails enormously over nurture" (p. 241), especially because his research on family resemblance could not by itself disentangle genetic and environmental influences. Although Galton (1876) suggested the twin design and the adoption design, the first twin and adoption studies were not carried out until the 1920s—each of these investigated intelligence (Burks, 1928; Freeman, Holzinger, & Mitchell, 1928; Merriman, 1924; Theis, 1924). The first animal model research on learning and problem solving

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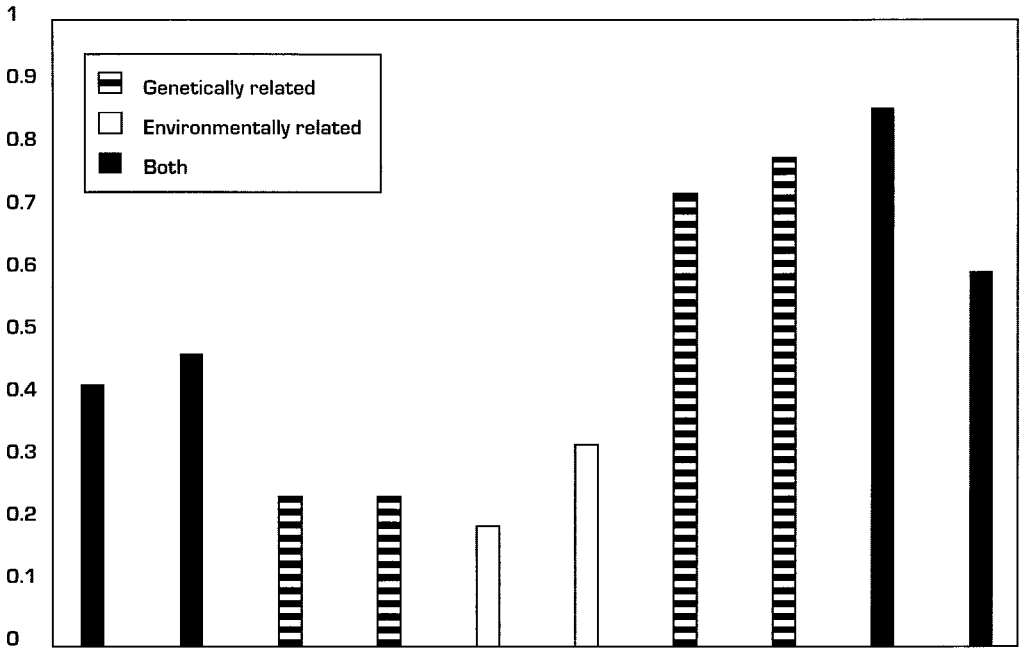
was also relevant to individual differences in intelligence, most notably the successful selection study of maze-bright and maze-dull rats bred initially by Tolman in 1924 and continued by Tryon (described by McClearn, 1963). In the 1950s and 1960s, studies of inbred strains of mice showed the important contribution of genetics to individual differences for most aspects of learning.

In 1963, a review in *Science* of genetic research on intelligence was influential in showing the convergence of evidence from family, twin, and adoption studies pointing to genetic influence (Erlenmeyer-Kimling & Jarvik, 1963). During the 1960s, environmentalism was beginning to wane in psychology and the stage was set for increased acceptance of genetic influence on intelligence. Then, in 1969, a *Harvard Educational Review* monograph (Jensen, 1969) almost brought the field to a halt because it suggested that ethnic differences might involve genetic differences. Exactly 25 years later, this issue was resurrected in *The Bell Curve* (Herrnstein & Murray, 1994) and caused a similar uproar.

The storm raised by Jensen's (1969) monograph led to intense criticism of all behavioral genetic research, but especially research in the area of intelligence (e.g., Kamin, 1974). These criticisms had the positive effect of generating about a dozen bigger and better behavioral genetic studies that produced much more data on the genetics of intelligence than had been obtained in the previous 50 years. Intelligence is the target of more genetic research than any other domain in science, with the exception of self-report personality questionnaires. Some of the new data and all of the old data were summarized in another influential *Science* article (Bouchard & McGue, 1981) that began to turn the tide in psychology toward acceptance of genetic influence on intelligence (Neisser et al., 1996; Snyderman & Rothman, 1987, 1988). Figure 1 summarizes the review and updates it (Plomin, DeFries, et al., 2001). For example, in studies of more than 10,000 monozygotic (MZ) and dizygotic (DZ) pairs of twins, the average MZ correlation is .86, which is near the test–retest reliability of the measures, in contrast



Relationship	P-O	Sib	P-O	Sib	P-O	Sib	Old MZ	New MZ	MZ	DZ
Number of pairs	8,433	26,473	720	203	1,397	714	65	93	4,672	5,533
Genetic relatedness	0.5	0.5	0.5	0.5	0.0	0.0	1.0	1.0	1.0	0.5
Same home?	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes

Figure 1. Average IQ correlations for family, adoption, and twin designs. On the basis of reviews by Bouchard and McGue (1981) as amended by Loehlin (1989). Data for "old" data for monozygotic (MZ) twins exclude the suspect data of Burt (1966); the "new" data include Bouchard, Lykken, McGue, Segal, and Tellegen (1990) and Pedersen, McClearn, Plomin, and Nesselroade (1992). DZ = dizygotic, P-O = parent–offspring; Sib = sibling. From *Behavioral Genetics* (4th ed., Figure 9.7, p. 168), by R. Plomin, J. C. DeFries, G. E. McClearn, and P. McGuffin (Eds.), 2001, New York: Worth. Copyright 2001 by W. H. Freeman/Worth. Adapted with permission.

to the DZ correlation of .60. Adoption data, including adopted-apart parents and offspring and adopted-apart siblings as well as MZ twins adopted apart, also point to substantial genetic influence. Model-fitting analyses that simultaneously analyze all of the family, adoption, and twin data summarized in Figure 1 yield heritability estimates of about 50% (Chipuer, Rovine, & Plomin, 1990; Loehlin, 1989). In other words, about half of the total variance (which includes error of measurement) can be attributed to DNA differences between individuals. Heritability is of course higher if corrections are made for error of measurement as in analyses of latent variables free of measurement error. Even an attempt to explain as much of the variance of *g* as possible in terms of prenatal effects nonetheless yielded a heritability estimate of 48% (Devlin, Daniels, & Roeder, 1997; McGue, 1997). Although most of this research was conducted in the United States and Western European countries, similar estimates of heritability have been found in countries such as Moscow, the former East Germany, Japan, and rural and urban India (Plomin, DeFries, et al., 2001).

The convergence of evidence on the conclusion that individual differences in intelligence are substantially heritable led to a decline in the 1990s of genetic research on intelligence that merely aimed to investigate the heritability of intelligence. Instead, genetic designs were used to go beyond estimating heritability in order to ask questions about environmental influences, developmental change and continuity, and multivariate issues. Before discussing these three topics, it should be noted that assortative mating for intelligence is substantial. Correlations between spouses are only about .10 for other personality traits and about .20 for height and weight, but assortative mating for intelligence is about .40 (Plomin, DeFries, et al., 2001). The importance of assortative mating is that it increases genetic variance generation after generation and may thus contribute to the high heritability of intelligence. Twin studies that do not take assortative mating into account underestimate heritability because the genetic effects of assortative mating inflate the DZ correlation but not the MZ correlation (Plomin, DeFries, et al., 2001).

Environment

Concerning the environment, genetic research provides the best available evidence for the importance of environmental influences on intelligence: If heritability is 50%, that means that environmental factors account for the rest of the reliable variance. Two of the most important findings from genetic research are about nurture rather than nature. First, nearly all personality traits show that, contrary to theories of socialization from Freud onwards, environmental influences operate to make siblings growing up in the same family as different from one another as children growing up in different families (Harris, 1998; Plomin & Daniels, 1987). However, intelligence is the exception to this rule of nonshared environmental influence (Plomin, 1988). Direct estimates of the importance of shared environmental influence come from correlations of .19 for adoptive parents and their adopted children and .32 for adoptive siblings (see Figure 1). Because adoptive siblings are unrelated genetically, what makes them similar is shared rearing, suggesting that about a third of the total variance can be explained by shared environmental influences. The factors responsible for this shared environmental influence have not been pinned down, although general family background variables such as socioeconomic status are likely to contribute. There has been one largely unsuccessful attempt to identify specific aspects of the home environment that are responsible for the shared environmental influence on intelligence in childhood (Chipuer & Plomin, 1992). However, as explained in the following section on development, although shared environment is important for intelligence in childhood, its importance declines to negligible levels after adolescence. In other words, shared environmental factors relevant to intelligence would be expected to show associations in childhood but not later in development. Moreover, this finding suggests that, even for intelligence, the salient environmental factors are nonshared after childhood.

The second finding has been called the *nature of nurture* (Plomin & Bergeman, 1991). When used as outcome measures in genetic research, environmental measures consistently point to some genetic influence, suggesting that genetic factors influence the way we react and interact with the environment, a type of genotype-environment correlation (Kendler & Eaves, 1986). For example, a widely used measure of the home environment in research on cognitive development is the Home Observation for Measurement of the Environment (HOME; Bradley, Convyn, Burchinal, McAdoo, & Coll, 2001). In an adoption study comparing nonadoptive and adoptive siblings, genetic influences were estimated to account for about 40% of the variance of HOME scores (Braungart, Fulker, & Plomin, 1992). Moreover, multivariate genetic analysis (described below) indicated that about half of the phenotypic correlation between the HOME and children's intelligence is mediated genetically. This research suggests that we create our experiences in part for genetic reasons and supports a current shift from thinking about passive models of how the environment affects individuals toward models that recognize the active role we play in selecting, modifying, and creating our own environments (Plomin, 1994). In quantitative genetics, this topic is referred to as active genotype-environment correlation (Plomin, DeFries, et al., 2001).

Development

Two types of developmental questions have been addressed in genetic research. The first question is: Does heritability change during development? Because it is so reasonable to assume that genetic differences become less important as experiences accumulate during the course of life, one of the most interesting findings about intelligence is that the opposite is closer to the truth. Research during the past decade has shown that the heritability of *g* increases during development. Figure 2 summarizes twin results by age (McGue, Bouchard, Iacono, & Lykken, 1993), showing that the difference between MZ and DZ twin correlations increases slightly from early to middle childhood and then increases dramatically in adulthood. Because relatively few twin studies of intelligence have included adults, summaries of intelligence data (see Figure 1) showing heritability estimates of about 50% rest primarily on data from childhood. Heritability in adulthood is higher, perhaps as high as 80%, although there is some evidence that heritability late in life might be lower (Finkel, Pedersen, McGue, & McClearn, 1995). A finer grained analysis of twin results indicates that heritability is lower in infancy (about 20%) than in middle childhood (about 40%; Plomin, 1986). The modest heritability of intelligence in early childhood was confirmed in a

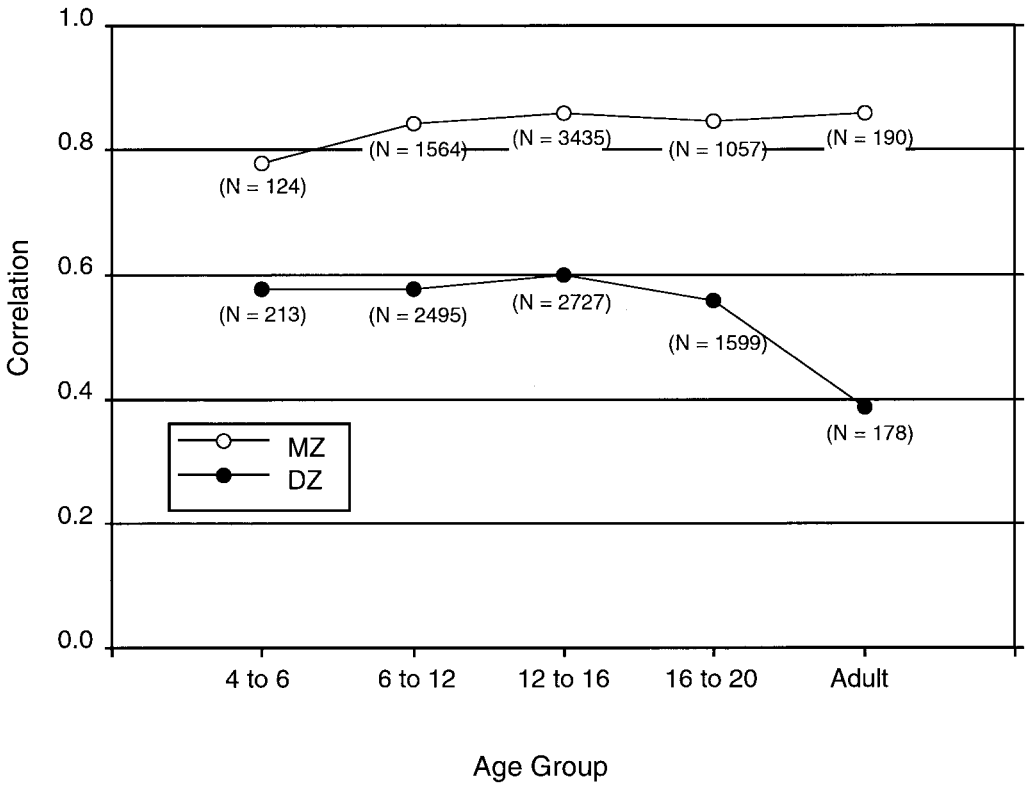


Figure 2. The difference between monozygotic (MZ) and dizygotic (DZ) twin correlations for intelligence increases during development suggesting increasing genetic influence. Adapted from "Behavioral Genetics of Cognitive Ability: A Life-Span Perspective" (Figure 1, p. 63, by M. McGue, T. J. Bouchard Jr., W. G. Iacono, & D. T. Lykken, in *Nature, Nurture, and Psychology,* by R. Plomin and G. E. McClearn (Eds.), 1993, Washington, DC: American Psychological Association. Copyright 1993 by the American Psychological Association.

recent study of nearly 7,000 twin pairs assessed longitudinally using parent-administered tests, which yielded heritability estimates of .27, .30, and .25 at 2, 3, and 4 years, respectively (Spinath, Ronald, Harlaar, Price, & Plomin, 2003).

Results from a 16-year longitudinal adoption study support this view of increasing heritability (Plomin, Fulker, Corley, & DeFries, 1997). As shown in Figure 3, parent–offspring correlations for parents (called *control parents*) who share both genes and environment with their offspring increase during childhood and adolescence, as has been found in other family studies, and this is not due to increased reliability of assessing infant intelligence (Bayley, 1969). The adoption design directly assesses the genetic contribution to this parent–offspring resemblance by studying biological (birth) parents and their adopted-away offspring. Correlations between biological parents and their adopted-away offspring are similar to the correlations for control parents and offspring. In contrast, these adopted children show no resemblance to the parents who adopted them.

Why does heritability of *g* increase during the life span? It is possible that completely new genes come to affect *g* as more sophisticated cognitive processes come on line during development. However, another hypothesis is that relatively small genetic effects early in life snowball during development, creating larger and larger phenotypic effects as individuals select or create environments that foster their genetic propensities (Plomin & DeFries, 1985). This hypothesis relates to the notion of active genotype-environment correlation, which was mentioned earlier.

Another developmental finding of great importance concerns shared environmental influence. As noted earlier, intelligence, unlike other personality traits, shows shared environmental influence. The twin data summarized in Figure 2 suggest that shared environment effects are negligible in adulthood. Data for adoptive siblings summarized in Figure 1, which provides a direct test of shared environment, indicate substantial shared environmental influence. However, the studies of adoptive siblings summarized in Figure 1 assessed the adoptive siblings when they were children. Recent studies of adoptive siblings assessed after adolescence show an average correlation of zero (McGue et al., 1993). These results indicate that although shared environment affects intelligence in childhood, in the long run environmental influences on intelligence are nonshared.

A second type of developmental question involves analyses of change and continuity using longitudinal data. Data of this type are analyzed using multivariate genetic analysis (described below), but a simple way to think about genetic contributions to developmental change is to ask whether changes in intelligence scores from age to age show genetic influence. Longitudinal research indicates that genetic factors account in part for such changes, especially in childhood (Fulker, Cherny, & Cardon, 1993) and perhaps even in adulthood (Loehlin, Horn, & Willerman, 1989), although most

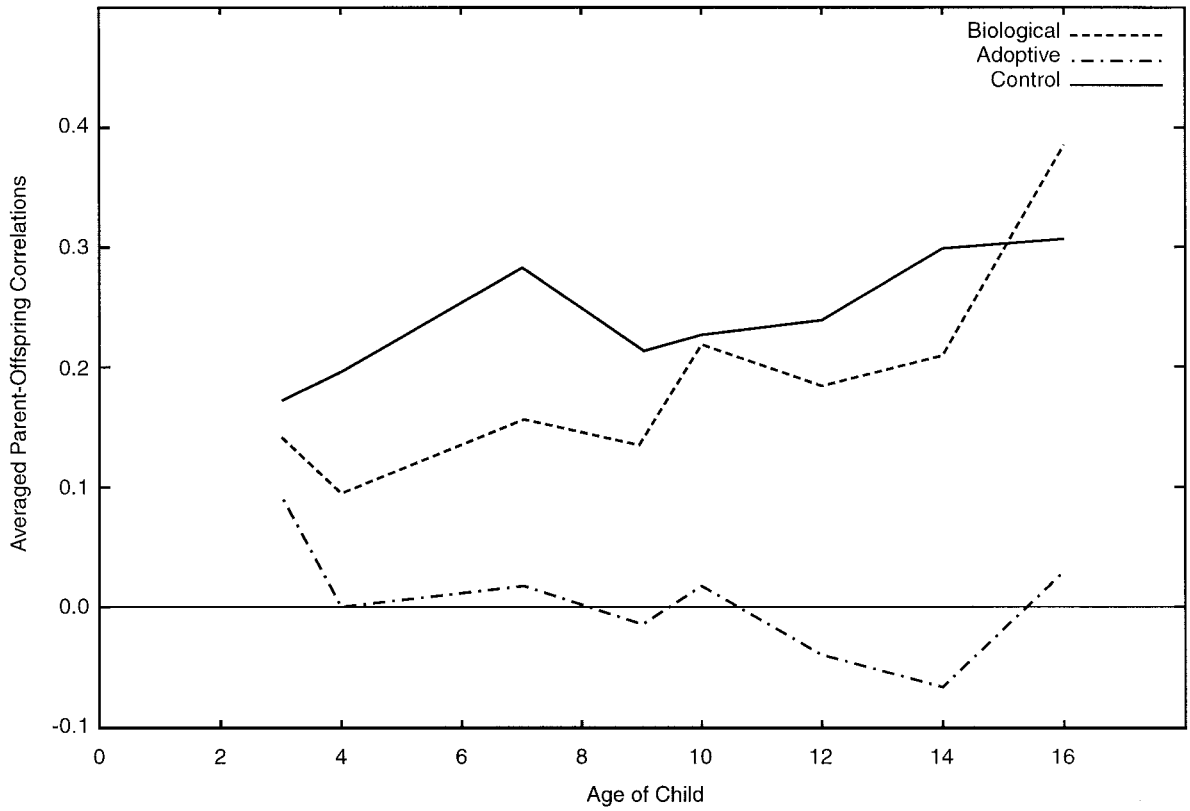


Figure 3. Parent–offspring correlations between parent and offspring intelligence scores for biological mothers and adoptive and control parents and their children at 3, 4, 7, 9, 10, 12, 14, and 16 years. Adoptive and control parent–offspring correlations are weighted averages for mothers and fathers in order to simplify the presentation. The sample sizes range from 159 to 195 for biological mothers, 153 to 194 for adoptive parents, and 136 to 216 for control parents. From "Nature, Nurture and Cognitive Development from 1 to 16 years: A Parent–Offspring Adoption Study," by R. Plomin, D. W. Fulker, R. Corley, and J. C. DeFries, 1997, *Psychological Science, 8,* Figure 1, p. 443. Copyright 1997 by Blackwell Publishers. Adapted with permission.

genetic effects on intelligence contribute to continuity rather than change even late in life (Plomin, Pedersen, Lichtenstein, & McClearn, 1994). Unlike genetic effects, longitudinal genetic analysis suggests that shared environmental effects contribute only to continuity in childhood. In other words, some relatively constant factors such as the family's socioeconomic status might account for the developmental continuity of shared environmental influence on intelligence.

Multivariate Analysis

Specific cognitive abilities such as verbal ability, spatial ability, and memory show substantial genetic influence, although less than for general intelligence (Plomin & DeFries, 1998). To what extent do different sets of genes affect different abilities? We know that diverse cognitive tests correlate moderately—this is the basis for Spearman's *g*. A meta-analysis of all cognitive studies yielded an average correlation of about .30 (Carroll, 1993), although studies using less restricted samples and more reliable measures yield higher intercorrelations (Jensen, 1998). A technique called *multivariate genetic analysis* can be used to examine genetic and environmental contributions to the phenotypic covariance among specific cognitive abilities (Plomin, DeFries, et al., 2001). Multivariate genetic analysis yields a statistic called *genetic correlation*, which is an index of the extent to which genetic effects on one trait correlate with genetic effects on another trait independent of the heritability of the two traits. That is, two traits could be highly heritable but the genetic correlation between them could be zero. Conversely, two traits could be only modestly heritable but the genetic correlation between them could be 1.0, indicating that even though genetic effects are not strong (because heritability is modest) the same genetic effects are involved in both traits. In the case of specific cognitive abilities that are moderately heritable, multivariate genetic analyses have consistently found that genetic correlations are very high—close to 1.0 (Petrill, 1997). That is, although Spearman's *g* is a phenotypic construct, *g* is even stronger genetically. These multivariate genetic results predict that when genes are found that are associated with one cognitive ability, such as spatial ability, they will also be associated just as strongly with other cognitive abilities, such as verbal ability or memory. Conversely, attempts to find genes for specific cognitive abilities independent of general cognitive ability are unlikely to succeed because what is in common among cognitive abilities is

largely genetic and what is independent is largely environmental. Identifying genes associated with cognitive abilities will test the hypothesis that the same genes affect diverse cognitive abilities.

This finding of substantial genetic overlap among cognitive abilities also has important implications for understanding the brain mechanisms that mediate genetic effects on intelligence. In contrast to the prevalent modular view of cognitive neuroscience that assumes that cognitive processes are specific and independent, these results suggest that genetic effects are general (Plomin & Spinath, 2002). Recent multivariate genetic research on so-called elementary cognitive processes thought to underlie general intelligence suggests that genetic correlations are just as strong among these elementary cognitive processes. In other words, the genetic version of Spearman's *g* also emerges at the level of elementary cognitive processes. It might also exist in the brain. For example, recent twin studies using magnetic resonance imaging to assess brain volume find that brain volume is highly heritable, substantially intercorrelated across brain regions, and moderately correlated with intelligence (Pennington et al., 2000; Thompson et al., 2001). Although the reductionistic model of brain → cognition → behavior is deeply embedded in our thinking, an agnostic model in which brain, cognitive, and psychometric measures are considered merely as correlates rather than causes of the genetic version of Spearman's *g* is all that is warranted from the data so far (Plomin & Spinath, 2002).

A second issue concerns the relationship between the normal and abnormal. For example, to what extent is mild mental retardation (MMR) genetically distinct from the rest of the distribution of intelligence? Surprisingly, no twin or adoption studies of MMR have been reported until recently (see the next paragraph). More than 200 rare single-gene disorders include mental retardation, often severe retardation, as a symptom (Zechner et al., 2001), and many chromosomal causes of mental retardation are also known (Plomin, DeFries, et al., 2001), including microdeletions of bits of chromosomes (Baker et al., 2002; Knight et al., 1999). In general, many of the single-gene mutations tend to be spontaneous in the affected individual as are most of the chromosomal anomalies. That is, these DNA causes of severe mental retardation are not usually inherited. Although no twin studies of severe mental retardation have been reported, an interesting sibling study shows no familial resemblance. In a study of over 17,000 children, 0.5% were moderately to severely retarded (Nichols, 1984). As shown in Figure 4 (dotted line), siblings of these retarded children were not retarded. The siblings' average IQ was 103, with a range of 85 to 125. In other words, moderate to severe mental retardation showed no familial resemblance, a finding implying that mental retardation is not heritable. In contrast, siblings of mildly retarded children (1.2% of the sample) tend to have lower than average IQ scores (see Figure 4, solid line). The average IQ for these siblings of mildly retarded children was only 85. Similar findings—that MMR is familial but moderate and severe retardation are not familial—also emerged from the largest family study of MMR, which considered 80,000 relatives of 289 mentally retarded individuals (Reed & Reed, 1965).

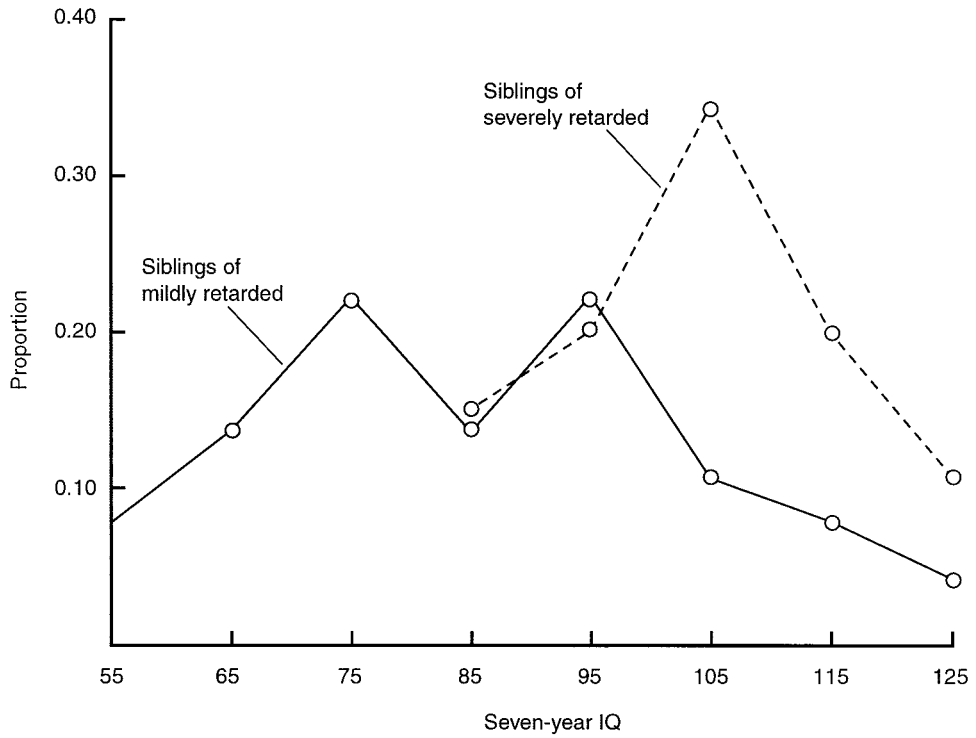


Figure 4. Siblings of severely retarded children tend to have normal IQs, whereas siblings of mildly retarded children tend to have lower than normal IQs. These results suggest that mild retardation is familial and perhaps heritable but severe retardation is not. From *Behavioral Genetics* (4th ed., p. 162) by R. Plomin, J. C. DeFries, G. E. McClearn, and P. McGuffin, 2001, New York: Worth Publishers. Copyright 2001 by W. H. Freeman/Worth. Reprinted with permission. From "Familial Mental Retardation," by P. L. Nichols, 1984, *Behavior Genetics, 14,* p. 167. Copyright 1984 by Kluwer Academic. Adapted with permission.

The vast majority of quantitative genetic research on disorders focuses on the dichotomous diagnosis itself rather than on a quantitative trait. Using a diagnostic or quantitative cutoff, most studies assess concordances—the risk that a family member of a proband will also have the disorder. For example, the first large twin study of MMR selected children from the lowest 5% of the distribution from a representative sample of 3,886 twins in same-sex and opposite-sex pairs on the basis of an aggregate intelligence score obtained at 2, 3, and 4 years of age (Spinath, Harlaar, Ronald, & Plomin, in press). Twin concordances were 74% for MZ twins, 45% for DZ same-sex (DZS) twins, and 36% for DZ opposite-sex (DZO) twins, suggesting substantial genetic influence for the lowest end of the distribution of intelligence. However, unlike twin similarity coefficients such as MZ and DZ intraclass correlations, concordances cannot be used to estimate heritability simply by doubling the difference in MZ and DZ concordances. Instead, concordances are typically converted into liability (tetrachoric) correlations on the assumption that a continuum of genetic risk or liability underlies the dichotomous diagnosis and that the disorder is seen only when a certain threshold of liability is exceeded (Falconer, 1965; Neale, Boker, Xie, & Maes, 1999).

Rather than assessing a dichotomy and assuming a continuum with a threshold, however, it is advantageous to use the continuum of IQ scores directly. An approach that uses quantitative scores to assess family resemblance for a dichotomous diagnosis has been systematized as an analytic strategy that is called *DF extremes analysis* (DeFries & Fulker, 1985, 1988). DF extremes analysis assesses the extent to which the mean quantitative trait score of cotwins of MMR probands differs from the population mean on the quantitative trait. "Group" familiality is indicated to the extent that the cotwin mean is closer to the proband mean than to the population mean. This familial resemblance is called *group familiality* because it refers to the familial origins of the average difference between the probands and the population, not to individual differences among the probands.

Genetic influence on the mean quantitative trait score difference between the probands and the population is indicated to the extent that the average quantitative trait score of MZ cotwins is more similar to the proband mean than is the DZ cotwin mean. This estimate of heritability is called *group heritability* because it indicates the extent to which the mean quantitative trait score difference between probands and the population can be explained by genetic factors. Initially conceptualized as a regression method that was limited to the analysis of same-sex twin pairs, the basic DF model has recently been reframed in model-fitting terms allowing DZO to be incorporated in a sex-limitation model that tests for sex differences in genetic and environmental parameters (Purcell & Sham, 2003). In the study of MMR in young children mentioned earlier, the mean quantitative trait score of DZS and DZO cotwins as compared with MZ cotwins regressed farther toward the population mean, suggesting genetic influence on the mean quantitative trait score difference between the MMR probands and the unselected population. DF extremes analysis yielded a group heritability (h^2g) estimate of .49 (CI = .29, .69). In other words, about half of the difference between the MMR probands and the population can be attributed to genes.

This group heritability estimate of .49 is significantly greater than the heritability of individual differences in the sample from which the MMR probands were selected, which is a typically modest heritability estimate for early childhood (h^2 = .24, CI = .21, .27), suggesting that genetic factors have a stronger effect at the low end of the distribution. This finding does not necessarily mean that different genes affect MMR and the rest of the distribution of intelligence. For example, it is possible that the environment has less impact on individuals at high genetic risk. The extent to which the same genes affect MMR and the rest of the distribution will not be known definitively until specific genes are found for MMR or intelligence. However, finding group heritability implies that there is a genetic relationship between MMR and individual differences in the quantitative trait across the normal range. For this reason, it seems likely that MMR is at the lower end of the distribution of genetic and environmental factors that are responsible for individual differences in intelligence, despite the higher heritability for MMR (Plomin, 1999). Research in this same vein on high intelligence suggests that group heritability is similar to the heritability of individual differences in intelligence (Plomin & Price, 2003; Ronald, Spinath, & Plomin, 2002).

Genes

The 20th century began with the rediscovery of Mendel's laws of heredity. The word *gene* was first coined in 1903. Fifty years later the double helix structure of DNA was discovered. The genetic code was cracked in 1966—the four-letter alphabet (G, A, T, C) of DNA is read as three-letter words that code for the 20 amino acids that are the building blocks of proteins. The crowning glory of the century and the beginning of the new millennium is the Human Genome Project, which has provided a working draft of the sequence of the 3 billion letters of DNA in the human genome, nucleotide bases that are the steps in the spiral staircase of DNA (International Human Genome Sequencing Consortium, 2001; Venter et al., 2001).

Progress is also being made toward identifying all of the genes from the genome sequence. In the traditional sense of the "central dogma" of DNA, a gene is DNA that is transcribed into ribonucleic acid (RNA), and then translated into amino acid sequences. Less than 2% of the more than 3 billion bases of DNA in the human genome are of this sort. It is not yet known how many such genes there are in the human genome. It used to be said that there are 100,000 genes, but the 2001 working draft of the human genome suggested far fewer, perhaps as few as 30,000, although estimates of the number of genes have been rising again subsequently. Moreover, some of the other 98% of DNA may be important. One example is DNA that is transcribed into RNA but not translated. For nearly all genes, a complicated process called *splicing* occurs between transcription and translation. All of the DNA within a gene is transcribed into RNA, but segments of RNA (called *introns*) are deleted and remain in the nucleus whereas the other segments (called *exons*) are spliced back together and exit the nucleus where they are translated into amino acid sequences. Although introns have been thought to be genetic junk that have hitched a ride evolutionarily, it is now known that in some cases introns regulate the transcription of other genes (Mattick, 2001). Exons are conserved evolutionarily—most of our exons are highly similar to DNA sequences in primates, mammals, and even invertebrates. This implies that the sheer number of such genes is not responsible for the greater complexity of the human species. More subtle variations in DNA rather than the number of genes may be

responsible for differences between mice and men (Brett, Pospisil, Valcarcel, Reich, & Bork, 2002). If subtle DNA differences are responsible for the differences between mice and men, even more subtle differences are likely to be responsible for individual differences within the human species. Although many single-gene disorders involve mutations in exons, introns might be sources of quantitative trait loci (QTLs) that have more subtle effects on gene regulation. Another example indicating that there is still much to learn about genes is the recent discovery of RNA genes called microRNA (Eddy, 2001). Rather than just encoding proteins, some very short noncoding RNA sequences produce functional RNA molecules that seem to be especially important in regulating gene expression.

For behavioral genetics, the most important next step is the identification of the DNA sequences that make us different from each other. There is no single human genome sequence—we each have a unique genome. Most of the DNA letters in the four-letter alphabet of DNA are the same for all human genomes—and many of these are the same for other primates and other mammals and even insects. Nevertheless, about one in every thousand DNA letters differs among people with at least 1% frequency, which means that there are about 3 million DNA variations in total, enough to make us each differ for almost every gene. Most of these DNA differences involve a substitution of a single base pair, called *single nucleotide polymorphisms* (SNPs, pronounced "snips"). These DNA differences are responsible for the widespread heritability of behavioral disorders and dimensions. That is, when we say that a trait is heritable, we mean that variations in DNA exist that cause differences in behavior. Particularly useful are SNPs in coding regions (cSNPs) that result in differences in the amino acid sequences coded by DNA and other SNPs that are potentially functional such as SNPs in DNA control regions that regulate the transcription of genes. The major beneficiary of these advances in molecular genetics will be research on complex traits such as intelligence that are influenced by multiple genes as well as multiple environmental influences.

One of the most exciting directions for genetic research on intelligence is to harness the power of the Human Genome Project to begin to identify specific genes responsible for the heritability of intelligence. It should be noted that DNA variation has a unique causal status in explaining behavior. When behavior is correlated with anything else, the old adage applies that correlation does not imply causation. For example, although aspects of the family environment correlate with children's intelligence, this correlation is not necessarily causal. As mentioned earlier, behavioral genetic research has shown that family environment in part reflects genetic influences on children's intelligence. When it comes to interpreting correlations between biology and behavior, such correlations are often mistakenly interpreted as if biology causes behavior. For example, correlations between neurotransmitter physiology and behavior or between neuroimaging indices of brain activation and behavior are often interpreted as if brain differences cause behavioral differences. However, these correlations do not necessarily imply causation because behavioral differences can cause brain differences. In contrast, in the case of correlations between DNA variants and behavior, the behavior of individuals does not change their genome. Expression of genes can be altered but the DNA sequence itself does not change (except in the evolutionary sense of natural selection). For this reason, correlations between DNA differences and behavioral differences can be interpreted causally: DNA differences can cause the behavioral differences but not the other way around.

Linkage

The first generation of DNA research, which began in the 1980s, focused on the thousands of rare single-gene disorders, such as Huntington's disease, in which a single gene is necessary and sufficient for the emergence of the disorder. The heritability of such single-gene disorders is 100%, which makes their localization on a chromosome and then the ultimate pinpointing of a particular DNA sequence relatively straightforward. The standard approach, first used successfully to localize the gene for Huntington's disease to the tip of chromosome 4 in 1983 (Gusella et al., 1983), was to look for linkage in large family pedigrees between the disease and one of a few hundred DNA markers evenly spread throughout the chromosomes. Linkage is a violation of Mendel's second law of independent assortment that posits that two traits will be inherited independently. Mendel did not know that genes are on chromosomes. If two genes—for example, a gene for a disorder and a DNA marker—are close together on a chromosome, they may be inherited as a package within families rather than independently as predicted by Mendel's second law. For example, the linkage of Huntington's disease with DNA markers was found in a single five-generation family of hundreds of individuals when a particular form (called *allele*) of a DNA marker on chromosome 4 was only found in family members who had Huntington's disease. Similar linkage studies have identified the chromosomal location of hundreds of single-gene disorders and the precise DNA fault has been found for many of these disorders.

Linkage studies of this type were also undertaken for psychiatric disorders even though there was no suggestion that such complex disorders are inherited as single-gene disorders. Early successes were claimed for bipolar depression (Egeland et al., 1987) and for schizophrenia (Sherrington et al., 1988), but neither claim was replicated. It is now clear that this traditional linkage approach can only detect a linkage if the gene has a very large effect on the disorder, a situation limited to relatively rare disorders such as Huntington's disease, which has a frequency of about 1 in 20,000 individuals. Common disorders including cognitive problems such as learning disabilities in childhood and dementia late in life seldom show any sign of single-gene effects and appear to be caused by multiple genes as well as by multiple environmental factors. Indeed, quantitative genetic research mentioned earlier suggests that such common disorders are usually the quantitative extreme of the same genes responsible for variation throughout the distribution (Plomin, Owen, & McGuffin, 1994). Genes in such multiple-gene systems are called QTLs because they are likely to result in dimensions (quantitative continua) rather than in disorders (qualitative dichotomies). In other words, in terms of the genetic etiology of common disorders, there may be no disorders, just dimensions. The QTL perspective is the molecular genetic extension of quantitative genetics in which genetic variation is viewed as normal and is distributed quantitatively.

The goal of QTL research is not to find *the* gene for a complex trait, but rather the multiple genes that make contributions of varying effect sizes to the variance of the trait. Perhaps one gene will be found that accounts for 5% of the variance, 5 other genes

might each account for 2% of the variance, and 10 other genes might each account for 1% of the variance. If the effects of these QTLs are independent, the QTLs would in total account for 25% of the trait's variance. All of the genes that contribute to the heritability of a complex trait are unlikely to be identified because some of their effects may be too small to detect. The problem is that we do not know the distribution of effect sizes of QTLs for any complex trait in plant, animal, or human species. Not long ago, a 10% effect size was thought to be small, at least from the single-gene perspective in which the effect size was essentially 100%. However, for behavioral disorders and dimensions, a 10% effect size may turn out to be a very large effect. If effect sizes are as small as 1%, this would explain the slow progress to date in identifying genes associated with behavior because research so far has been woefully underpowered to detect and replicate QTLs of such small effect size (Cardon & Bell, 2001).

Recent research has been more successful in finding QTLs for complex traits because designs have been used that can detect genes of much smaller effect size. The problem with the traditional large-pedigree linkage method in relation to intelligence and other personality traits is that there is no dichotomous disorder that can be used to chart coinheritance with DNA markers within families. There have been no traditional linkage studies of intelligence or other quantitative traits, although, as mentioned earlier, linkage has been successful in leading to the identification of more than 200 rare single-gene syndromes for which mental retardation is a symptom (Zechner et al., 2001). Linkage has been extended to consider QTLs by using many small families (usually siblings) rather than a few large families. These QTL linkage methods can be used to study the extremes of a quantitative trait or a diagnosed disorder and are able to detect genes that account for about 10% of the variance of the quantitative trait or the assumed liability or susceptibility to the disorder. The essence of the most popular method, called sib-pair QTL linkage analysis, is to ask whether sharing alleles for a particular DNA marker makes siblings more similar phenotypically. Siblings can share zero, one, or two of the alleles that they inherit from their parents. Thus, in relation to a particular DNA marker, a pair of siblings can be like adoptive siblings sharing no alleles, like DZ twins sharing one allele, or like MZ twins sharing the same two alleles. An analysis similar to the twin analysis can be used to analyze the extent to which allele sharing affects sibling phenotypic resemblance. This method was used to identify the first QTL linkage, which was a linkage for reading disability (Cardon et al., 1994), a linkage that has been consistently replicated in several studies (Willcutt et al., 2003). Other QTL linkages for reading have also been reported (S. Fisher, 2003).

Association

A second method, called *allelic association*, can detect QTLs that account for much smaller amounts of variance than linkage (Risch, 2000; Risch & Merikangas, 1996). Association is also simpler than linkage: Association is the correlation between a particular allele and trait in the population. For example, one of the first associations reported for personality was an association between the neuroreceptor gene, dopamine D4 receptor (*DRD4*), and novelty seeking (Benjamin et al., 1996; Ebstein et al., 1996). The DNA marker in the *DRD4* gene has two types of alleles that vary in length. In both studies, individuals with long *DRD4* alleles had significantly higher novelty-seeking scores than did individuals with short alleles. The distributions of novelty-seeking scores for individuals with the short and the long *DRD4* alleles show that the effect is small, accounting for about 4% of the variance in this sample. As would be expected for an association of small effect, many studies have failed to replicate the association, although at least a dozen studies have found it (Prolo & Licinio, 2002). Considering the power of the studies, the results are consistent with a QTL that accounts for about 1% of the variance (Plomin & Caspi, 1998).

The vast majority of association studies involves case-control comparisons for diagnosed disorders. For example, *DRD4* also shows an association with hyperactivity in the expected direction—long alleles are associated with greater risk for hyperactivity (Thapar, 2003). Of 15 published studies, 11 have found evidence of association comparing cases and controls, and a meta-analysis indicates a significant effect with an odds ratio of about 2 (Faraone, Doyle, Mick, & Biederman, 2001). The first such association with a disease was identified for late-onset Alzheimer's disease in 1993 (Corder et al., 1993) and has been replicated in scores of studies (Williams, 2003). The gene is apolipoprotein E (*APOE*), which codes for a serum lipoprotein involved in cholesterol metabolism. One of the *APOE* alleles (*APOE-4*) has a frequency of about 40% in individuals with late-onset Alzheimer's disease and about 15% in controls. In a meta-analysis of 40 studies involving 15,000 individuals, elevated frequencies of *APOE-4* was found for Alzheimer's patients in each study, although the association was stronger among Caucasians and Japanese and weaker in African Americans (Farrer et al., 1997). *APOE* has a large effect for a QTL, but it is a QTL in that the *APOE-4* allele is by no means necessary or sufficient for the development of the disorder—it is a risk factor that increases susceptibility to the disorder. At least one third of individuals with Alzheimer's disease lack the allele, and up to half of individuals who have a double dose of this allele survive to age 80 without developing the disease (Williams, 2003). It sounds contradictory to refer to a QTL association with a dichotomous disorder such as Alzheimer's disease because diagnosed disorders are not quantitative traits. However, if several genes affect the disorder, which is implied if a particular gene has a small effect, the genes will produce a continuum of susceptibility to the disorder. This implies that the disorder is actually the extreme of a dimension, as discussed earlier. Much ongoing QTL research on intelligence is coming from the intense research effort on dementia, which usually assesses intelligence prior to the decline of dementia.

Association Studies of Intelligence

Intelligence is a reasonable target for QTL research for three reasons. First, it is substantially heritable. More interestingly, multivariate genetic research reviewed above indicates that intelligence is the level at which genes affect cognitive abilities, much more so than at the level of specific cognitive abilities. The third reason is that QTLs have been found for the cognitive disorders of reading disability and dementia and more than 200 rare single gene disorders have been isolated that include mental retardation among their symptoms.

One project called the IQ QTL Project has systematically attempted to identify QTLs associated with intelligence (Plomin, Hill, et al., 2001). Although no solid QTL associations have yet emerged, the IQ QTL Project is described in this section because the project raises many current issues relevant to the pursuit of specific genes associated with any complex traits, not just intelligence. For example, the IQ QTL Project is the first molecular genetic study to focus on ability rather than disability. This focus highlights the point that genetic variation occurs throughout the distribution—genetic variation does not just consist of rare mutations that cause severe disorders. Rather than using the entire distribution as in QTL studies of other personality traits (Benjamin et al., 2002), the IQ QTL Project selected very high-functioning individuals in order to increase power to detect QTLs of small effect size. Its goal is not to find genes for genius but rather to use very high-functioning individuals in order to identify QTLs that operate throughout the entire distribution, including the low (MMR) end of the ability distribution. This approach is based on the simple hypothesis that, although any one of many genes can disrupt normal development, very high functioning requires most of the positive alleles and few of the negative alleles. This is just a hypothesis, but one that can be tested when QTLs are found because it predicts that QTLs found for high ability will have a similar effect throughout the rest of the distribution including the low end of the distribution.

The IQ QTL Project currently includes an original sample of 101 cases with mean IQ of 136 and 101 controls with mean IQ of 100. The high group for the original sample, which is more than two standard deviations above the population mean, represents the equivalent of the top 2% of an unselected sample of 5,000 individuals. Because greater power is needed to replicate results, a replication sample included 96 individuals of some of the brightest adolescents in the United States with estimated IQs greater than 160 (equivalent to the top .00003 of an unselected sample of 3 million) as well as another sample of 100 controls with mean IQ of 100. For QTLs with 5%, 2.5%, and 1% effect sizes, the original sample provides 100%, 93%, and 56% power, respectively; the replication sample provides even greater power because the sample is more extreme: 100%, 100%, and 99%, respectively. However, these power estimates assume that the marker is very close to the QTL—power drops off rapidly as the distance between the marker and the QTL increases.

The first phase of the project, which had much smaller sample sizes, consisted of genotyping 100 DNA markers in or near genes involved in brain functioning (Plomin et al., 1995). For example, the association between *APOE-4* and dementia makes this gene a reasonable candidate for association with intelligence. There was a suggestion of an association involving the *APOE* gene in the expected direction, with the *APOE-4* allele—which is in higher frequency in individuals with dementia—showing a lower frequency in the high-intelligence group. However, a follow-up analysis that included a sample twice as large as the original found little evidence for association (Turic, Fisher, Plomin, & Owen, 2001). The earlier survey of 100 markers also included two markers for the catechol-o-methyltransferase gene (*COMT*) that did not suggest associations (Plomin et al., 1995). The *COMT* gene has been reported recently to correlate with working memory (Egan et al., 2001), which is highly correlated with intelligence (Deary, 2001).

One problem with such a candidate gene approach is that many of the thousands of genes expressed in the brain could be considered as candidate genes for intelligence. Allelic association can be made more systematic by using a dense map of markers. The IQ QTL Project took a first step in this direction by genotyping 47 DNA markers on the long arm of chromosome 6 (Chorney et al., 1998). A replicated association for a marker was found, which happened to be in the gene for insulin-like growth factor-2 receptor (*IGF2R*), which has been shown to be especially active in brain regions most involved in learning and memory (Wickelgren, 1998). We replicated this result using larger samples and using a different polymorphism in *IGF2R* (Hill, Chorney, et al., 1999). However, this QTL association did not hold up when another large independent sample was analyzed (Hill, Chorney, & Plomin, 2002).

The problem with using a dense map of markers for a genome scan for QTLs of small effect is the amount of genotyping required. The number of markers needed for a complete genome scan is a matter of some uncertainty (Abecasis et al., 2001; Kruglyak, 1999; Reich et al., 2001), but it seems likely that at least 100,000 markers would be needed. Furthermore, these thousands of markers would need to be genotyped for large samples in order to detect QTLs of small effect size. For example, in order to detect a QTL of 1% heritability in an unselected sample with 80% power ($p < .05$), 800 individuals would need to be genotyped (Cohen, 1988). However, in order to protect against false positive results caused by genotyping so many markers, much lower alpha values and much larger samples are needed, resulting in the need for millions of genotypings when samples consist of thousands of individuals.

To address these issues, the IQ QTL Project developed DNA pooling (J. Daniels, Holmans, Plomin, McGuffin, & Owen, 1998). DNA pooling greatly reduces the need for genotyping by pooling DNA from all individuals in a group and genotyping the pooled groups. In the IQ QTL Project, DNA is pooled for the 101 cases and for the 101 controls so that genotyping a single marker involves just two genotypings rather than 202 genotypings. In other words, for the cost of individually genotyping one marker for 200 individuals, DNA pooling makes it possible to genotype 100 markers for two groups of 100 individuals each. DNA pooling is a sensitive method for detecting the largest differences in allele frequencies between samples, as confirmed by individual genotyping (J. Daniels et al., 1998; Norton et al., 2002).

As an example, Figure 5 shows DNA pooling results from the IQ QTL Project for a marker on chromosome 2. The markers used in the project are called *simple-sequence repeat* (SSR) markers because their alleles consist of short sequences of two, three, or four DNA bases that repeat a variable number of times. For example, the marker (*D2S427*) shown in Figure 5 includes a sequence of four DNA bases (GATA) that repeats typically 10, 11, 12, 13, 14, or 15 times. The function of such SSR markers, of which there are tens of thousands in the genome, is not known but the number of repeats is stably inherited and can be used as a DNA marker. Although each individual has two alleles, the genotyping results in Figure 5 show five alleles for all pools—these are the bumps in Figure 5, which indicate the length of the DNA sequence and thus the number of repeats—because the DNA was pooled across individuals in each group and thus represents all of their alleles. The heights of the bumps indicate the relative frequencies

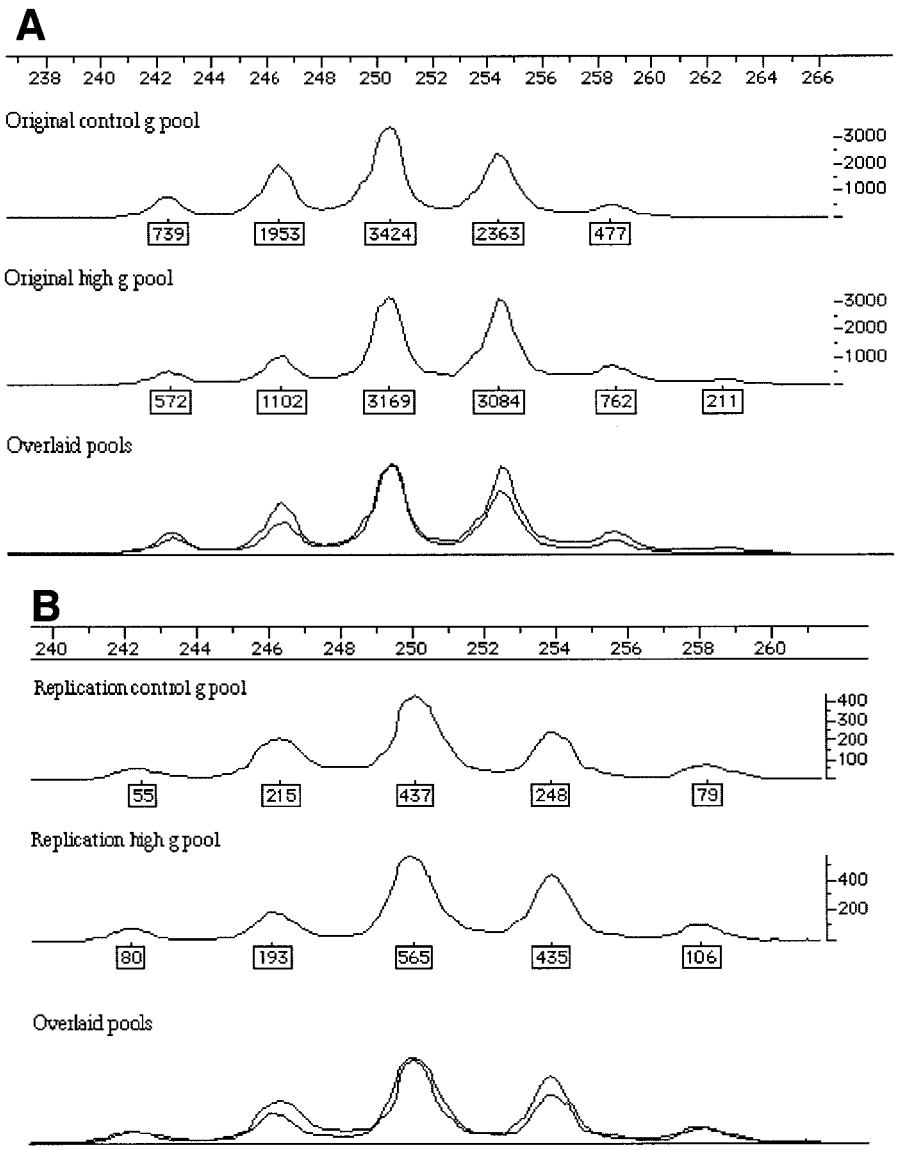


Figure 5. DNA pooling results from the IQ QTL Project in the (A) original and (B) replication case-control samples for a tetranucleotide DNA marker (i.e., the polymorphism involves the number of repeats of a four base-pair motif) on chromosome 2 (*D2S427*) for the high-intelligence group (middle), control group (top), and their overlaid images (bottom). In all of the pools, five alleles for *D2S427* are represented by the number of repeat units in the marker—the numbers above the allele image patterns (AIPs) represent the size (number of DNA base pairs) of the marker's alleles, each of which differ by four base pairs. The relative frequencies of the alleles are represented by the height of each bump as indicated by the numbers below and to the right of the AIPs. (A sixth allele 262 base-pair units in length has a low frequency and can be seen only in the original high *g* pool.) The differences in the vertical scales of Panels A and B are due to differences in the amount of DNA that was amplified. The difference in the AIPs (ΔAIP) for the two groups was calculated from the overlaid images by measuring the total area that was not shared by the two images irrespective of how many times the curves from the two pools crossed. This was then expressed as a fraction of the total shared and nonshared area (J. Daniels et al., 1998). The ΔAIP simulated *p* values that test an overall difference in allele frequencies between the groups is .026 for the original sample and .003 for the replication sample. An allele-specific test of allele 2 (246 bp) comparing the high group and the control group yielded significant differences in the original sample but not in the replication sample. From "A Genome-Wide Scan of 1842 DNA Markers for Allelic Associations With General Cognitive Ability: A Five-Stage Design Using DNA Pooling," by R. Plomin, L. Hill, I. Craig, P. McGuffin, S. Purcell, P. Sham, D. Lubinski, L. Thompson, P. J. Fisher, D. Turic, and M. J. Owen, 2001, *Behavior Genetics, 31,* p. 504. Copyright 2001 by Kluwer Academic. Adapted with permission.

of the alleles because the heights represent the number of copies of each allele in the pooled group. (For the original high *g* pool, a sixth low-frequency allele can be seen.) For this *D2S427* DNA marker, the second allele (which is 246 base pairs in length, 4 base pairs longer than the first allele) indicates a lower frequency in the high-intelligence group than in the control group. This pattern was found in both the original sample (Panel A) and the replication sample (Panel B). When DNA pooling nominates a marker in this way, individual genotyping can be conducted to confirm the association. Individual genotyping for *D2S427*, shown in Figure 6, confirms the pattern of results suggested by DNA pooling although the association did not reach significance in the replication sample.

Proof-of-principle articles for a systematic search of the genome using DNA pooling were published for chromosome 4 (P. J. Fisher et al., 1999) and chromosome 22 (Hill, Craig, et al., 1999), with samples only half the size of the current analyses. The first systematic genome scan for association for intelligence, using the complete samples described above, examined 1,842 markers (Plomin, Hill, et al., 2001). DNA pooling was used to screen the markers in the original and replication samples and then markers that met multiple conservative criteria for acceptance were individually genotyped in the two samples. DNA pooling of the original sample yielded 108 markers that yielded differences between cases and controls. Of these 108 markers, 6 met criteria using DNA pooling in the replication sample. These six markers were genotyped individually for the 202 subjects in the original sample and four yielded significant associations, which supports the validity of DNA pooling. The four markers that were significant in the original sample were then genotyped individually for the 196 subjects in the replication sample. Two of these four markers were also significant in the replication sample, markers on chromosome 4 (*D4S2460*) and chromosome 14 (*D14S65*). Although these two replicated QTL associations are noteworthy, when so many markers are genotyped, the possibility of false positive associations remains until the association is replicated in other studies.

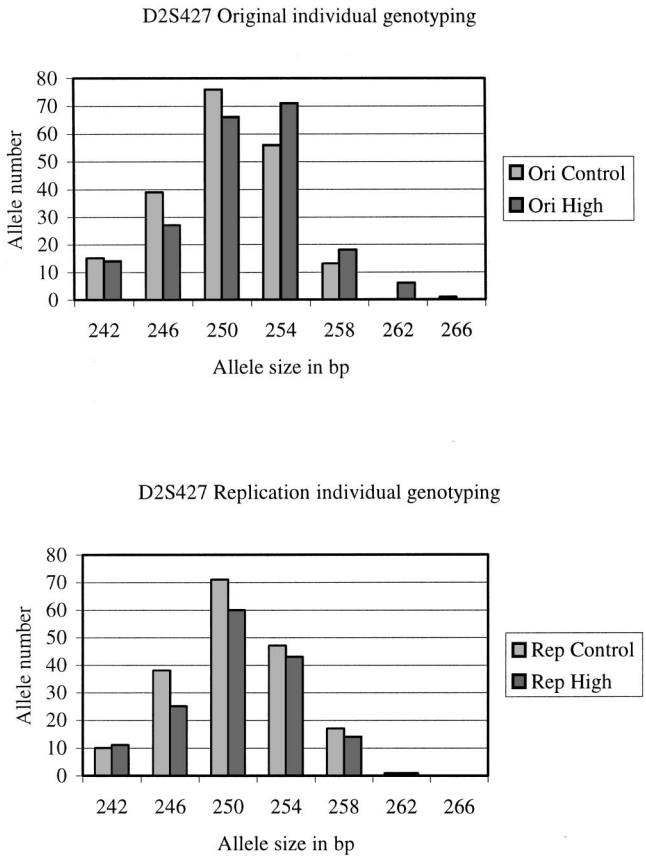


Figure 6. Individual genotyping results for the marker *D2S427*, whose DNA pooling results are shown in Figure 5. Individual genotyping picked up a seventh rare allele, whereas DNA pooling detected only six alleles. An allele-specific test of allele 2 (246 bp) comparing the high group and the control group yielded significant differences in the original sample and the replication sample. Ori = original; Rep = replication; bp = base pairs. From "A Genome-Wide Scan of 1842 DNA Markers for Allelic Associations With General Cognitive Ability: A Five-Stage Design Using DNA Pooling," by R. Plomin, L. Hill, I. Craig, P. McGuffin, S. Purcell, P. Sham, D. Lubinski, L. Thompson, P. J. Fisher, D. Turic, and M. J. Owen, 2001, *Behavior Genetics, 31,* p. 505. Copyright 2001 by Kluwer Academic. Adapted with permission.

Moreover, a concern about case-control studies is that demographic differences, most notably ethnic differences, between the cases and controls might yield false positive results. Although all subjects in the IQ QTL Project are Caucasian, it is nonetheless possible that QTL associations could be due to some hidden ethnic stratification. For this reason, replication was sought in a third sample consisting of 196 parent–child trios in which the offspring had estimated IQs greater than 160, which provides a within-family analysis called the Transmission Disequilibrium Test (TDT) that protects against population stratification as a possible source of QTL associations. When *D4S2460* and *D14S65* were genotyped individually for the 784 individuals in the 196 parent–child trios, neither was significant. Although it is possible that the case-control results were caused by some hidden ethnic stratification within the Caucasian samples, another possibility is that the TDT lacks the power of the case-control design to detect QTLs of small effect. Nonetheless, the failure of the two candidate QTL associations to replicate in the TDT analysis led the IQ QTL Project to the conservative conclusion that this initial genome scan had not identified any clear QTL associations. Several markers that were nearly significant at all stages are being explored further in additional replication samples.

The criteria for replication used in this study were extremely conservative. For example, no other QTL study has demanded replication in three samples using two different designs (case-control and parent–offspring trios). However, a conservative approach is warranted given frequent failures to replicate QTL association results (Cardon & Bell, 2001). Although the multiple-stage design with three extreme selected samples attempted to balance false positives and false negatives in an effort to detect QTLs of small effect size, the balance is in fact tilted very much in favor of avoiding false positives than false negatives for two reasons. The first reason is that the study only had power of about 50% to detect QTLs with 1% heritability, as mentioned earlier. For this reason these results should not be taken as an indictment of the QTL approach but rather they should serve as a warning of the exorbitant demands needed to obtain sufficient power to detect QTLs of small effect size.

A second reason why the balance was tilted against finding QTLs is that it is now known that perhaps a hundred thousand or even more DNA markers may be needed to exclude QTL association. As mentioned earlier, the problem for allelic association analysis is that power drops off rapidly when a marker is not very close to the QTL. For this reason, the IQ QTL Project is now focusing on potentially functional polymorphisms that may themselves be QTLs. However, rather than focusing on a few candidate genes or gene systems, we can look forward in the near future to a systematic search using all functional polymorphisms in coding sequences (cSNPs) and in regulatory regions. These tens of thousands of cSNPs can be genotyped using high-throughput techniques such as DNA pooling. In the meantime, the IQ QTL Project is using, as they become available, cSNPs that result in an amino acid substitution (called *nonsynonymous cSNPs*) as well as functional SNPs in regulatory regions. Although the problem remains that a QTL association with a functional SNP might in fact be due to another nearby SNP, it is a reasonable assumption that a functional SNP is the QTL, which greatly increases the power of QTL association. In addition to DNA pooling, other high-throughput techniques can genotype thousands of genes simultaneously, although these techniques are much more expensive than DNA pooling when used to genotype the large samples needed for QTL analysis (Craig & McClay, 2003). Other developments will also make genome-wide QTL searches more feasible. For example, haplotype mapping is a recent development that will greatly reduce the number of markers needed for a genome scan (Goldstein, 2001). Groups of contiguous markers across a chromosome are inherited as a package for hundreds of generations so that strategic selection of a few key markers can identify these chunks of chromosomes rather than genotyping all the other markers within a chunk.

The road ahead will be much more difficult than generally assumed if, as we suspect, there are many QTLs associated with intelligence, which means that QTLs may account for less than 1% of the variance. Although the distribution of effect sizes is not known for intelligence or for any other complex trait, if QTL heritabilities are less than 1%, it will be difficult to detect them reliably. Nonetheless, the convergence of evidence for the strong heritability of intelligence from family, twin, and adoption studies indicates the existence of DNA polymorphisms associated with intelligence. The solution is that power will need to be increased in order to track down the QTLs responsible for the heritability of intelligence even if the QTL heritabilities are less than 1%. DNA pooling will be useful in this context because it costs no more to genotype 1,000 individuals than 100 individuals.

Genomics and Postgenomics

As the advances from the Human Genome Project begin to be absorbed in DNA research on intelligence and other personality traits, optimism is warranted about finding more QTLs. The future of genetic research will involve a shift from finding genes to finding out how genes work—the pathways from genes to behavior. This research direction, generally referred to as functional genomics, is happening already in basic molecular biology as we approach the postgenomic era in which the complete human genome sequence and all functional variations in the genome sequence are identified (Plomin, DeFries, Craig, & McGuffin, 2003). Three huge areas of functional genomic research have emerged: gene manipulation, gene expression profiling, and proteomics. Nearly all of this research has been conducted using animal models, primarily the mouse (Silver, 1995). Mouse models of personality traits such as activity and emotionality have been available for decades and, surprising as it may sound, mouse models of intelligence are also being developed (Plomin, 2001). These models use Spearman's *g* as a key. That is, *g* can be sought in the covariation among diverse measures of learning and memory and puzzle solving (Galsworthy, Paya-Cano, Monleon, & Plomin, 2002). Mouse models of intelligence are especially valuable for functional genomic research because, unlike the human species, both the genome and the environment can be controlled and manipulated. In addition, although the specificity of neuroimaging in humans is improving rapidly, much more precise analyses of brain function, such as single-cell recordings, can be conducted in mice.

Gene Manipulation: Targeted Mutations, Mutagenesis, and Antisense DNA

One way to study how a gene works is to knock it out by breeding mice for whom DNA sequences have been deleted so that the gene can no longer be transcribed, so-called gene knock-out studies (Capecchi, 1994). One of the first knock-out genes for behavior showed that knocking out a kinase gene interfered with learning a spatial task (Silva, Paylor, Wehner, & Tonegawa, 1992). There has been an explosion of research using targeted mutations in mice to study learning and memory, even though each experiment requires 2 or 3 years (Mayford & Kandel, 1999; Wahlsten, 1999). Newer techniques can produce more subtle changes that alter the gene's regulation and lead to increases or decreases in the frequency with which the gene is transcribed. Techniques are even available to affect particular brain regions and to turn genes on and off at will. The approach is not without problems, however. Currently, there is no way to control the location of gene insertion in the mouse genome nor can the number of inserted copies of the gene be controlled, both of which can affect gene function.

Another major approach, *mutagenesis screening*, is the opposite of targeting. Chemical mutagens are used to mutate genes at random, and thousands of mutated mice are screened for a wide variety of phenotypes (Nolan et al., 2000). The focus of this work is usually on single genes of major effect rather than QTLs with more subtle effects. Moreover, the necessity for screening thousands of mice makes it difficult to include intensive behavioral measures as needed, for example, to assess learning and memory.

A different approach, called *antisense DNA*, circumvents some of these problems and does not require breeding. Antisense DNA is a DNA sequence that binds to a specific RNA sequence and thus prevents some of the RNA from being translated, which "knocks down" gene function. Injected in the brain, antisense DNA has the advantage of high temporal and spatial resolution (Ogawa & Pfaff, 1996). An early antisense "knockdown" study demonstrated the importance of the CRE-binding protein (CREB) gene in memory formation (Guzowski & McGaugh, 1997). Antisense DNA knockdowns have been shown to affect behavioral responses for dozens of drugs (Buck, Crabbe, & Belknap, 2000). The principal limitations of antisense technology currently are its unpredictable efficacy and a tendency to produce general toxicity.

A more fundamental issue involves the interpretation of manipulating genes by knocking them down or out. Many genes, perhaps hundreds or thousands, provide the substrate for any behavior. Knocking out or knocking down the function of any one of these genes could affect a particular behavior, but this would not imply that the gene causes that behavior. An analogy is an automobile that requires hundreds of parts to work properly, but disabling any single part such as a spark plug or even a wheel will interfere with its functioning. Conversely, living systems have evolved redundancies that can compensate for malfunctions—it often happens that genes that are ostensibly crucial have little effect when knocked out. Moreover, the effect of a knockout is often very different in different inbred strains, suggesting the importance of other genes (Nadeau, 2001). Finally, showing that a gene affects behavior when the gene is knocked out or knocked down does not necessarily imply that naturally occurring variation in the gene is responsible for the heritability of that behavior.

Gene Expression Profiling

Genes are transcribed, or expressed, as their products are needed. As you read this sentence, you are creating new neurotransmitters by transcribing neurotransmitter genes. Gene expression can be indexed by the presence of RNA, which transcribes DNA, and then travels outside the nucleus to be translated into amino acid sequences, the building blocks of proteins. Microarrays are now available that can detect the expression of thousands of genes simultaneously. Such gene expression profiling was first used in cell lines to diagnose diseases on the basis of the profile of genes that are expressed in response to the disease (Golub et al., 1999) and to study the response to drugs (Iyer et al., 1999). Unlike DNA studies in which every cell in the body has the same DNA, gene expression studies depend on the tissue that is sampled. For personality traits, the brain is of course the critical tissue, which will make it difficult to apply this technology to the human species. However, gene expression profiling is being used widely in research on animal models, especially mice. Gene expression profiling comparing brain tissue before and after an event—learning or stress, for example—can point to genes whose expression is triggered by the event. Gene expression profiling can also be put to use to compare mice that differ genetically, such as mice bred for differential response to learning or stress, or inbred strains of mice that differ for many behaviors. It is also possible to combine these two approaches to study genotype-environment interaction. For example, a gene expression profiling study of more than 7,000 genes investigated gene expression in the hippocampus during ethanol withdrawal following chronic ethanol exposure for two inbred strains of mice (G. M. Daniels & Buck, 2002). Approximately 2% of genes in one strain and 1% of genes in the other strain were differentially expressed before and after withdrawal, and a few genes were identified that showed the largest differential response to withdrawal in the two strains. Similar results appear to be emerging for other manipulations, such as drug-induced seizures (Sandberg et al., 2000). Gene expression profiling may be useful in nominating QTLs and it will certainly be useful in understanding how QTLs associated with complex traits function. It is analogous to functional neuroimaging at the level of the gene.

Proteomics

Gene expression profiling assesses gene transcription as indexed by RNA. The next step toward functional genomics is to study the proteins that result from translation of RNA and their interactions. The phrase *protein genomics* led to the neologism *proteomics*. Just as there is no single human genome, there is no single human proteome. For understanding how individual differences in behavior are caused by DNA differences, the first step is to investigate the differences in protein function for which the key is their shape and complexes that they form with other proteins. Proteomics is much more difficult than genomics because, unlike the triplet code of DNA that governs the genome, there is no simple code for understanding the proteome. Moreover, there are many more proteins than genes for two reasons. First, it has been estimated that about half of all human genes are alternatively spliced into exons and introns and thus translated into different proteins (Venter et al., 2001). Second, after translation, proteins are modified—it has been estimated that for each human gene three different modified proteins with different functions are produced (Banks et al., 2000).

Behavioral Genomics

Gene manipulation, gene expression profiling, and proteomics are examples of "bottom-up" molecular biological approaches to functional genomics. However, there are other levels of analysis at which we can understand how genes work. For example, one step up from proteomics is the analysis of molecular changes in the synapse, which is the focus of neurogenetics research on learning and memory (Grant, 2003). Pathways in the brain between genes and intelligence can be traced using neuroimaging techniques in the human species (Kosslyn & Plomin, 2001) and even more precise techniques can be used in the mouse (Crusio & Gerlai, 1999). As Spearman noted in 1927, ultimate understanding of *g* "must needs come from the most profound and detailed direct study of the human brain in its purely physical and chemical aspects" (p. 403).

At the other end of the continuum from bottom-up approaches of molecular biology is a top-down level of analysis that considers the behavior of the whole organism. The phrase *behavioral genomics* has been suggested to emphasize the potential contribution of a top-down psychological level of analysis toward understanding how genes work (Plomin & Crabbe, 2000). For example, part of understanding how genes work is to understand how genetic effects interact and correlate with experience, how genetic effects on behavior contribute to change and continuity in development, and how genetic effects contribute to overlap between traits. As discussed earlier, these are issues central to quantitative genetic analyses. Behavioral genomic research using DNA will provide sharper scalpels to dissect these issues with greater precision. Table 1 describes examples of environmental, developmental, and multivariate findings mentioned earlier from quantitative genetic research on intelligence and poses questions they raise for behavioral genomic research on intelligence.

Behavioral genomics will make important contributions toward understanding the functions of genes and DNA will open up new horizons for understanding behavior. Few personality researchers are likely to join the hunt for genes because it is difficult and expensive, but once genes are found, it is relatively easy and

Table 1
Examples of Quantitative Genetic Findings on Intelligence and the Questions They Raise for Behavioral Genomics

Issues	Quantitative genetic findings	Behavioral genomics questions
Environmental		
GE correlation	Associations between environmental measures and intelligence are often mediated genetically.	To what extent do QTLs drive experience?
GE interaction	Heritability can differ as a function of environment.	Do QTL associations differ as a function of environment?
Developmental		
Cross-sectional	Heritability increases with age.	Which QTL associations increase with age?
Longitudinal	From age to age, genetic influence shows much continuity and some change.	To what extent do QTLs expressed early in life predict later behavior?
Multivariate		
Genetic *g*	The same genes affect diverse cognitive abilities.	Which QTLs are responsible for genetic overlap?
Links between normal and "abnormal"	MMR is the quantitative extreme of the same genes responsible for heritability throughout the distribution.	Which QTLs associated with MMR are also associated with normal variation?

Note. GE = genotype–environment; QTLs = quantitative trait loci; MMR = mild mental retardation. From *Behavioral Genetics in the Postgenomic Era* (p. 533), by R. Plomin, J. C. Defries, I. W. Craig, and P. McGuffin, 2003, Washington, DC: American Psychological Association. Copyright 2003 by the American Psychological Association.

inexpensive to use them. DNA can be obtained painlessly and inexpensively from cheek swabs—blood is not necessary. Cheek swabs yield enough DNA to genotype thousands of genes, and the cost of genotyping is surprisingly inexpensive. What has happened in the area of dementia in the elderly will be played out in many other areas of the behavioral sciences including personality. As noted earlier, the only known risk factor for late-onset Alzheimer's dementia (LOAD) is *APOE*. Although the association between allele 4 of *APOE* and LOAD was reported a decade ago (Corder et al., 1993), it has already become routine in research on dementia to genotype subjects for *APOE* in order to ascertain whether the results differ for individuals with and without this genetic risk factor. For example, the association between *APOE* and dementia appears to interact with head injury, smoking, cholesterol level, and estrogen level (Williams, 2003). For these reasons, we predict that personality researchers will routinely collect DNA in their research and incorporate identified QTLs in their research, which will greatly enrich behavioral genomics.

Conclusions

The future for genetic research in intelligence and other areas of personality looks brighter than ever in the dawn of the postgenomic era. The genetics of such complex traits will be swept along in the wake of the Human Genome Project as it increasingly provides the tools needed for the genetic analysis of complex traits. The most exciting prospect is the integration of quantitative genetics, molecular genetics, and functional genomics in a new focus on behavioral genomics (Plomin et al., 2003). Behavioral genetics will profit from as well as contribute to this integration. It will profit from the advances coming from intense molecular genetic research on common complex medical disorders such as diabetes, hypertension, and obesity. Behavioral genetics will contribute a quantitative genetic and QTL perspective that shifts the focus of common disorders to dimensions of normal variation in which common disorders are viewed as the quantitative extreme of the same genetic and environmental factors that create variation throughout the distribution. This shift has begun in genetic research on psychopathology, the most active area of behavioral genetic research (McGuffin, Gottesman, & Owen, 2002). This shift is leading to renewed interest in personality as the source of normal variation. This integration is more than methodological and technological. Because DNA is the ultimate common denominator for research, postgenomic research on intelligence and personality will increasingly become integrated into the life sciences. The bottom-up approaches of molecular biology will eventually meet the top-down approaches of behavioral genomics in the brain.

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