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Abstract Individual differences in intelligence (cognitive abilities) are a prominent aspect of human psychology, and play a substantial role in influencing important life outcomes. Their phenotypic structure—as described by the science of psychometrics—is well understood and well replicated. Approximately half of the variance in a broad range of cognitive abilities is accounted for by a general cognitive factor (*g*), small proportions of cognitive variance are caused by separable broad domains of mental function, and the substantial remainder is caused by variance that is unique to highly specific cognitive skills. The heritability of *g* is substantial. It increases from a low value in early childhood of about 30%, to well over 50% in adulthood, which continues into old age. Despite this, there is still almost no replicated evidence concerning the individual genes which have variants that contribute to intelligence differences. Here, we describe the human intelligence phenotype, summarise the evidence for its heritability, provide an overview of and comment on molecular genetic studies, and comment on future progress in the field.

The existence of individual differences in intelligence is a prominent aspect of human psychology. These differences influence important life outcomes. Their phenotypic structure—as described by the science of psychometrics—is well understood and well replicated. In this overview we shall summarise what is known about genetic—and sometimes environmental—contributions to people's differences in intelligence. Intelligence may be read as cognitive abilities, mental abilities, and IQ in its lay and broad usage. It is a quantitative trait. But it is not like height and weight: it does not afford straightforward measurement using basic scientific units. Therefore, before addressing the genetic and environmental findings, we describe the phenotype of intelligence.

Intelligence: the phenotype

If we test a large group of individuals on their ability to, say, explain to us the meanings of words, there are marked individual differences. Why do some people perform better than others? Is it because people differ on a general cognitive ability that means they are better on almost all mental tasks, no matter what the content? Or is it that people differ on a mental faculty that helps us with cognitive tasks containing verbal materials generally, without implications for nonverbal types of mental work? Or is it that people simply differ on the specific skill of explaining the meanings of words, without implications for their performance on any other mental task? Or is it that people differ in their exposure to words, and they tend to be able to explain best the words to which they have had the most exposure?

All four suggestions are true to varying degrees. Take the ability to explain what words mean, for example, and a specific but entirely ordinary dataset. Over 2,000 children and adolescents, reasonably representative of the US population, took the Wechsler Intelligence Scale for Children-IV (WISC-IV), the newest version of one of the most widely used and comprehensive mental test batteries (Watkins 2006). It includes such a vocabulary test, and nine other mental tests with a diverse range of content. Scores on the ten tests were positively correlated; those who did better on one of the tests tended to do better on all of the others. Of the total variance among the ten mental tests, 54% was variance shared among the tests, and 46% was variance unique to individual tests. Of the shared variance, 71% was due to a general cognitive ability factor. The remaining 28% was due to four less-general factors representing broad cognitive domains that were independent of the general

cognitive ability factor and of each other: verbal comprehension (12%); nonverbal reasoning (4%); working memory (4%); and processing speed (8%). For the vocabulary subtest, 50% of the individual differences in scores was due to the general cognitive ability factor, 19% to the verbal comprehension factor, 1% to the perceptual reasoning factor, and 31% was unique to that subtest.

Another WISC-IV test is Block Design. It involves reproducing two-dimensional patterns using cubes that have red, white, and half-red-half-white faces. It can be completed without use of language. In that test (Watkins 2006) 42% of the individual differences were due to the general cognitive ability factor; 8% due to the nonverbal reasoning factor; and 49% were specific to that test. In this useful example dataset, the ten individual WISC-IV tests were correlated with the general factor between .47 and .72 (mean = .62). That is, in ten very different tests of mental ability, a general cognitive ability factor accounted for between 22% and 51% (mean = 38%) of the individual differences on each test. Of the rest, a mean of 46% of the variance in each subtest was explained by variance unique to each test, which includes variance attributable to states such as fatigue, mood, motivation, etc. The specific percentages are not important here. What is important is the very ordinariness of these results. They mean that, when people engage in mental work there are two principal contributions to how well they do: their level of general cognitive ability, and the very specific capability they have for the particular mental task at that moment. Still, a little of the performance is accounted for by broad domains of thinking skill, such as verbal or nonverbal skills that are less general than the general cognitive factor, but more general than the specific task. At the same time, if the vocabulary test were given in Spanish to this sample, most of the participants would have scored much lower due to their lack of exposure to Spanish vocabulary.

Broadly, these facts have been known for about a century (Spearman 1904, 1927). Examine any dataset in which a number of diverse mental tests has been administered to a large sample of people—Carroll (1993) did so, in a re-analysis of over 400 datasets gathered throughout the 20th century—and a strong general cognitive ability factor appears (Gustaffson 1984; Johnson and Bouchard 2005a). It typically accounts for around 40% to 50% (or even more) of the variance. Spearman (1904) denoted the general cognitive ability factor with the symbol *g*, hoping that a non-word character would forestall controversy and reification. It did not happen so. *g* has been the subject of controversy for most of that time. The major criticisms have come from theories proposing that there might be a number (usually less than 10) of broad, independent domains of cognitive ability.

The best known of these are Thurstone's (1938) 'Primary Mental Abilities' (PMAs), and Gardner's (1983) 'Multiple Intelligences' (MI). But neither account holds water as a counter to *g*. It has been known for 70 years that Thurstone's supposedly-independent PMAs were positively correlated, and that even his own data contained a strong *g* factor (Eysenck 1939; Johnson and Bouchard 2005b). Gould's well-known book (Gould 1981, 1996) on intelligence is incorrect and uninformed on the Spearman-Thurstone debate; it portrays their ideas as exclusive competitors, but aspects of both are incorporated in the well-founded hierarchical model of intelligence (Carroll 1993; Johnson and Bouchard 2005a,b). Gardner's theory has led to few empirical studies, but the majority of his MI are positively correlated and allow a *g* factor to be extracted, and some are not what psychologists would include as 'cognitive' abilities (Visser et al. 2006).

The *g* factor is among the most replicated findings in psychology (Carroll, 1993). There is some continuing debate about the organization of the broad domains of thinking skill that link between *g* and the specific test variance. But these discussions need not detain us here, because it is principally *g* that carries the predictive validity as well as most of the variance in the intelligence trait. However, lest people wonder whether *g* factors extracted from different assemblages of mental tests would differ—and therefore might rank people quite differently—it has been demonstrated that, when test batteries are even reasonably diverse, *g* scores from different batteries of tests correlate all-but perfectly (Johnson et al. 2004; Johnson et al. 2008b). In addition to *g*, though, some of the broad domains of thinking skill (correlated with *g*) have attracted the attention of those seeking the genetic foundations of mental abilities. These include memory (important in ageing research), executive function (often a prime target for those investigating psychiatric illnesses), and language and mathematics (because specific, genetically-influenced disorders of these skills are found). We must emphasise that *g* contributes to these domains. So, when we look at them, we are looking at a composite of *g* and the independent broad cognitive domain as well as the very specific skill tested.

As a preparation for the studies on heritability and molecular genetics of intelligence that are discussed below, it is important to appreciate that they are rarely conducted using a statistically-derived *g* factor, and factors representing the major mental domains that are more specific than *g*. Some are, but others are often conducted using total IQ scores from a battery of tests (like the Wechsler tests), or single tests that load highly on the general cognitive ability factor. The intelligence phenotype—whether it be the *g* factor score, a total IQ score, or a score from a single highly-*g*-loaded

test—has remarkable psychometric credentials. It is highly stable across many decades (Deary et al. 2000). It is highly predictive of educational attainments, occupational success, income and social mobility in longitudinal studies (Strenze 2007; Deary et al. 2005a). It is predictive of how long people live, and many other aspects of illness, health and health behaviours (Batty et al. 2007; Deary 2008). It is important in the practicality of decision-making in people's everyday lives (Gottfredson 1997; Jensen 1998). Therefore, it is appropriate that scientists inquire after its neurological and broader biological origins. Surprisingly, though there are many studies indicating possible associations, the well-attested findings are relatively few. Intelligence test scores correlate moderately with tests of speed of more fundamental information processing (Deary 2000)—such as reaction times—and they correlate modestly with overall brain size (McDaniel 2005). The mechanisms of these associations are not known, though evidence is accumulating around the idea that intelligence involves the efficient working of an integrated parietal-frontal brain network (Jung and Haier 2007) and good white matter integrity (Chiang et al 2009). By far the best evidence about the origins of intelligence differences comes from studies asking about environmental and genetic foundations.

Basic heritability of *g*

Investigation of the relative importance of nature and nurture in the manifestation of human intelligence predates both the understanding of the mechanisms of inheritance and the systematic measurement of intelligence. One year before the publication of Mendel's classic paper on the laws of heredity and 39 years before Spearman's (1904) publication, Francis Galton (1865) published two papers on the hereditary transmission of high intelligence and other abilities. He concluded that high abilities were substantively natural in origin, and transmitted via heredity from one generation to another. Since then, our understanding of genetic mechanisms has grown explosively, yet a steady parade of investigators has reached very similar conclusions despite often hostile political reception (Plomin et al. 2008). Studies have been based on the comparison of similarity in monozygotic (MZ) and dizygotic (DZ) twins (e.g., Bouchard et al. 1990; Nichols 1978), adoptive and biological siblings (e.g., Scarr and Weinberg 1977; Skodak 1950), and parents and their adoptive and biological offspring (e.g., Plomin et al. 1997; Skodak and Skeels 1949), and include major systematic reviews (e.g., Bouchard and McGue 1981). None of the classic papers we cite here is recent, but this is precisely the point: more recent studies have done nothing to change the conclusion that there are

substantial genetic influences on human intelligence, ranging from 30-80% of its total variance including the error with which it is measured. By way of comparison, genetic influences on broad domains of cognitive ability are generally similar (Johnson et al. 2007; Posthuma et al. 2001; Posthuma et al. 2003; Rijsdijk et al. 2002), with the exception of memory, which tends to show smaller genetic influence (Finkel et al. 1995; Johnson et al. 2007; Pedersen et al. 1992). Consistent with the presence therein of tests' error variances, genetic influences on abilities unique to specific tests are generally substantially lower.

This large range of heritability estimates might seem to indicate uncertainty, but it is systematic. The heritability of *g* increases with age (McCartney et al. 1990; McGue et al. 1993; Plomin 1986; Wilson 1978). Again we cite older studies because it is well established that heritability increases from about 30% in very young childhood (Spinath et al. 2003) to as much as 80% in adulthood (Edmonds et al. 2008; Jacobs et al. 2007; Johnson et al. 2007). More recent studies have tended to focus on measuring the extent to which genetic influences contribute to stability and change in *g*. For example, using Dutch twin pairs assessed at ages 5, 7, 10, 12, and 18 years, Hoekstra et al. (2007) found that the heritability of verbal ability increased from 48% at age 5 to 84% at age 18, while the heritability of nonverbal ability increased from 64% at age 5 to 74% at age 18. Stability in nonverbal ability could be attributed completely to genetic influences. Stability in verbal ability was attributable to both genetic and shared environmental influences. The correlation between verbal and nonverbal ability could be attributed completely to genetic influences.

In fact, one of the older studies still provides some of the clearer and more informative data on this subject. Wilson (1978) documented results from the Louisville Twin Study, which measured cognitive development in twins and their singleton siblings at the ages of 3, 6, 9, 12, 18, 24, 30, and 36 months, and 4, 5, and 6 years. The data showed the now-standard pattern of increasing heritability, with MZ twin correlations increasing quite steadily from .66 at 3 months of age to .85 at age 6, while DZ twin correlations remained essentially constant at an average of .67. Estimated heritability increased from 0% at 3 months to 44% at age 6, with MZ twins showing less within-pair variance than DZ twins at each age. In addition, Wilson documented the similarity of the developmental trajectories of the twin pairs by comparing MZ and DZ changes in relative level within the first year, the third year, and the final two years. In each period, changes in MZ pairs were significantly more correlated than in DZ pairs, and within-pair variance over the period was

significantly greater in DZs than in MZs. Moreover, for all twins, correlations of mental development with birth weight and gestational age decreased steadily with chronological age from .50 and .48 to .18 and .11 respectively, while correlations with mother's education and father's social status increased steadily from effectively from 0 to about .35 in both.

Perhaps most importantly, Wilson (1978) documented many of the twin pairs' mental developmental trajectories. They are reproduced here as Figure 1 because they are not as well known as they should be. Across pairs (the panels of the figure), the differences in trajectories are striking. Within pairs or panels, the similarities are also striking, particularly for the MZ pairs. Wilson concluded that cognitive development in young childhood was characterized by genetically regulated individual differences in developmental trajectories that affected both period-to-period change and ultimate level, and largely buffered from environmental insults involved in prematurity. At the same time, he explicitly acknowledged the likely importance of environmental influences to actualize optimal development.

How heritability may increase with age

The brain clearly undergoes morphological changes with development (Bell and Fox 1992; Shaw et al. 2006; Sowell et al. 1999). Strong genetic influences (on the order of 70-90% of variance) have been reported for many brain structures, components, and regions in adults, including gray and/or white matter volumes and/or densities in corpus callosum, superior frontal and temporal cortex, medial frontal cortex, amygdala, hippocampus, Broca's area, anterior cingulate, Heschl's gyrus, postcentral gyrus, and overall brain volume (Hulshoff Pol et al. 2006; Pennington 2000; Peper et al. 2007; Posthuma et al. 2002; Thompson et al. 2001). Many of these genetic influences have also been linked to *g* and/or intelligence (Hulshoff Pol et al. 2006; Peper et al. 2007; Posthuma et al. 2002). Similar data have been reported for aspects of brain function that may be related to intelligence, such as the dynamic complexity of measuring brain oscillations assessing executive function output (Anokhin et al. 2006), suggesting that these physiological brain measures may be endophenotypes (Gottesman and Gould 2003), or physiological markers of intelligence. Similar data have also been reported for performance on tasks considered by many to reflect more elementary information processing capacity, than performance on intelligence tests (Roberts and Stankov 1999), such as inspection time (Edmonds et al. 2008) and executive control (Friedman et al. 2008). Moreover, even

in 10-year-olds, genetic correlations among different aspects of intelligence such as reading and mathematics abilities have shown substantial genetic correlations (Davis 2008).

Perhaps of even greater relevance is one longitudinal brain imaging study of typically and atypically developing children and adolescents being carried out by the Child Psychiatry Branch of the US National Institute of Mental Health (Giedd et al. 2007). Typically developing twins and singletons in this study ranged in age from 5 to 18 at recruitment beginning in 2001, and have been assessed at approximately 2-year intervals since then. Cross-sectionally, data from this study have indicated that developmental trajectories of cortical thickness better predict age 20 IQ than differences in cortical thickness at age 20 (Shaw et al. 2006), providing endophenotypic support for Wilson's (1978) observations. At the same time, the midsagittal area of the corpus callosum, the volume of the caudate nucleus, and gray and the white matter volumes of the total cerebrum, parietal lobes, and temporal lobes showed genetic influences accounting for 77-88% of total variance. Genetic influences on the volume of the cerebellum and lateral ventricles were lower, at 49% and 31%, respectively. There were few shared environmental effects. Total variance tended to increase with age, but genetic variance in white matter increased with age while nonshared environmental variance in gray matter increased with age. Genetic influences across brain regions were more important than those specific to any one brain region. Earlier developing brain regions such as primary sensory motor cortex showed stronger genetic influences in early childhood, while later developing regions within the dorsal prefrontal cortex and temporal lobes showed increasing genetic influences with age (Lenroot et al. 2009).

Neuronal repair might provide another mechanism to account for there being different heritabilities at different ages. As the brain ages, there is an accumulation of environmental insults (via, for example, oxidative stress and inflammation) that can harm neurons and must be protected against and repaired. To the extent that these defence and repair processes are based on genes that show genetic variation, one would expect these genetic contributions to intelligence to appear at some point in adulthood, once individual differences in brain repair had an effect on cognitive phenotypes. Some support for this suggestion came from the finding that variation in the gene for apolipoprotein E was associated with general cognitive ability at age 79 but not at age 11 years (Deary et al. 2002).

Molecular genetic studies

Despite its high heritability, it is not possible confidently yet to name one genetic locus unequivocally associated with the quantitative trait of intelligence. Intelligence is not unusual in the difficulties it has found in trying to identify the genes responsible for its high heritability (Maher 2008). Certainly, there are some associations between *APOE* variation and cognitive functions (including general mental ability and memory) in old age (Small et al. 2004), and there are some associations with language functions (Fisher 2006) but, with respect to individual differences in intelligence in healthy samples, there are no firmly replicated findings. We state at the outset that there are other overviews of this and related fields where the reader can find some similarly bracing judgements about the power of genetic association studies (Plomin et al. 2006) and inconsistency in the literature concerning candidate gene studies (Payton 2006a). There are also more upbeat judgements than ours (Posthuma and de Geus 2006).

In part, the lack of replicated molecular genetic findings might be because intelligence as a trait has as yet attracted small samples and few studies, by comparison with disease-related traits, and other traits such as height and weight. Examinations of genes related to intelligence have sometimes been the result of studies with a primary interest in mild mental handicap (e.g. Butcher et al. 2005), cognitive ageing and ageing more generally (e.g. Payton 2006a; Deary et al. 2004), and schizophenia and other psychiatric disorders that involve cognitive decrements (e.g. Porteous et al. 2006). Likewise, some of the candidate genes that have been examined are those related to the same disorders, including those associated with brain size (e.g. *ASPM* and *MCPH*; Mekel-Bobrov et al. 2007), dementia (especially *APOE*; Small et al. 2004), dopamine (e.g. *COMT*; Barnett et al. 2008) and other cognition-related neurotransmitter-receptor systems (e.g. *CHRM2*; Dick et al. 2007) and synaptic mechanisms (e.g. *SNAP25*; Gosso et al. 2006a), longevity (e.g. *KLOTHO*; Deary et al. 2005b), and oxidative stress (e.g. *PRNP*; Kachiwala et al. 2005). Table 1 describes more than 20 candidate genes and the results obtained, but is given with a warning that many of the associations shown as significant, have failed to replicate in a study of about 1,000 subjects with a large battery of cognitive tests and the same genetic variants (Houlihan et al. 2009). There are, as yet, few meta-analyses for specific candidate genes, and the one for *COMT* is not encouraging (Barnett et al. 2008). The biological functions of the several possible candidate genes for cognition have not been discussed here, or included in Table 1. It appeared to us that this was not useful in advance of better

replication status for individual associations. As the area matures, and if it brings increasing evidence for more replicated intelligence-genetic variant associations, then the mechanistic biology of the gene functions and pathways should be explored in detail. In common with other quantitative traits, estimates for the effect of any one genetic variant are well below 1% of the variance, which means that much larger samples are required than have typical been employed (Plomin et al. 2006).

Beyond candidate genes, more omnibus approaches have been taken. Hypothesising that protection against oxidative stress might be associated with neural health and intelligence, over 300 SNPs in over 100 genes were studied in relation to intelligence at age 11 and age 79 in the same subjects (Harris et al. 2007). There were no replicable gene-intelligence associations. Based on the idea that mild mental handicap represents the low end of the normal distribution of intelligence, 432 brain-expressed nonsynonymous SNPs were tested for associations with intelligence (Butcher et al. 2005). This produced a five-SNP candidate set that was not replicated in the meta-analysis of a later study using six population-based samples (Luciano et al. 2008). However, within that study one sample did replicate the original findings, and one found significant results in the opposite direction. Other factors that might have led to non-replication were the ages of the samples in the different cohorts, the different cognitive tests used in the different samples, and variation in completeness of the five-SNP set in the replication samples, owing to some failed genotyping. The 'pathway' approach is also being taken by the Genes-to-Cognition project, whereby genes coding for proteins in the postsynaptic NRC/MASC complex (NMDA Receptor Complex or MAGUK-Associated Signalling Complex)—which is known to be associated with learning and memory in rodents—are being studied for variations that might be associated with cognitive functions (Croning et al. 2009; Laumonnier et al. 2007; www.genes2cognition.org).

Several genome-wide linkage studies of intelligence provided suggested regions of linkage, and have some concurrence with associations with individual genes and SNPs, though none of these is well replicated. The linkage studies are summarised in Table 2. The first large-scale genome-wide association scan of general intelligence (*g*) used a two stage process (Butcher et al. 2008). First, pooled DNA from selected high *g* and low *g* 7-year-olds was examined for allele frequency differences on 500,000 SNPs. Forty-seven SNPs were tested in a separate group of over 3000 children representing the whole range of *g*. Six of these were significant—more than the two expected by

chance—though only one (rs2496143) survived after a false discovery rate of 0.05 was imposed. None was in a coding region. They accounted for between 0.1% and 0.4% of the variance in *g*.

Studies will continue to appear that utilise the candidate gene, pathways, and genome wide association approaches. None of these, to date, has been successful in accounting for any of the large genetic contribution to intelligence differences. Indeed, only one of the promising candidate genes listed in Table 1 is located in a region of linkage for intelligence as listed in Table 2 (*CHRM2*), confirming the lack of consistency of results. Other approaches will be used, but have yet substantially to get off the ground. These will include well-conceptualised gene-environment interaction studies, such as the one that showed that breast feeding and variation in the *FADS2* (involved in the control of fatty acid pathways) gene contributed to intelligence differences in children (Caspi et al. 2007).

Known complications in studying genetic contributions to intelligence

Though results from studies of adoptive and biological siblings and parents and both adoptive and biological offspring are very consistent with those from twin studies (Bouchard in press), twin studies have supplied the majority of the data on genetic influences on *g* to date. The twin study is a powerful natural experiment but, like any other natural experiment, its use relies on the accuracy of some important assumptions. As for many other heritable traits, violations of these assumptions, such as the assumption that MZ twins are genetically identical, may be contributing to the difficulties in identifying the specific genes involved in *g*.

From a quantitative genetic perspective, however, the arguably most fundamental assumption actually applies to studies of all kinships. This is the assumption that genetic and environmental influences on *g* are independent. There are at least two dynamic processes through which this assumption is probably commonly violated (Johnson 2007; Moffitt et al. 2006): gene-environment correlation, or the association between genetic differences and differential environmental exposure; and gene-environment interaction, or the association between differential environmental effects and genetic differences. Because individual humans have some control over their exposure to environments related to the development of intelligence, these two forms of gene-environment interplay tend to co-exist in systematic ways (Johnson 2007). Where environmental effects are toxic, all those who possibly can will move to escape them, creating a correlation between whatever genetic

influences limit ability to escape the environment and environmental exposure, and an interaction between the environmental effects and genetic sensitivity to them.

One such process that may be involved in the development of intelligence has been partially explored in several studies. These studies have generally indicated that genetic influences unique to IQ and not shared with genetic influences on socioeconomic status (SES) are more important in environments of higher rather than lower socioeconomic status (SES), at least in childhood (Guo and Stearns 2002; Harden et al. 2007; Turkheimer et al. 2003; but see van den Oord and Rowe 1997; van der Sluis et al. 2008). But IQ and SES tend to be correlated (Deary et al. 2005c; Herrnstein and Murray 1994; Higgins 1961; Jencks 1979; Korenman and Winship 2000; Waller 1971), and the extent to which and manner in which genetic influences contribute to this correlation have not been addressed. It would be surprising if genetic influences did not contribute (Hegmann and DeFries 1970; Johnson 2007), but understanding how they do contribute would help in understanding how intelligence develops and thus the biological meaning of its apparently high heritability. Bouchard (1997) has proposed that we inherit not intellectual capacity as such; rather, species-typical affective-motivational systems shaped by the environment of evolutionary adaptation that drive both capacity and preferences. Following Hayes (1962), he suggested that manifest intelligence is the demonstration of skills and knowledge accumulated during the experiences created by these affective-motivational systems. Van der Maas et al. (2006) have demonstrated that such a conceptualization of intelligence as an emergent rather than latent trait can account just as well for the correlations among mental ability tests that we use to define *g*. Such a conceptualization also implies that the specific genes contributing to any particular level of manifested intelligence may differ considerably from individual to individual, making them very difficult to isolate with the techniques currently available. There is psychometric and neuroscientific evidence that this could be the case as well (Johnson et al. 2008a; Johnson and Bouchard 2007a, b).

This kind of gene-environment interplay model could also help to account for the Flynn Effect, named after James Flynn, who has amassed most of the data. The Flynn Effect is the robust observation that, over the last hundred years or so, performance on intelligence tests has risen consistently over time. The increases vary from nation to nation and test to test, but they average about five IQ points, or a third of a standard deviation, per decade, and have led to the ongoing necessity of re-norming commonly used IQ tests (Flynn 1995; Flynn 2007). The existence of the Flynn

Effect is generally accepted, though some suggest that it may be levelling off at least in western countries in recent years (Ronnlund and Nilsson 2008; Teasdale and Owen 2008). There has been no consensus on the reasons for it, however, though a model featuring gene-environment correlation has been proposed by Flynn (Flynn 2007; Dickens and Flynn 2001).

Some new directions to consider

Though at this writing we have no knowledge of any specific genes reliably associated with normal-range intelligence, we do know of some 300 genes associated with mental retardation (see Inlow and Restifo 2004 for a review). This is generally considered to be an underestimate of the number actually involved (Chelly et al. 2006). Penke et al. (2007) suggested that genetic variance in intelligence may result from mutation-selection balance, or the accumulation of many mildly harmful mutations, both old and new, that natural selection has not yet wiped from the population. This would be consistent with our ability to isolate genetic variants involved in mental retardation but not in normal-range intelligence with currently available methods. It would also be consistent with the common disease-rare variant hypothesis (Goldstein and Chikhi 2002; McClellan et al. 2007) as an explanation for genetic influences on intelligence.

Of the approximately 300 identified genes associated with mental retardation, about 20% are located on the X chromosome (Ropers and Hamel 2005). About 3.4% of all genes are located on the X chromosome (Skuse 2005). It is relatively easy to identify genes on the X chromosome because females have two X chromosomes while males have only one. Our current knowledge may thus overstate the proportion of total genes involved in mental retardation that are located on the X chromosome. Still, it is possible that genes on the X chromosome are over-represented among genes involved in intelligence, as the genes on the X chromosome tend to be expressed in the brain, along with the reproductive tissues (Laumonnier et al. 2007). Moreover, many of the genes on the X chromosome do not appear to be polymorphic in the general population (Ross et al. 2005), suggesting that these genes could be involved in fundamental brain organization. This would be consistent with the idea that variation in intelligence could result from many individually rare mutations in these genes.

Individuals with X chromosome anomalies also provide evidence that genes on the X chromosome may be involved in specific abilities copntributing to general intelligence, particularly

verbal and spatial abilities. Females with Turner's syndrome, who have only a single X chromosome, tend to display deficits primarily in spatial and numerical abilities (Skuse 2005), while males with Klinefelter's syndrome, who have an extra X chromsome (XXY), tend to display deficits primarily in verbal and executive functioning (DeLisi, et al. 2005). The existence of genes, on any chromosome, with differential effects on specific kinds of abilities would be consistent with the idea of *g* as an emergent trait influenced by different genes to different degrees in different individuals. Johnson et al. (in press) provide a more complete review of the reasons for thinking genes on the X chromosome may be involved in intelligence.

The approach adopted by the Genes to Cognition project is a broader variant of the pathway approach that has merit. It started with the idea that, if the postsynaptic NRC/MASC complex is a key part of the mechanism for thinking and memorising, then it is worth exploring to discover whether genetic variation in its almost 200 genes is associated with cognitive ability differences and cognitive pathology-related disorders (Laumonnier et al. 2007). The human studies include sequencing and SNP testing, parallel animal studies involve making knock-out mice and analysing their behavioural profiles, and bioinformatics studies analyse the proteomic networks. Such large scale, organised, picking-apart of the molecular engines of cognition have considerable merit in principle (www.genes2cognition.org).

Progress will be made along the routes already being explored as offering sources of variance for other quantitative traits and psychologocical and psychiatric disorders. The extent to which copy number variation contributes to intelligence differences should be tested: it is possible that people with lower *g* levels have larger numbers of small chromosomal deletions and duplications (cf. International Schizophrenia Consortium 2008). The possibility—revealed by sequencing—that the load of rare genetic variants might be a contributing factor to schizophrenia is an obvious one to apply to cognitive ability, not least because cognitive decrements are a key feature of schizophrenia. The degree to which runs of homozygosity (McQuillan et al. 2008) are associated with intelligence will be used to test the 'heterosis' hypothesis of intelligence differences (Mingroni 2007). We can expect to see more testing of genetic variants on so-called intermediate phenotypes for intelligence, such as processing speed and brain-imaging parameters (e.g. Chiang et al. 2009). Routes into the genetic contributions to intelligence will continue to come from studies of cognitive pathologies—reading and other language disorders, autism, schizophrenia, mild mental handicap, etc.—not least because of the

‘generalist genes’ idea that many of the genes associated with specific cognitive disorders will contribute to normal-range variation in *g* (Kovas and Plomin 2006; Davis et al. 2008). As is the case with height—which is probably even more highly heritable than general intelligence—much work in the next years will be devoted to seeking the loci of the as-yet ‘missing heritability’ (Maher 2008).

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Table 1 Results of candidate gene studies of intelligence

Gene	Gene Name	Chromosome band	Cognitive Phenotype	Sample	Genotype:Phenotype Association	Reference
ASPM	Asp (abnormal spindle) homolog, microcephaly associated (Drosophila)	1q31	Mental ability: Wonderlic Personnel Test and Multidimensional Aptitude Battery	644 Canadian adults	N	1
OXTR	Oxytocin receptor	3p25	General intelligence: WISC, Kaufman Assessment Battery for Children, Bayley Scales of Infant Development, Merrill–Palmer Scale of Mental Tests, Mullen Scales of Early Learning, Cattell Measurement of Intelligence of Infants and Young Children, Leiter International Performance Scale, Stanford–Binet Intelligence Scale	152 autism spectrum disorder individuals	Y	2
CCKAR	Cholecystokinin A receptor	4p15	General intelligence: Japanese WAIS-R SF	2251 community-dwelling Japanese men and women aged 40 to 79 years	Y	3
SLC6A3	Solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	5p15	Vocabulary and Block Design subtests: WISC III	3 independent Brazilian cohorts (242 ADHD children, 220 ADHD adults,	N	4

				100 ADHD inattentive type children)		
ADRB2	β_2-Adrenergic receptor	5q33	General Intelligence: Wechsler Intelligence Scale, Performance IQ (Dutch), Matrix reasoning & MHT (Scottish)	2 cohorts: 2 family-based Dutch samples n=391& 409; 1 Scottish population sample n=1,063	Y	5
DTNBP1	Dysbindin-1	6p22	General Intelligence: WRAT-3, WAIS-R-Digit Span, CPT-I/P, CVLT-Abridged, COWAT and Trail Making Tests A&B.	213 schizophrenia individuals, 126 controls	Y	6
ALDH5A1	Aldehyde dehydrogenase 5 family, member A1	6p22	General Intelligence: WISC-R and WAISIII-R	197 high-IQ cases, 201 average-IQ controls, 196 parent high-IQ offspring trios	Y	7
IGF2R	Insulin-like growth factor 2 receptor	6q26	a) WISC-R b) Study of Mathematically Precocious Youth	2 cohorts: a) Children with high IQ (n=51) and average IQ (n=51) (US) b) Children with high IQ (n=52) and controls (n=50)	Y	8
			WISC-R[a]	N=188	N	9
CHRM2	Cholinergic muscarinic 2 receptor	7q33	General Intelligence: WAIS-R subtests of Vocabulary, Information, Block Design, and Picture Arrangement	1 population study of 828 adults	Y	10

			WISC-R and WAISIII-R consisting of performance IQ and full scale IQ [2,3], not verbal IQ	1 family based sample of 667 participants in 304 families,	Y	11
			WISC-R and WAISIII-R consisting of performance IQ and full scale IQ (not verbal IQ),	2 independent Dutch cohorts n=371 & 391	Y	12
			Performance IQ (WAIS-R)	200 families, containing 2,158 individuals	Y	13
MCPH1	Microcephalin 1	8p23	Mental ability: Wonderlic Personnel Test and Multidimensional Aptitude Battery	644 Canadian adults	N	1
DRD4	Dopamine D4 receptor	11p15	Spatial working memory and an interaction with lead and gender on executive functions	US population sample of 174 children	Y	14
			IQ: short form of the Wechsler Preschool and Primary Scale of Intelligence–Revised comprising vocabulary and block design subtests	2 independent cohorts Britain (n=171) and New Zealand (n=55)	Y	15
			Vocabulary and Block Design subtests: WISC III	3 independent Brazilian cohorts (242 ADHD children, 220 ADHD adults, 100 ADHD inattentive type children)	N	4

CTSD	Cathepsin D	11p15	General Intelligence: Alice Heim intelligence test score (AH4-1)	767 healthy adults	Y	16
			Processing speed (random letters test, alphabet-coding task) spatial recall, fluid intelligence	766 healthy adults (same cohort as above)		17
FADS2	Fatty acid desaturase 2	11q12	Moderates an association between intelligence and breastfeeding (WISC-R NZ, Wechsler Preschool and Primary Scale of Intelligence–Revised UK)	2 cohorts: New Zealand n=858; British n=1848	Y	18
DRD2	Dopamine receptor D2	11q23	IQ:a speed of information processing measure and a short-term memory test	Seventy-one high IQ individuals and 78 controls	N	19
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A	13q14	CPT and WCST.	82 schizophrenia individuals (Turkey)	Y	20
			Longitudinal change in a semantic memory task	150 monozygotic twins (Sweden)	N	21
CHRNA7	Cholinergic receptor, nicotinic, alpha 7	15q14	Episodic memory function (WMS)	251 subjects (96 schizophrenia individuals, 116 unaffected relatives, and 39 healthy individuals)	Y	22

			Sustained attention (CPT Boring Phase) Response inhibition	100 female college students current or past smokers and 144 non smokers	Y	23
APOE	Apolipoprotein E precursor	19q13	Global cognitive functioning, episodic memory, and executive functioning	Meta-analysis of 38 studies	N	24
SNAP-25	Synaptosomal-associated protein 25	20p12	General Intelligence: WISC-R and WAISIII-R consisting of performance IQ, full scale IQ, and verbal IQ	2 family based Dutch samples n=391& 276	Y	25
			General Intelligence: WISC-R and WAISIII-R consisting of performance IQ, full scale IQ, and verbal IQ	2 independent Dutch cohorts n=371 & 391	Y	26
S100B	S100 calcium binding protein B	21q22	Cognitive Function: MMSE score	3 elderly (demented and non-demented) cohorts; n=815 (French), n=513 (Denmark), n=1049 (Leiden)	Y	27

None of the following (below) genetic associations were replicated by Houlihan et al. 2009, details of which are found in the cells immediately to the right			MHT at ages 11 and 70 and battery of diverse cognitive tests[b]	1,301 healthy individuals aged ~70 years old		28
NCSTN	Type I transmembrane glycoprotein Nicastrin	1q23	IQ: MHT at age 11 and age 79	462 healthy people	Y	29
DISC1	Disrupted in schizophrenia	1q42	IQ and normal cognitive ageing in women: MHT scores at age 79	462 healthy people	Y	30
WRN	Werner protein	8p12	General Intelligence: a test of fluency (number of animals named in one minute), forward and backward digit span, and a modified 12-word learning test)	426 dizygotic Danish twins age 70–90 years	Y	31
BDNF	Brain-derived neurotrophic factor	11p14	Memory: WMS-R	US samples, n=641 subjects (normal controls, patients with schizophrenia, and their unaffected siblings)	Y	32
			Age-related change in reasoning skills: Raven's Standard Progressive Matrices	2 UK samples, n=462 & 433 healthy people	Y	33

KL	Klotho peptide	13q13	Cognitive ability: MHT of verbal reasoning in childhood	462 healthy people	Y	34
PPP1R1B	Dopamine- and cAMP-regulated phosphoprotein	17q12	General intelligence: IQ and WRAT-reading; working memory (N-back test); WCST and letter fluency tests; and also sequencing, response alternation, and attention, as measured by the Gordon Continuous Performance Test D', trails B and trails A	257 families with schizophrenia proband	Y	35
PRNP	Prion protein	20p13	Cognitive performance: MMSE and global composite score (nine different neuropsychological test)	1,163 individuals	Y	36
			IQ: MHT scores at age 79	460 healthy individuals	Y	37
COMT	Catechol-*O*-methyl transferase	22q11	Executive cognition: WCST	US sample: n=175 individuals with schizophrenia, 219 unaffected siblings, 55 controls	Y	38
			Logical memory	460 healthy individuals (UK)	Y	39
PLXNB3	Plexin B3	Xq28	General Intelligence: Wortschatztest vocabulary test	303 healthy volunteers & 42 male	Y	40

		patients with schizophrenia

Note. The table is ordered according to chromosome position and split between possible candidate genes for intelligence and those improbable candidate genes for intelligence that failed replication (Houlihan et al. 2009). ADHD is attention deficit/hyperactivity disorder. COWAT is Controlled Oral Word Association Test. CPT is Continuous Performance Test. CPT-I/P is Continuous Performance Test-Identical Pairs Version. CVLT is California Verbal Learning Test-Abridged. MHT is Moray House Test. MMSE is Mini-Mental State Examination. WAIS-R is Wechsler Adult Intelligence Scale-Revised. WAIS-R SF is Wechsler Adult Intelligence Scale-Revised shorter form. Wisconsin Card Sorting Test is WCST. WISC-R is Wechsler Intelligence Scale for Children-Revised. WMS-R is Wechsler Memory Scale, revised version. WRAT is Wide Range Achievement Test-Third Edition-Reading Subtest. WRAT-3 is Wide Range Achievement Test-Third Edition-Reading Subtest. [a]This is the only available information on the *IGF2R* replication study. [b]Cognitive phenotypes tested in Houlihan et al. 2009 are described in detail (Deary et al. 2007). Y represents a positive association of variants in the specific gene to intelligence. N represents a study that failed to replicate the association. This table was prepared with help from the Genetic Association Database (Becker et al. 2004). References are; 1= Rushton et al. 2007; 2= Lerer et al. 2008; 3= Shimokata et al. 2005; 4= Genro et al. 2006; 5= Bochdanovits et al. 2009; 6= Burdick et al. 2006; 7= Plomin et al. 2004; 8= Chorney et al. 1998; 9= Hill et al. 2002; 10= Comings et al. 2003; 11= Gosso et al. 2006a; 12= Gosso et al. 2007; 13= Dick et al. 2007; 14= Froehlich et al. 2007; 15= Mill et al. 2006; 16= Payton et al. 2003; 17= Payton et al. 2006b;18= Caspi et al. 2007; 19= Moises et al. 2001; 20= Ucok et al 2007; 21= Reynolds et al 2007; 22= Dempster et al 2006; 23= Rigbi et al 2008; 24= Small et al. 2004; 25= Gosso et al. 2006b; 26= Gosso et al. 2008; 27= Lambert et al 2007; 28= Houlihan et al. 2009; 29= Deary et al. 2005c; 30= Thomson et al. 2005; 31= Bendixen et al. 2004; 32= Egan et al. 2003; 33= Harris et al. 2006; 34= Deary et al. 2005b; 35= Meyer-Lindenberg et al. 2007; 36= Berr et al. 1998; 37= Kachiwala et al. 2005; 38= Egan et al. 2001; 39= Harris et al. 2005; 40= Rujescu et al. 2007.

Table 2 Linkage findings for intelligence

Linkage Region	Genetic Evidence	Cognitive Phenotype	Sample	Reference
1q41	LOD 2.5	8-choice reaction time	Brisbane adolescent twin sample: 378 families (information processing) & 285 families (delayed response working memory)	1
1q43	LOD 2.8	General intelligence: Full scale IQ	1,111 individuals from 201 families (COGA)	2
2q21-q33	LOD 4.4	Performance IQ	634 sib-pairs (329 Australian families & 100 Dutch families)	3
	LOD 4.2 (Reading) LOD 3.7 (Performance IQ)	Cambridge Reading Test Performance IQ	361 Australian and Dutch twin families	4
3q13	LOD 2.4	Wechsler Symbol Search test, Strop CWI, Digit span	1,212 individuals from 271 families	5
6p25-p22	LOD 3.2 (Full-scale IQ) and 2.3 (Verbal IQ)	General intelligence: Full scale IQ and verbal IQ	634 sib-pairs (329 Australian families & 100 Dutch families)	3
	LOD 2.2 (Full IQ) LOD 3.1 (Arithmetic—verbal subtest) LOD 3.1 (Schonell reading test)	General intelligence: Full scale IQ Arithmetic & verbal subtest (Schonell reading test)	361 Australian and Dutch twin families	4
	LOD 3.2	General intelligence: Full Scale IQ	1,111 individuals from 201 families (COGA)	2
7q31-36	LOD 2.4	Verbal IQ	361 Australian and Dutch twin families	4

7q36	LOD 2.9	Delayed response spatial precision	Brisbane adolescent twin sample: 378 families (information processing) & 285 families (delayed response working memory)	1
8p12	LOD 2.3	4-choice reaction time	Brisbane adolescent twin sample: 378 families (information processing) & 285 families (delayed response working memory)	1
11p15	LOD 2.5	8-choice reaction time	Brisbane adolescent twin sample: 378 families (information processing) & 285 families (delayed response working memory)	1
11q22-q23	LOD 2.2	Vocabulary—verbal subtest	361 Australian and Dutch twin families	4
11q25	LOD 3.1	Digit Span Test (WAIS-R)	1579 individuals in 217 families (COGA)	6
14q11, 14q24	LOD 6	Digit Symbol Substitution Test (WAIS-R)	1579 individuals in 217 families (COGA)	6
14q13-q21, 14q32	LOD 2.2 (Arithmetic), 3.2 (Reading)	Arithmetic—verbal subtest Schonell reading test	361 Australian and Dutch twin families	4
14q23	LOD 2.3	Delayed response initiation time	Brisbane adolescent twin sample: 378 families (information processing) & 285 families (delayed response working memory)	1
17q12	LOD 2.2	General intelligence: Full Scale IQ	1,111 individuals from 201 families (COGA)	2
22q12	LOD 2.3	Schonell reading test	361 Australian and Dutch twin families	4

Note. This table summarises the six genome-wide linkage studies for cognitive traits: 1= Wright et al. 2008, 2 = Dick et al. 2006; 3 = Posthuma et al. 2005; 4 = Luciano et al. 2006; 5 = Doyle et al. 2008, 6= Buyske et al. 2006. Suggestive and significant linkage regions as defined (LOD > 2.2 are suggestive, LOD > 3.6 are significant) are shown (Lander and Kruglyak 1995). COGA = is the Collaborative Study on the Genetics of Alcoholism.

Figure Captions

Figure 1

Illustrative mental development curves for monozygotic (MZ) and dizygotic (DZ) twins. From Wilson (1978).

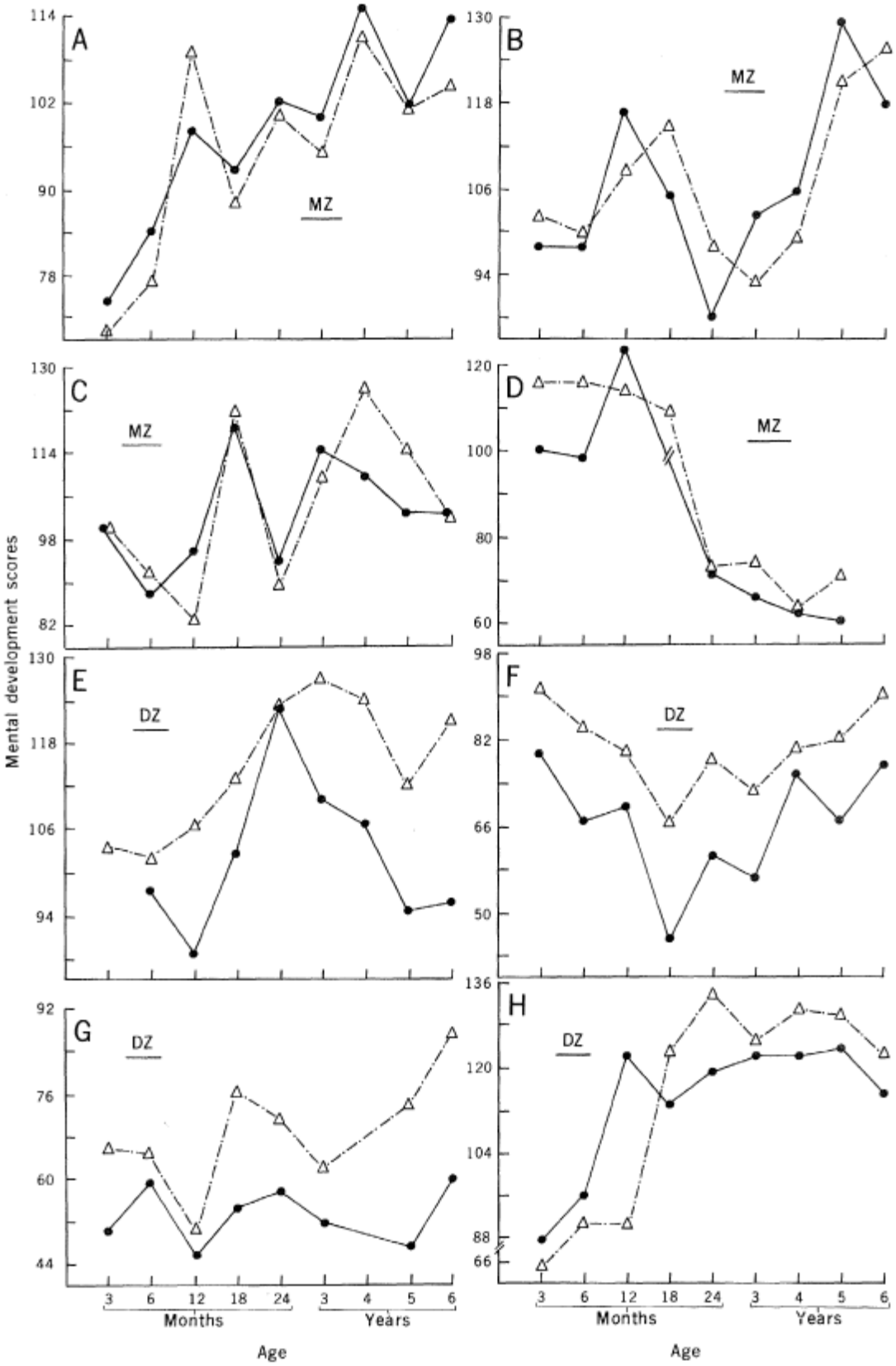
A
MZ
B
MZ
C
MZ
D
MZ
E
DZ
F
DZ
G
DZ
H
DZ
Mental development scores
Months
Years
Age

Figure 1