# 4 The Genetics of Intelligence

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## Intelligence

In this chapter we provide an overview of the current state of knowledge on the genetic contribution to individual differences in intelligence. This includes a brief overview of the heritability of intelligence across the life span and of some behavioral and neurophysiological correlates of intelligence, as well as a discussion of molecular genetic studies on intelligence.

Although having been the topic of empirical research for more than a century, the definition of intelligence changes across time and across studies (Sternberg and Detterman 1986). Intelligence was described by fifty-two researchers in the field as follows (Gottfredson 1997):

> Intelligence is a very general mental capability that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience. It is not merely book learning, a narrow academic skill, or test-taking smarts. Rather, it reflects a broader and deeper capability for comprehending our surroundings—"catching on," "making sense" of things, or "figuring out" what to do.

In practice, intelligence is usually assessed using psychometric (IQ-type) tests, of which there are now hundreds. Scores on these different tests tend to have positive correlations, despite a huge variety in the mental demands of the tests. Principal components or factor analysis of a battery of mental tests applied to a large sample reveals a large first unrotated component or factor, on which all tests have substantial loadings. Scores on this unrotated component are measures of the general factor in intelligence. This general cognitive factor is sometimes referred to as just *g*. It was discovered by Charles Spearman (1904) and is one of the most replicated findings in psychology, as demonstrated in a reanalysis of over 400 data sets collected during the twentieth century (Carroll 1993). *g* is a trait with considerable lifelong stability and important predictive validity. A sixty-eight-year follow-up of almost 500 people who took part in the Scottish Mental Survey of 1932 found a raw correlation (stability coefficient) of

0.66 between IQ scores on the same IQ-type test taken at age 11 years and 79 years (Deary et al. 2004). IQ test scores are strongly associated with academic success (Neisser et al. 1996; Deary et al. 2007). They are about the single best predictor of job success (Schmidt and Hunter 1998). Finally, childhood IQ is a significant predictor of how long people live (Batty et al. 2007).

## Heritability of Intelligence

A summary of all research on the genetic contributions to intelligence differences in humans reads as follows: "When data across all studies are collapsed, genetic influences account for around 50% of the variance" (Plomin and Spinath 2004). Bouchard and McGue (1981) reviewed the world literature on IQ correlations between relatives with different degrees of genetic and family rearing overlap. They found 111 adequate studies, yielding 526 correlations based on 113,942 pairings. The results were compatible with the prediction that the correlations were higher among people who were genetically more similar. The greater correlations between siblings reared together further suggests an influence of the rearing environment on general intelligence. Many of these studies were based on young children in whom rearing environment effects are especially strong.

### From Infancy to Old Age: Twin and Adoption Studies

In children ages 2 to 4, the heritability of mental ability tends to be relatively low (25% to 30%), whereas shared environmental estimates explain 61% to 65% of the variance (Spinath and Plomin 2003). Parental socioeconomic status (SES) and disorganization in the home mediate some of the shared environmental effect, but most of the shared environmental effects on infant IQ are still unexplained (Petrill et al. 2004). The importance of genetic effects increases from infancy to childhood as demonstrated in longitudinal analyses of twin data from different research groups (e.g., Boomsma and van Baal 1998; Spinath and Plomin 2003). At the age of 7, about 47% of the variance in intelligence is due to genetic variance (Spinath and Plomin 2003), whereas at the ages of 11 to 12, 60% to 70% of the variance is due to genetic variance (Bartels et al. 2002; Benyamin et al. 2005; Polderman et al. 2006b). It has been shown that, although the *impact* of genetic factors increases with increasing age, the genetic factors remain the same across ages. In other words, the increasing heritability is not explained by emerging effects of a new set of genes coming into play at different ages in childhood (Plomin and DeFries 1985; Bartels et al. 2002; Polderman et al. 2006b). Instead, the effects of the same set of genes become larger with increasing age ("genetic amplification"). Shared environmental influences show a related decrease in importance and explain around 20% of the variance in intelligence at the age of 11 to 12 (Bartels et al. 2002; Benyamin et al. 2005; Polderman et al. 2006b). Heritability

estimates based on adoption studies show a pattern similar to those based on twin studies: the heritability increases from early to late childhood with heritability estimates of 9% at age 1 year, 14% at age 2 years, 10% at age 3 years, 20% at age 4 years, and 36% at age 7 years (Fulker et al. 1988).

In adolescence, the importance of shared environmental influences has completely disappeared, whereas the importance of genetic variance continues to increase; at the age of 17, the heritability of intelligence is estimated to be between 70% and 80% (Luciano et al. 2001a,b; 2006; Rijsdijk et al. 2002). The estimated heritability of intelligence in late adolescence based on adoption studies is 78% (Loehlin et al. 1997). In adulthood, intelligence remains highly heritable (70%–80%), with no significant increases between the ages of 20 and 60 years (Posthuma et al. 2001; 2003). As in young children, adult heritability estimates based on twin studies show a pattern similar to those based on adoption studies. A particularly strong adoption design is the "twins reared apart design," in which twins are separated at a very early age and are adopted by different families. Bouchard (1997) summarized the world literature on monozygotic (MZ) twins reared apart. There are five studies on MZ twins reared apart, with *N*s of 12, 19, 38, 45, and 48. The weighted average intraclass correlation is 0.75, which is also an estimate of the heritability, given assumptions about lack of contact and no bias in placement. Bouchard et al. (1990) had shown earlier, in the Minnesota Study of Twins Reared Apart, that the amount of contact between separated twins was not correlated with their similarity on general intelligence.

Much of the information on genetic and environmental contributions to intelligence in old age has come from various analyses within the Swedish Twin Registry, which also has twins reared apart. The Swedish Adoption Twin Study of Ageing is a subset of 25,000 registered same-sex twins born in Sweden between 1886 and 1958. It involves around 300 pairs of MZ and dizygotic (DZ) twins reared apart (MZA, DZA) and together (MZT, DZT; Pedersen et al. 1992). At a mean age of 65.6 years, broad heritability of general intelligence was estimated at about 80%, with evidence of nonadditive genetic effects (Finkel et al. 1996; Pedersen et al. 1992). This corresponds to what is found in old age by others (around 76%; Petrill et al. 1998). Later an even higher heritability of 91% was reported when they corrected for unreliability of measurement at the age of 65 (Reynolds et al. 2005). Shared environment effects were very small, with unique environment accounting for most of the nongenetic variance.

A subsample of the Swedish Twin Registry, the OctoTwin project, includes twins 80 years or older and alive in 1991–1993. The heritability of intelligence was 62%, uncorrected for error of measurement, at a median age of 82 years (range = 80 to >95); 89% lived independently (McClearn et al. 1997). All of the significant environmental contribution was nonshared.

In summary, the heritability of intelligence changes across the life span from about 30% around the age of 3 with, perhaps, a peak of as much as 91% around the age of

65, and some decline in heritability afterwards. Figure 4.1 provides an overview of heritability estimates based on twin samples across the life span (ages 3 to 82 years).

### Twin–Singleton Comparisons

Heritability estimates for intelligence are mostly based on twin samples. Twin samples, however, have been criticized for their alleged nongeneralizability. Twin–singleton differences in intrauterine and family environments may lead to different mean levels on phenotypes such as intelligence. It is, therefore, important to investigate whether findings from twin populations can be generalized to singletons.

Twin deliveries are often characterized by prematurity, low birth weight, and lower weight for gestational age (Powers and Kiely 1994). Negative effects of very low birth weight on intellectual development and later IQ are well documented (Shenkin et al. 2004). When growing up, twins may suffer from twin-related stresses in the family environment in which they are reared. A multiple birth puts stress on a family, which may have a negative effect on the (cognitive) development of the twins (Hay and O'Brien 1983).

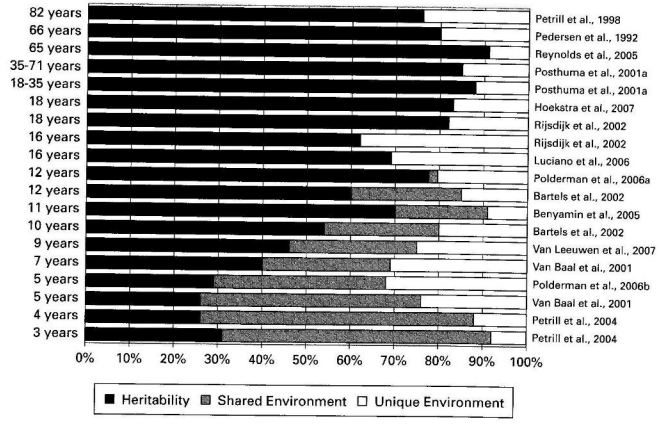


**Figure 4.1**

Proportion of the variance in IQ explained by genetic factors, shared environmental factors, or unique environmental factors across the life span, based on estimates from twin samples.

A relatively small number of studies have been devoted to detecting twin–singleton differences in cognition (e.g., Nathan and Guttman 1984; Posthuma et al. 2000; Record et al. 1970; Deary et al. 2005; Ronalds et al. 2005; Christensen et al. 2006). Generally, studies that involve children under the age of 12 report significant differences in IQ (up to 5 IQ points) between twins and singletons, favoring singletons (Nathan and Guttman 1984; Record et al. 1970; Deary et al. 2005c; Ronalds et al. 2005). However, after the age of 12 this difference has completely disappeared (Webbink et al. 2008; Posthuma et al. 2000), suggesting there is no lasting cognitive cost of being a twin. The latter was confirmed by Christensen et al. (2006), who found no difference between academic performance of 7,796 singletons compared to 3,411 twins who took the Danish national test of academic achievement in ninth grade (age 15).

It should be noted, however, that even if twins and singletons show mean differences in IQ before the age of 12, this does not necessarily imply that heritability estimates based on samples in this age range are not representative. In fact, the most important issue in generalizability of heritability estimates from twin samples to the general populations is equality of variances. After all, heritability is a ratio of the genetic variance to the total variance of IQ. Thus, the correct question would be "Do twins and singletons show differences in variances on IQ?" This test is usually not carried out. The only exception is in Posthuma et al. (2000). In their adult populations, no differences in either means or variances in IQ were found. Ronalds et al. (2005), who report a large twin–singleton difference in mean IQ score at ages 7 and 9, provide the standard deviations (SD) as well, although they do not formally test for equality of variances. From their table 1 it can be seen that at age 7 the SD for IQ is 15.7 for singletons and 15.8 for twins, and at age 9 it is 16.8 for singletons and 17.6 for twins. These numbers suggest that the variance is not significantly different between twins and singletons and that heritability estimates based on twin samples can thus be generalized to the general population.

### Multivariate Studies of IQ and Its Correlates

In this section, we shall address two areas of research in which multivariate modeling approaches have been used to decompose the covariance between IQ and (1) *brain volume* and (2) *brain functioning*.

#### IQ and Brain Volume

An obvious source of individual differences in intelligence is the size of the brain, which in itself is highly heritable (Baare et al. 2002; Hulshoff Pol et al. 2006; Pennington et al. 2000; Thompson et al. 2001). Since the second half of the nineteenth century, positive relations between head size and intelligence have been observed.

Correlations generally have been around 0.20 (Jensen 1994; Posthuma et al. 2002, 2003) but can be as high as 0.44 (van Valen 1974). Head size is easily measured with a measuring tape as circumference of the head. A more accurate measure of the size of the brain can be obtained through magnetic resonance imaging (MRI). Willerman et al. (1991) correlated brain size as measured with MRI with IQ (measured by the Wechsler Adult Intelligence Scale—Revised; WAIS-R) in a sample of 40 unrelated subjects. They found a correlation of 0.51, which was higher in men (0.65) than in women (0.35). In a follow-up study, Willerman et al. (1992) suggested that, in men, a relatively larger left hemisphere better predicted verbal IQ than it predicted performance IQ, whereas in women the opposite was true. Since then, several studies have provided confirmative evidence that brain volume and IQ correlate around 0.40 (e.g., Egan et al. 1994; Andreasen et al. 1993; Raz et al. 1993; Storfer 1999; Wickett et al. 2000; Posthuma et al. 2002). MacLullich et al. (2002) applied structural equation modeling to one of the largest studies to date ($N = 97$ healthy older men) and found a correlation of 0.42 between a latent general cognitive ability factor from eight mental tests and a latent brain volume factor from six brain areas. McDaniel's (2005) meta-analysis of studies into the relation between brain volume and intelligence found thirty-seven studies with a total $N$ of 1,530. Corrected for range restriction in some samples, the estimated population correlation between brain volume and intelligence was 0.33. Thus, because individual differences in both intelligence and brain volume are partly heritable, and because the two phenotypes are correlated, researchers have examined whether shared genetic effects account for some part of the correlation.

A number of such studies suggest that the correlation between brain volume and IQ derives from the same set of genes' influencing both traits (Hulshoff Pol et al. 2006; Pennington et al. 2000; Posthuma et al. 2002; Wickett et al. 1997). Using a sample of MZ and DZ twins for whom data on both brain volume and IQ was available, Posthuma et al. (2002) calculated correlations between brain volume of a twin and the IQ score of his or her cotwin. They found that this so-called "cross-trait cross-twin" correlation was larger in MZ twins than in DZ twins, which indicates that genes must mediate the correlation between brain volume and IQ. In support of this, they also found that the MZ cross-trait cross-twin correlation was the same as the correlation between brain volume and IQ *in the same person*. This means that the prediction of one's IQ score can be made with similar reliability from one's own brain volume as from the brain volume of one's genetically identical cotwin. A follow-up study that examined genetic correlations between the WAIS-III dimensions of verbal comprehension, perceptual organization, and processing speed and gray and white matter volumes, as well as cerebellar volume, yielded a more complex pattern of results; for example, all three brain volumes were related to working memory capacity, yet verbal comprehension was not related to any of the three (Posthuma et al. 2003). A recent paper by Hulshoff Pol et al. (2006) based on the same sample as Posthuma et al. (2002)

explored the genetic influence on focal gray and white matter densities using voxel-based MRI maps of the brain. Intelligence shared a common genetic origin with superior occipitofrontal, callosal, and left optical radiation white matter and frontal, occipital and parahippocampal gray matter. Phenotypic correlations with IQ were around 0.35 and were completely due to genetic overlap.

### IQ and Brain Functioning

Brain volumes, an aspect of structure, provide an important point of entry to the genetic sources of individual differences in IQ but may also be associated with functional aspects of the brain, such as speed of information processing and reaction times. Below we summarize some multivariate genetic studies on IQ and selected measures of brain functioning.

**IQ and Speed of Information Processing** Galton (1883) was the first to propose that reaction time is correlated with general intelligence and may be used as a measure of it. His observations and the results of empirical studies afterwards led to the general belief in the speed-of-processing theory of intelligence: the faster the accomplishment of basic cognitive operations, the more intelligent a person will be (Eysenck 1986; Vernon 1987). Since then, reaction times have consistently been negatively related to intelligence (e.g., Vernon 1987; Deary et al. 2001)—that is, a shorter reaction time corresponds to a higher IQ. Correlations with IQ generally range between –0.20 and –0.40 but can be as high as almost –0.50 (Deary et al. 2001) or even –0.60 (Fry and Hale 1996).

Results from twin studies suggest heritabilities for reaction time that are of the same magnitude as those for IQ as reviewed in Spinath and Borkenau (2000). Vernon (1989) found a heritability of 49% in 50 MZ and 52 DZ twins. In the same study it was also found that reaction time tests requiring more complex mental operations show higher heritabilities. A bivariate analysis of the same data set with IQ in 50 MZ and 32 same-sex DZ pairs (15 to 57 years) was reported by Baker et al. (1991). Phenotypic correlations of Verbal and Performance IQ with general speed were both –0.59 and were entirely mediated by genetic factors. This is in line with results from an earlier study in which phenotypic correlations between reaction time (measured as the total number of correct responses on a timed task) and IQ ranged between 0.37 and 0.42, from which 70% to 100% was attributed to genetic factors influencing both reaction time and IQ (Ho et al. 1988).

More recently, Rijsdijk et al. (1998) conducted a multivariate genetic analysis on reaction time data and IQ data, using 213 twin pairs measured at ages 16 and 18. Heritabilities were reported for age 16 of 58%, 57%, and 58% for simple reaction time, choice reaction time, and IQ (measured by Raven's Matrices), respectively. Phenotypic correlations of simple reaction time and choice reaction time with IQ were –0.21 and

–0.22, respectively, and were completely mediated by common genetic factors. Virtually the same picture was shown at age 18, where the same reaction time battery was correlated with IQ as measured with the WAIS.

Neubauer et al. (2000) reported heritability estimates of reaction time data and IQ (measured using Raven) ranging from 11% to 61% and 39% to 81%, respectively. Phenotypic correlations between reaction time data and IQ data were between –0.08 and –0.50, where higher correlations with IQ were found for more complex reaction time tasks. Again, these correlations were mainly (65%) mediated by a common genetic factor.

Evidence for a genetic mediation between reaction time and IQ also emerges from a large twin study by Luciano et al. (2001b). Using reaction time data and IQ data from 166 MZ pairs and 190 DZ pairs, Luciano et al. (2001b) report high heritabilities for both reaction time (79%–90%) and IQ (89%) with phenotypic correlations between –0.31 to –0.56. At least 70% of each of these correlations was due to a common genetic factor.

Another measure of processing speed is inspection time; this is a measure of central nervous system processing and is defined as the minimum display time a subject needs for making an accurate perceptual discrimination on an obvious stimulus (Deary 2001). It is distinct from reaction time; since there is no need to make the discrimination quickly, all that is required is an accurate response. Visual inspection time can easily be measured in a computerized version of the paradigm in which subjects are asked to decide which leg of a vertically asymmetrical Π-shaped figure is longest. Visual inspection time is generally thought to reflect speed of apprehension or perceptual speed. The less time a person needs to make an accurate decision on an obvious stimulus, the higher the IQ. The overall consensus on the relation between inspection time and IQ is given by Deary and Stough (1996): "inspection time accounts for approximately 20% of intelligence-test variance."

Two twin studies have investigated whether the relation between inspection time and IQ is mediated by shared genetic factors or by shared environmental factors (Luciano et al. 2001a; Posthuma et al. 2001a). These two studies were also the first to report on the heritability of inspection time per se. Using 184 MZ pairs and 206 DZ pairs age 16, Luciano et al. (2001a) reported a heritability estimate for inspection time of 36%. Using 102 MZ pairs and 525 DZ/sib pairs belonging to two age cohorts (mean ages = 26 and 50), Posthuma et al. (2001a) reported a slightly higher heritability estimate of inspection time (46%) at both ages.

Luciano et al. (2001a) reported a correlation between inspection time and performance IQ of –0.35 and between inspection time and verbal IQ of –0.26. Posthuma et al. (2001a) reported slightly lower correlations; –0.27 and –0.19, respectively. Both studies unanimously found that the phenotypic correlations between inspection time and performance IQ/verbal IQ were completely mediated by common genetic factors.

In summary, reaction time explains between 10% and 30% of IQ test variance, and this covariance is nearly completely (between 65% and 100%) due to a common genetic origin. Inspection time explains between 10% and 42% of IQ test variance, and this covariance is completely due to a common genetic origin.

### Gene–Environment Interaction and Correlation

In the above we have shown the increasing heritability of IQ across the life span and have summarized some of the possible underlying biological pathways that may lead to individual differences in IQ. However, the established high heritability of intelligence of around 60% to 80% in late adulthood is based on the observation that MZ twins correlate about 0.60 to 0.80 on tests of intelligence, whereas DZ twins score around half of that. The results described above are obtained under the assumption that such a pattern of twin correlations is explained by simply adding the separate effects of genes and environmental factors. However, the same pattern of twin correlations may also be the result of *interactions* between genetic and (shared) environmental effects (G × E), or by *correlations* (rGE) between the presence of genes and environmental factors. Below we shall describe the concepts of G × E and rGE and the impact of ignoring these influences in statistical methods.

G × E refers to the situation where the effect of environmental influences is dependent on genotype, or vice versa, when the expression of genes depends on the presence of certain environmental influences. In the context of intelligence, this may, for example, be reflected in a differential impact of an intellectually stimulating family environment on individuals with different genotypes. The hypothesis that there is a nonlinear association between heritability and shared environment and family background was tested in 114 MZ and 205 DZ pairs of 7-year-olds (54% black, 43% white) from the National Collaborative Perinatal Project (Turkheimer et al. 2003). This sample has a high proportion of impoverished families. One useful summary is an analysis in which families were dichotomized into high and low SES. For high-SES families, heritability was 71% and shared environmental contribution was 15%. For low-SES families, heritability was 10% and shared environmental contribution was 58%. This suggests that the causes of individual differences in intelligence are mainly due to environmental differences in low-SES families, whereas in high-SES families differences in intelligence are mainly genetic in origin. Environmental mediation of genetic effects for intelligence has also been shown by Rowe et al. (1999), who found that for low parental education the heritability of intelligence in the offspring was lower (26%) than in the high parental education group (74%). Gene by shared environment (such as parental SES or parental education) interaction will mimic purely additive genetic effects in statistical models that ignore G × E, whereas gene by nonshared environment interaction will mimic nonshared environmental influences.

Whereas G × E refers to genes moderating sensitivity to the environment (or vice versa), rGE refers to genes controlling the exposure to environmental factors, or environmental factors controlling gene frequencies. Generally three types of rGE can be described (Plomin et al. 2001):

*Passive* This type of rGE occurs when parents transmit both genotypes and relevant environmental factors, a mechanism known as "cultural transmission." For example, intellectually gifted parents may transmit genes influencing intellectual capabilities and also provide an intellectually stimulating environment for their children. This type of rGE necessitates the interaction between related subjects.
*Evocative (also known as reactive)* This type of rGE occurs when the treatment of individuals by others is based on their genetic predispositions. For example, bright children may be offered additional study materials by their teachers and be selectively admitted to higher type education.
*Active* This type of rGE occurs when individuals seek out environments based on a genetic predisposition. For instance, intellectually less advantaged children may avoid the library and educational opportunities on the Internet.

Such gene–environment correlation tends to increase the DZ correlation, while the MZ correlation remains the same. Even more complex models allow reciprocal causation between intelligence and environmental factors, resulting in strong correlations between genetic endowment and favorable environmental conditions (Dickens and Flynn 2001).

A final well-known form of actively induced gene–environment correlation is assortative mating, which not only affects the presence of environmental factors in a person himself or herself but also affects resemblance in the offspring. Assortative mating is reflected in a spousal correlation greater than zero, and it is known to indeed exist for intelligence, where spousal correlations are around 0.30. When high-IQ mothers more often elect high-IQ fathers as mates (and vice versa), this will increase the resemblance between parents and offspring as well as among siblings and dizygotic twins. In twin studies, this may conceal the presence of nonadditive genetic effects (gene–gene interactions or genetic dominance) and overestimate the influence of additive genetic factors.

How can we show that complex mechanisms such as gene–gene interaction, gene–environment interaction, and gene–environment correlation are indeed important for intelligence? Finding the actual genes may be a crucial step forward. When genetic variation is no longer a "latent factor" in our model but can actually be measured, investigating genetic effects while allowing for the interplay between genes and environmental factors becomes a realistic goal. Measuring actual genetic variation would further allow testing the effects of genes under different naturally occurring "experimental" environmental conditions, using simple designs—for example, comparing the

effect of variation in the gene in groups of children with high- or low-educated parents.

In the past decade genotyping large samples has become feasible, and many clues have emerged as to the genetic basis of intelligence. Below we shall review the progress made.

## Molecular Genetics and Intelligence

### Whole Genome Approach

A fail-safe approach to identify genes influencing intelligence is to type a large group of subjects at each DNA base pair. However, genotyping thousands of individuals at each of 3 billion loci is currently beyond our means. Researchers therefore adopt strategies of whole genome linkage and association analysis to identify quantitative trait loci (QTLs; Carlson et al. 2004).

Association analysis is similar in design to a classic case–control study in epidemiology. DNA is collected from all participants, and the cognitive trait is compared across the various allelic variants of the DNA marker. Vice versa, frequencies of the various allelic variants may be compared in subjects with a particular deviation in cognition (e.g., schizophrenia) to detect an association between a particular allele and the occurrence of the cognitive deviation. DNA markers can be mutations in a single base pair (single nucleotide polymorphisms; SNPs) or a variable number of repeats of two or more base pairs (microsatellites). Recently, copy number variations—that is, variations in the number of deleted or duplicated versions of segments of the genome—were suggested as additional markers for genetic association studies (Redon et al. 2006). Genetic markers used for association studies need not be part of a functional gene—they are just landmarks in the genome. In a genome-wide association (GWA) study, tens or hundreds of thousands of markers (mostly SNPs) are tested simultaneously. Although only a subset of all possible markers are tested, the ones selected are chosen to represent the untested markers as well as possible, that is, their variation is expected to correlate highly with the variation in unassayed markers. This allows associations to be detected on a genome-wide basis.

The costs of doing GWA studies have been prohibitive until very recently. The existing genome-wide direct association studies for IQ, therefore, used a more cost-effective approach called allelic or "pooled" association. In pooled allelic association, pools of DNA are formed by combining samples from individuals differing in mean score on the trait. The two or more pools are then typed, and a comparison is made of the frequency of alleles for each marker between the comparison groups. False positives are controlled by generating candidates from one sample and then examining these in additional samples to ensure that they replicate. Over the last decade, this method has been championed by Plomin and coworkers, beginning with an association

analysis of 100 markers close to candidate genes in high and low IQ groups. Extensions of this approach have led to the report of the association of a functional polymorphism in ALDH5A1 (MIM 271980) with cognitive ability (Plomin et al. 2004). Recently, this group reported the first genome-wide level allelic association study for cognition (Butcher et al. 2005). They found significant association for a composite of cognitive measures (a *g* factor) taken at age 7 years in a sample of 7,000 twins. Five of the 10,000 SNPs showed replicable association. These lay on chromosomes 2, 6, 7, 11, and 18 and together accounted for less than 1% of the variance in cognition. The genes or functions associated within these SNPs are unknown.

In genome-wide linkage analysis, evidence for genetic linkage is obtained through statistical procedures that trace how often the trait and the DNA marker are jointly passed along in familial lineages. If such a cosegregation of DNA marker and trait can be established with sufficient statistical confidence, then one or more genes in those regions are possibly involved in trait similarity among individuals. Linkage analysis thus serves to detect the regions (QTLs) of the genome where genetic variants with a quantitative effect on the trait must be located.

The first whole genome linkage scan for intelligence was published in 2005 (Posthuma et al. 2005). The sample used in this study consisted of a Dutch sample (159 sibling pairs) and an Australian sample (475 sibling pairs). Results indicated two significant areas of linkage to general intelligence (on the long arm of chromosome 2 and the short arm of chromosome 6), and several areas of suggestive linkage (4p, 7q, 20p, 21p). The chromosome 2 area has been implicated in linkage scans for autism and dyslexia, while the chromosome 6 area is the main linkage area for reading ability and dyslexia. The chromosome 6 linkage lies close to, but a bit further downstream to the association that was reported in the genome-wide allelic association study by Butcher et al. (2005).

Four linkage studies for IQ have been published since (Buyske et al. 2006; Dick et al. 2006; Luciano et al. 2006; Wainwright et al. 2006). Two studies with a partly overlapping sample confirmed the importance of the areas on chromosomes 2 and 6 for specific aspects of intelligence (Luciano et al. 2006) as well as academic achievement, which is highly correlated with IQ scores (Wainwright et al. 2006). The Luciano et al. (2006) study additionally showed that both word recognition and IQ were linked to chromosome 2, confirming the notion of the same genes' influencing different aspects of cognitive ability (Plomin and Kovas 2005).

A completely independent study by Dick et al. (2006) using data collected as part of the Collaborative Study on the Genetics of Alcoholism (COGA) also confirmed linkage of intelligence to the chromosome 6 area. A second scan based on that data set (Buyske et al. 2006) found strong evidence for linkage of specific cognitive abilities on chromosome 14, an area that showed suggestive evidence for linkage in three of the five linkage studies. Although the COGA data set has been selected for alcohol dependence and may

thus not be representative of the general population, Dick et al. (2006) showed that alcohol dependence explained less than 1% of the variance in IQ scores. Moreover, a correction for ascertainment did not change the results significantly.

These first genome-wide linkages of normal ability in unselected samples show convergence with linkage in clinical disorder. For instance, 2q21–33 holds a gene related to autism (Buxbaum et al. 2001) and has been linked to cognitive deficits in childhood-onset schizophrenia (Addington et al. 2004), while the 6p region has been associated with dyslexia, especially speeded reading measures. It might be more generally the case that small mutations or slightly inefficient variants of genes detected in linkage analyses affect normal ability, while more severe mutants which greatly alter gene function or expression result in disorders such as autism, attention-deficit/hyperactivity disorder, and Williams syndrome.

### Candidate Gene Approach

In candidate gene association analysis, known "candidate" genes are selected based on existing neuroscientific evidence. Allelic variation in these genes is measured and tested for association with intelligence. The measured allelic variants can either be (1) the functional variant that is responsible for the gene's effect on intelligence or (2) variants that do not alter the gene effect but are closely correlated with the true (but unmeasured) functional variant, that is, in linkage disequilibrium (LD) with it. Case–control association studies in which, for example, a sample of subjects with high IQ scores (cases) is compared with a sample of subjects with lower IQ (controls) have the highest statistical power but may provide spurious associations as a result of the use of stratified samples. Any trait that has a different distribution across cases and controls (e.g., due to cultural differences between ethnic strata or assortative mating within strata) will show a statistical association with any allele that shows a different frequency across cases and controls. Family-based association studies are statistically less powerful but control for these effects of population stratification, as allelic association is tested exclusively within members of the same family.

In association analysis, the choice of candidate genes is crucial. It is usually based on prior knowledge of the gene's involvement in biological functions relevant to intelligence, such as neurophysiological systems known to influence human memory and cognition. Candidate genes can also be selected based on results from animal studies, in which they have been shown to influence test performance of animal learning and memory. Another source of candidates is genes associated with mental retardation (Inlow and Restifo 2004; Ramakers 2002). Alternatively, allelic variants that show continuous adaptive evolution in modern humans may pose good candidate genes for intelligence (Zhang 2003; Evans et al. 2005; Gilbert et al. 2005). Recently, several studies using a variety of methods have appeared that provide lists of such genes (Dorus et al. 2004; Pollard et al. 2006; Sabeti et al. 2006; Voight et al. 2006).

It is unwise, however, to rely on biological plausibility only. Poor replication of an initially promising association result is a common concern in the molecular genetic study of complex brain functioning. This is illustrated by studies with two allelic variants that have been reported to show continuous adaptive evolution in modern humans, the abnormal spindle-like microcephaly associated (ASPM; Mekel-Bobrov et al. 2005) and microcephalin (MCPH1; Evans et al. 2005) genes. These genes are known to be under positive selection and to be involved in human brain volume, and they therefore pose good candidate genes for IQ (see, e.g., Thompson et al. 2001; Posthuma et al. 2002). Recently, Mekel-Bobrov et al. (2007) used three family-based samples (one Australian and two Dutch) as well as the population-based Scottish Aberdeen (ABC1936) and Lothian (LBC1921) birth cohorts, totaling 2,393 subjects. For the ASPM gene, a significant association was found in four of the five samples, with the nonsignificant result in the youngest (12-year-olds) sample. However, in two samples (Dutch adults and LBC1921) the beneficial allele was the allelic variant under selective pressure (the derived allele), whereas in the other two samples it was the ancestral allele. For MCPH1, a significant positive association was seen for the derived allele in the Dutch 12-year-olds, but this was not replicated in any of the other samples. These results thus remain inconclusive and can probably not be explained by differences in LD patterns across populations (as in that case the specific polymorphism would not have been under selective pressure). Woods and colleagues (2006) further showed that, although it is known that other genetic variants in both ASPM and MCPH1 are involved in the determination of brain volume, selective pressure on these genes cannot be explained by selective pressure on brain volume.

Although the example above encourages caution, association analysis can be very effective. Below we review three cognition–genotype associations that are plausible and have held up in independent replication (see also Posthuma and de Geus 2006). A meta-analysis of thirty-eight studies (more than 20,000 subjects) found that possession of the E4 allele of apolipoprotein E was associated in older people with poorer performance on tests of global cognitive function, episodic memory, and executive function (Small et al. 2004). The E2 allele appeared to be protective. The effect size was small, at about one-tenth of a standard deviation unit. This is an interesting case of variation in a gene that is related to cognition in old age but not in youth (Deary et al. 2002). The mechanisms whereby the variations are detrimental and protective to cognition are not understood, although there are various suggestions (Smith 2002). The follow-up studies of the Scottish Mental Survey of 1932 reported that variation in the genes for Klotho (Deary et al. 2005b) and nicastrin (Deary et al. 2005a) might be associated with general intelligence at both ages 11 and 79 years, but these are, as yet, unreplicated.

The catechol-O-methyltransferase (COMT) gene has been one of the most extensively studied candidate genes in relation to cognitive ability. Decreased COMT activ-

ity might be beneficial from a functional perspective, because it increases frontal dopamine signaling. In line with this, Savitz et al. (2006) found that in twenty of the twenty-six studies on the association between the *COMT* val$^{108/158}$met polymorphism and cognitive function, a significant association was reported. All but two of these studies suggested that the low-activity *Met* allele allows for better performance on cognitive tasks that have a working memory component. The association with intelligence may be more complex. Gosso et al. (2008) showed that the link between *COMT* and cognitive functioning follows a complex pattern in which the COMT gene interacts with the dopamine receptor D2 (DRD2) gene. They found an association between the *COMT* gene and intelligence reflecting positive heterosis such that the Met/Met and Val/Val homozygotes performed less well than the Met/Val heterozygotes on working memory tasks. Gosso and colleagues also found a significant interactive effect of the *DRD2* and *COMT* genes, such that heterosis was present only in the *DRD2* genotype that has been linked to lower receptor density. These results support previous findings (Reuter et al. 2005) that suggest that working memory performance requires an optimal level of dopamine signaling within the prefrontal cortex. This optimum level depends on enzymatic activity controlling dopamine level as well as dopamine receptor sensitivity, both of which may differ as a function of genotype. As a consequence, the effects of a single polymorphism in a dopaminergic gene on a well-defined cognitive trait may easily remain hidden if the interaction with other genes in the pathway is not taken into account.

One of the strongest associations in the current literature is the association between intelligence and the cholinergic muscarinic receptor 2 (CHRM2) gene. In 2003, Comings et al. reported that this gene explained 1% of the variance in full-scale IQ. Two years later, suggestive linkage for intelligence was found on 7q, right above the CHRM2 gene (Posthuma et al. 2005). Subsequently, Gosso et al. (2006b) replicated the association between the *CHRM2* gene and intelligence in a combined sample of Dutch 12-year-olds and Dutch young adults. Here the gene explained 2% of the total variance in full scale IQ. Recently Dick et al. (2007) confirmed the same area to be positively associated with intelligence. Although Comings et al. (2003), Gosso et al. (2006b), and Dick et al. (2007) did not include functional variants of the *CHRM2* gene, the variants that showed positive association were all in the same region of this gene, suggesting that functional variants within that region are of importance to intelligence.

Other genes with variations related to intelligence are the SNAP-25 gene (Gosso et al. 2006), the dysbindin 1 (DTNBP1) gene (Burdick et al. 2006), and the cathepsin D gene (Payton et al. 2003). Although it was originally associated specifically with memory, the gene for brain-derived neurotrophic factor has been associated with intelligence (Tsai et al. 2004) and reasoning skills (Harris et al. 2006). All of these have small effects, consistent with a polygenic view of the heritability of intelligence. Most of these genes are also related to other domains of cognitive functioning.

To understand the underlying mechanisms linking individual differences in specific cognitive abilities to intelligence or to brain pathology, we should adopt a multivariate approach in which we allow the same genes to influence these multiple traits. This multivariate approach has the added advantage of increasing the power of gene-finding studies as has been shown, for example, by Zhang et al. (2005), who used multivariate electrophysiological measures from the COGA study that had been linked previously to alcoholism. They found evidence for genetic linkage on two new chromosomes that were not detected in univariate analyses.

## Conclusion

The last decade has just started to dissect the now well-established heritability of cognitive ability into its molecular genetic elements. Most researchers ascribe to a polygenic view of the genetic contributions to intelligence differences but are as yet in the dark as to how many genetic variants are involved or how big their effects are. Genome-wide studies to date strongly suggest that there will be no genes with a large or moderate effect, and, therefore, studies aimed at securely identifying genetic contributions to cognitive differences will probably require very large samples, especially when a genome-wide approach is adapted. Statistically more powerful candidate gene studies have so far identified a handful of genes, but only a few of these have as yet shown replicated associations with intelligence. All of the identified genes have small effects, consistent with a polygenic view of the heritability of intelligence. Most of these genes are also related to other domains of cognitive functioning, supporting the recently introduced "generalist genes" theory, which states that the same genes affect multiple cognitive abilities (Plomin and Kovas 2005; Kovas and Plomin 2006; Butcher et al. 2006), as opposed to the classic "specialist genes" view, which states that each gene affects one trait. The "generalist genes" hypothesis also implies that some cognitive disabilities are the extremes of normally distributed dimensions of cognitive abilities. Therefore, some of the same genes that have been associated with normal cognitive abilities could provide important clues to underlying mechanisms of milder but more prevalent forms of impaired cognitive functioning, like reading disorder, dyslexia, and attention-deficit/hyperactivity disorder or even the severe cognitive deficits seen in autism and schizophrenia.

Figure 4.2 summarizes the genetic association and linkage studies for intelligence reviewed above. The figure clearly shows that identifying genes with an influence on cognition is feasible but that we have still a long way to go. Also, identifying these polygenes is only a first step; we still face the daunting task of charting the exact route from genetic variation to variation in brain function and on to individual differences in intelligence. Fortunately, as many chapters in this book show, using state-of-the-art brain imaging in subjects carefully selected for genotype is proving to be a powerful

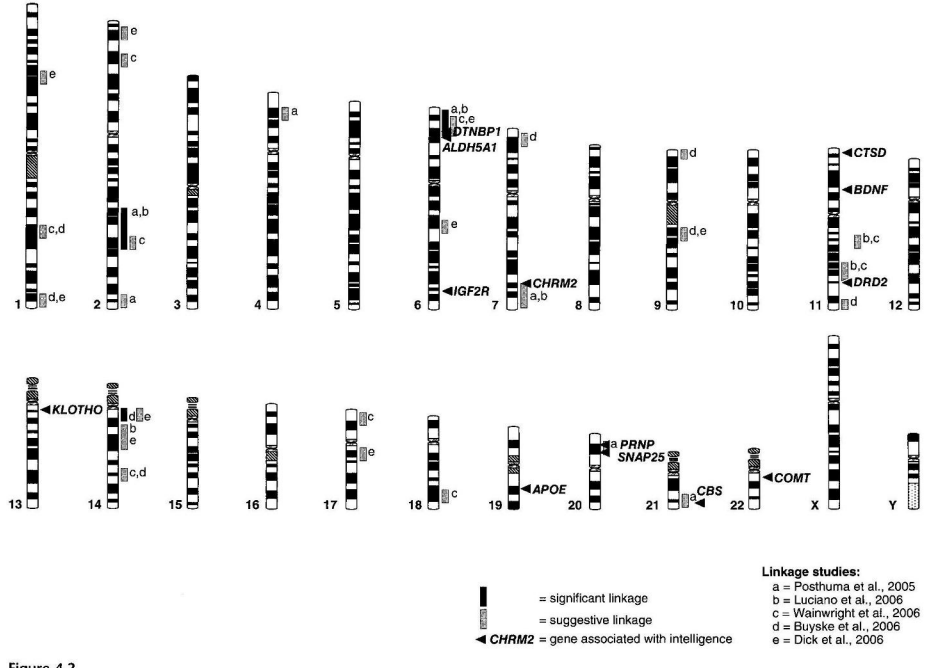


**Figure 4.2**

Ideogram of the human genome indicating which regions in the genome are likely to contain genes for intelligence, as based on the five linkage studies for intelligence that have been conducted to date. It also shows the chromosomal regions of all the genes that have been associated with intelligence so far (Reprinted with permission from Posthuma and De Geus, 2006).

way to do just that. Nonetheless, understanding how genetic variation affects brain functioning related to cognition remains one of the greatest scientific challenges of the twenty-first century.

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