GUEST EDITORIAL

Genetics, genes, genomics and g

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This issue includes three papers^{1–3} on a topic of increasing interest to molecular psychiatrists: the genetics of intelligence. There was also a related article in a previous issue of *Molecular Psychiatry*.⁴ These four papers represent the range of research on genetics (quantitative genetic twin studies), genes (molecular genetic attempts to identify genes) and genomics (understanding the function of genes). The goal of this editorial is to put these papers in perspective.

Intelligence is the most complex—and most controversial—of all complex traits. So why study the genetics of such a complex and controversial trait? The word ‘intelligence’ has so many connotations that the symbol ‘g’ was proposed nearly a century ago to denote the operational definition of intelligence as a ‘general cognitive ability’ representing the substantial covariance among diverse tests of cognitive abilities such as abstract reasoning, spatial, verbal and memory abilities.⁵ In a meta-analysis of 322 studies, the average correlation among such diverse tests is about 0.30⁶ and a general factor (first unrotated principal component) typically accounts for about 40% of the tests’ total variance.⁷ As discussed below, multivariate genetic analysis shows that the genetic overlap among cognitive tests is twice as great as the phenotypic overlap, suggesting that g is where the genetic action is. Although g is not the whole story, trying to tell the story of cognitive abilities without g loses the plot entirely.

This strong genetic g factor running through diverse cognitive processes has important implications for genetic research in neuroscience since g is molar and flies in the face of the widespread assumption in cognitive neuroscience that the brain functions in a modular manner.⁸ In addition, the long-term stability of g after childhood is greater than for any other behavioral trait,⁹ it predicts important social outcomes such as educational and occupational levels far better than any other trait,¹⁰ and it is a key factor in cognitive aging.¹¹ g is specifically relevant to molecular psychiatry because, as discussed below, mild mental retardation appears to be the low extreme of the normal distribution of g. Moreover, at least 200 single-gene disorders include mental retardation among their symptoms.¹²

Quantitative genetics

Quantitative genetic research—twin and adoption studies—estimates the net effect of genetic variation

on phenotypic variation regardless of the number of genes involved or the complexity of their interactions. Such research charts the course for molecular genetic studies by identifying the most heritable components and constellations of phenotypes. The first twin and adoption studies were conducted in the 1920s on g and suggested substantial genetic influence.^{13–15} Since then, with the exception of personality assessed by self-report questionnaires, more research has addressed the genetics of g than any other human characteristic. Dozens of studies including more than 10 000 twin pairs and hundreds of adoptive families as well as more than 8000 parent–offspring pairs and 25 000 sibling pairs consistently indicate substantial heritability.¹⁶ Heritability estimates vary from 40 to 80% but meta-analyses based on the entire body of data yield estimates of about 50%,^{17,18} with increasing heritability from infancy (20%) to childhood (40%) to adulthood (60%).¹⁹ Most of the genetic variance for g is additive, which facilitates attempts to identify genes responsible for its heritability.²⁰

Since the substantial heritability of g is better documented than for any other biological or behavioral dimension or disorder, quantitative genetic research has moved beyond heritability to ask more refined questions about development, about the interface between nature and nurture, and about multivariate issues.²¹ A finding of great significance for molecular psychiatry and neuroscience has emerged from multivariate genetic research that analyzes the covariance among cognitive tests rather than the variance of each test considered separately.²⁰ As noted earlier, the average phenotypic correlation among diverse cognitive tests is about 0.30. In contrast, multivariate genetic research indicates that genetic correlations among such tests are at least 0.80 on average.²² (A genetic correlation indexes the extent to which genetic effects on one trait correlate with genetic effects on another trait independent of the heritability of the two traits.) The extremely high genetic correlation among diverse cognitive tests means that genes associated with one cognitive ability are highly likely to be associated with all other cognitive abilities. This evidence for ‘genetic g’ means that g is an excellent target for molecular genetic research in the cognitive domain.

It should be noted that genetic g does not necessarily imply that there is a single fundamental brain process that permeates all other brain processing, such as a ‘speedy brain’,⁸ neural plasticity,²³ or the quality and quantity of neurons.²⁴ It has been proposed that g exists in the brain in the sense that diverse brain processes are genetically correlated.²⁵

For example, gray and white matter densities in diverse brain regions are highly heritable, substantially intercorrelated across brain regions, and correlated genetically with *g*.^{26,27}

One of the papers in this issue provides a good example and description of multivariate genetic analysis.³ Rather than analyzing the covariance between cognitive tests, the study investigated the genetic and environmental origins of the covariance between normal variation in behavior problems and *g* in children. For 376 pairs of twins from 6 to 17 years of age, nearly all of the modest phenotypic correlation (−0.19) between behavior problems and *g* could be accounted for by genetic covariation. Similar results were obtained in another study of 4000 pairs of young twins assessed at 2, 3 and 4 years; the large sample made it possible to show that phenotypic and genetic links may be stronger at the extremes of behavior problems and cognitive problems.²⁸

Another multivariate genetic finding of great importance concerns genetic links between common disorders and dimensions of normal variation. This research suggests that common disorders (but not rare disorders) are merely the quantitative extreme of the same genetic and environmental influences that operate throughout the normal distribution. For example, a sibling study of mental retardation found that the average IQ of siblings of severely retarded probands was normal, 103, which implies that severe mental retardation shows no familial links with normal variation in *g*.²⁹ This finding makes sense in relation to the rare single-gene¹² and chromosomal causes³⁰ of severe retardation that are not usually inherited because they occur spontaneously. In contrast, siblings of mildly retarded probands showed a substantially lower mean IQ score of 85.²⁹ In other words, mild mental retardation but not severe retardation shows familial (presumably genetic) links with normal *g* variation. The first twin study of mild mental retardation confirms that mild mental retardation is strongly linked genetically to normal variation in *g*.³¹ This evidence for strong genetic links between disorders and dimensions—evidence that is typical of common disorders such as hyperactivity, depression and alcoholism—provides support for the quantitative trait locus approach to molecular genetics, discussed later.

Identifying genes

There is a lot of life left in the old workhorse of quantitative genetics, especially in investigating developmental, multivariate and environmental issues that go beyond merely estimating heritability. However, the most exciting direction for research on intelligence and cognition is to move beyond genetics to genes, that is, to identify some of the genes responsible for the substantial heritability of *g* and other cognitive abilities and disabilities. In contrast to the slow progress in identifying genes for schizophrenia and manic-depression, greater progress has

been made in the cognitive domain, most notably the well-documented association between apolipoprotein E gene and dementia³² and a solid 6p21 linkage with reading disability that is beginning to be narrowed down in association studies.³³

The quantitative trait locus (QTL) perspective has come to dominate molecular genetic research on complex quantitative traits such as *g* as well as common disorders such as dementia and reading disability. The QTL perspective is the molecular genetic extension of quantitative genetics whereby multiple genes are assumed to be responsible for heritability, implying that genetic variation is distributed quantitatively.³⁴ For this reason, a QTL perspective on *g* naturally leads to molecular genetic research on normal variation, as is also the case for personality research.³⁵ Two papers on molecular genetics in this issue are distinctive in that they focus on normal variation in *g* using large unselected samples.^{1,4} They report positive associations between normal variation in *g* and two candidate genes: Cathepsin D (*CTSD*; 4) and cholinergic muscarinic 2 receptor (*CHRM2*; 1). The effect sizes are small (heritabilities of 3 and 1%, respectively) as expected for QTLs, but are easily detected as significant with the large sample sizes of these studies (767 and 828, respectively). Research on complex traits should be aiming to break the 1% QTL barrier, that is, 80% power to detect QTLs when they account for as little as 1% of the total variance (1% heritability), which requires an unselected sample of about 800 individuals when a single marker is studied ($P = 0.05$, two-tailed; 36).

The *CTSD* paper⁴ is especially interesting in relation to the extensive molecular genetic research on dementia, which will be the source of much more molecular genetic research on *g*. Beginning with individuals at least 50 years old, *g* was assessed during a 15-year period in order to investigate the cognitive decline indicative of dementia. As in other studies, initial *g* scores are correlated negatively with decline across the 15 years, supporting the brain reserve capacity theory of dementia, as explained in the paper. However, *CTSD* is not associated with cognitive decline, which confirms the results of several other studies that found no association between *CTSD* and dementia. The exciting finding is that *CTSD* is associated with *g* at the first test session. Longitudinal quantitative genetic research on *g* indicates that age-to-age stability is largely mediated genetically whereas change is largely environmental in origin.²¹ This suggests that the heritability of dementia defined as decline might be modest in contrast to the heritability of *g*. We do not yet know how heritable dementia is because only a few small twin studies have been reported and their results are mixed.³⁷ What is needed is a multivariate genetic analysis of *g* and dementia in order to investigate the extent of their genetic overlap.

Other reports are beginning to emerge of candidate gene associations with *g*. Most notably, a functional

polymorphism (VAL158MET) in the enzyme catechol O-methyltransferase (*COMT*) has been reported to be associated with g-related cognitive functioning in two studies.^{38,39} An association with g has also been reported for a gene involved in controlling homocystein/folate metabolism.⁴⁰ Because research on dementia will be the immediate source of more molecular genetic research on g as in the *CTSD* study in this issue,⁴ it is worth noting that the apolipoprotein gene, which shows a strong association with dementia, shows no association with g in childhood^{41,42} or in adults.⁴³

Despite the power of the two studies in this issue to detect QTL associations, replication will be crucial because the track record for replicating candidate gene associations is not good.⁴⁴ This is of particular concern with studies using unselected samples because it is tempting to study many measures as well as many candidate genes thus increasing vulnerability to false positives. As a chastening confession to underline the need for replication, both papers cite our report of an association between *IGF2R* and g in two samples,⁴⁵ but our new independent sample as large as the previous two samples combined has not replicated the association.⁴⁶

Other molecular genetic issues relevant to these *CTSD* and *CHRM2* reports are generic issues involved in any attempt to find QTLs for complex traits whether assessed as disorders or dimensions. One such issue is the use of functional polymorphisms. In the *CTSD* study,⁴ the candidate gene polymorphism is functional (C>T, Ala>Val); in the *CHRM2* study,¹ the single nucleotide polymorphism (SNP) is in the 3' untranslated region of the gene. The use of functional polymorphisms involves direct association that greatly increases power because it tests the hypothesis that the polymorphism *is* the QTL rather than relying on the marker being in linkage disequilibrium with the QTL associated with the trait (indirect association). Another advantage of using functional polymorphisms is that when associations are found, the usual house-to-house search for the culprit gene is circumvented, although it is always difficult to identify beyond reasonable doubt the QTL suspect from a line-up of genes in the neighborhood.

Another generic issue is that more systematic approaches to candidate genes are needed because any of the tens of thousands of genes expressed in the brain could be proposed as candidate genes for g.⁴⁷ One early association study of g examined 100 candidate genes (not including *CTSD* or *CHRM2*) but found no more replicated associations than expected by chance, although the design only provided power to detect QTLs of about 2% heritability.⁴⁸ A more systematic strategy is to investigate all polymorphisms in particular gene systems.⁴⁹

Another strategy is to conduct genome-wide scans for association analogous to genome scans for linkage except that many thousands of markers are needed in the case of association. The first genome-wide search for association with g has been reported using 1842

simple sequence repeat (SSR) markers using DNA pooling and groups selected for high g and controls.⁵⁰ Despite a highly conservative replication procedure designed to avoid false positives, two SSRs replicated cleanly in two independent case-control samples but neither SSR association was replicated in a transmission disequilibrium test using parent-offspring trios. Genomic control analyses showed that the failure to replicate using the parent-offspring trios was not due to population stratification. Since SSR markers are unlikely to be functional, they rely on indirect association for which power falls off quickly as a function of the linkage disequilibrium distance between the marker and the QTL.^{51,52} Using indirect association, tens or hundreds of thousands of markers are needed for genome scans in order to exclude QTLs of 1% heritability, although haplotype maps can reduce the required number of markers.^{53,54}

Ultimately what is needed for genome-wide association scans is to genotype every functional polymorphism in the genome. As a step in this direction, we are currently using DNA pooling to conduct a genome-wide g scan of all brain-expressed nonsynonymous SNPs in coding regions that are currently available in public databases with allele frequencies greater than 10% in Caucasian samples.⁵⁵ Polymorphisms in promoters and other gene regulatory coding regions seem even better candidates for QTLs but they are much more difficult to identify and to demonstrate their functionality. Moreover, coding DNA does not have a monopoly on QTLs—noncoding RNA is likely to be a source of QTLs too,⁵⁶ although determining functionality of polymorphisms in noncoding RNA will be even more difficult.

It remains to be seen whether increasing power using large samples and direct association will yield replicable QTLs. DNA pooling will be useful in this context because it costs no more to genotype 1000 individuals than 100 individuals.⁵⁷ Pessimists can reasonably worry about the gloomy prospect that the culprit genes will never be caught because the heritability of g might be caused by many genes with miniscule heritabilities. Some might hope that such research is never successful because of the ethical issues that would be raised if genes for g were found.²¹ Interesting discussions of these issues are available specifically in relation to genes and g⁵⁸ and more generally in relation to behavioral genetic research.⁵⁹

Behavioral genomics

Quantitative genetics assesses the net effect of genes on behavior without knowing anything about which genes are involved. Molecular genetics identifies genes associated with behavior without knowing anything about the mechanisms responsible for the association. As we approach the postgenomic era in which the complete human genome sequence and all functional variations in the genome sequence are identified, the future of behavioral genetics is

functional genomics, that is, understanding how genes affect behavior.⁶⁰

Functional genomics usually refers to the bottom-up agenda of molecular biology such as gene expression profiling and proteomics. However, there are higher levels of analysis for understanding how genes function which need not wait until the bottom-up approach reaches them. At the other end of the continuum is the top-down approach that investigates the function of genes in relation to behavior of the whole organism. For example, the issues about multivariate relationships of heterogeneity and comorbidity, developmental change and continuity, and the interface between genes and environment can be addressed with much greater precision once genes are identified. The term *behavioral genomics* has been proposed to emphasize the value of this top-down level of analysis.⁶¹

Rodent models will be valuable for functional genomic research because of their ability to manipulate both genes and environment and the power they offer for investigating brain processes such as single cell recordings, micro-stimulation, targeted gene mutations, antisense DNA that disrupts gene transcription, and DNA expression. The value of rodent models rests with understanding genetically driven brain processes, not with phenotypic validity. For example, mouse models have made the greatest progress in understanding the psychopharmacogenetics of alcohol-related processes even though mice do not become drunk of their own volition.⁶² In this sense, although it sounds absurd, mouse models of reading disability will be valuable for understanding the brain processes underlying the genetics of reading disability. The ultimate test is whether the same genes affect the same brain processes in mouse and man.

In terms of rodent models of g, clearly there are major differences in brain and mind between the human species and other animals, most notably in the use of language and the highly developed prefrontal cortex in the human species. However, g in man does not depend on the use of language—a strong g factor emerges from a battery of completely nonverbal tests.⁷ Moreover, low-level tasks—for example, information-processing tasks assessed by reaction time—contribute to g.⁶³ Indeed, g can be used as a criterion to identify animal models of individual differences in cognitive processes. If g represents the way in which genetically driven components of the brain work together to solve problems, it would not be unreasonable to hypothesize that g exists in all animals.⁶⁴ Although much less well documented than g in humans, increasing evidence exists for a g factor in mice across diverse tasks of learning, memory and problem solving.⁶⁵ A large-scale integrative program of research called genes-to-cognition is under way that uses mouse models for functional genomic research in the cognitive domain.⁶⁶

One of the papers in this issue serves as an example of the value of rodent models for functional research.²

The research brings together neurotransmitter assays, brain anatomy, a broad battery of behavioral measures, a development approach from infancy to adolescence to adulthood, and pharmacology in an experimental study in which epidermal growth factor (EGF) was administered to neonatal rats. Although a test of learning ability did not appear to be affected by the neonatal treatment, other abnormalities were observed in adults but not in adolescents such as sensorimotor gating, motor activity and social interaction in a pattern reminiscent of schizophrenic symptoms and which were ameliorated by clozapine. This research covers a wide range of functional approaches, but the missing link from a functional genomics perspective is genetics. Although transgenic studies indicate the important role of the EGF gene family on brain structures and monoamine pharmacology, there is as yet no evidence that polymorphisms in genes related to EGF are involved in schizophrenia or other cognitive disabilities or abilities. This program of research showing the importance of EGF is likely to stimulate genetic research using EGF candidate genes.

In our age of increasing specialization, the most exciting prospect for functional genomic research in the postgenomic era is that DNA will integrate research in the life sciences from cells to societies and that bottom-up approaches will meet top-down approaches in the brain. g is an excellent target for such integrative research because an exciting synergy will quickly emerge simply by connecting the dots of knowledge already available, for example, in gene targeting studies of learning and memory in mice, brain imaging studies of cognitive processes in the human species, and extensive quantitative genetic research.

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