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The Genetic Basis of Complex Human Behaviors

Robert Plomin, Michael J. Owen, Peter McGuffin

Quantitative genetic research has built a strong case for the importance of genetic factors in many complex behavioral disorders and dimensions in the domains of psychopathology, personality, and cognitive abilities. Quantitative genetics can also provide an empirical guide and a conceptual framework for the application of molecular genetics. The success of molecular genetics in elucidating the genetic basis of behavioral disorders has largely relied on a reductionistic one gene, one disorder (OGOD) approach in which a single gene is necessary and sufficient to develop a disorder. In contrast, a quantitative trait loci (QTL) approach involves the search for multiple genes, each of which is neither necessary nor sufficient for the development of a trait. The OGOD and QTL approaches have both advantages and disadvantages for identifying genes that affect complex human behaviors.

The received wisdom of the behavioral sciences concerning the importance of "nature" (genetics) and "nurture" (environment) in the origins of behavioral differences among people has changed dramatically during the past few decades. Environmentalism, which attributes all that we are to nurture, peaked in the 1950s. A more balanced view that considers both nature and nurture swept into psychiatry in the 1960s and 1970s. Although this balanced view has been slower to reach some realms of psychology, there are signs that it has arrived. For example, at its centennial meeting in 1992, the American Psychological Association identified genetics as one of the themes that best represent the present and especially the future of psychology (*1*).

Behavioral genetic research began in the 1920s with inbred strain and selection studies of animal behavior and family, twin, and adoption studies of human behavior (*2*). These quantitative genetic designs assess the "bottom line" of transmissible genetic effects on behavior, regardless of the number of genes involved, the complexity of their interactions, or the influence of nongenetic factors. As discussed in the first part of this article, quantitative genetic research has built a strong case for the importance of genetic factors in many complex dimensions and disorders of human behavior.

Although more quantitative genetic research is needed, the future of behavioral genetics lies in harnessing the power of molecular genetics to identify specific genes for complex behaviors. In the second part of this paper, initial successes are described and research strategies are discussed. Although more powerful methods and results are available for the investigation of animal than human behavior, animal work is discussed in accompanying articles in this issue.

R. Plomin is director of the Center for Developmental and Health Genetics, Pennsylvania State University, University Park, PA 16802, USA. M. J. Owen is in the Departments of Psychiatry and Medical Genetics, and P. McGuffin is chair of the Department of Psychiatry, University of Wales College of Medicine, Cardiff, Wales CF4 4XN, UK.

Quantitative Genetics

The change from antipathy to acceptance of genetic factors in the behavioral sciences has occurred so rapidly and thoroughly, especially in psychiatry, that a reminder is warranted about how environmentalistic the behavioral sciences were, even in the 1960s. For example, the major explanation for schizophrenia was abnormal parenting.

Adoption studies were pivotal in leading psychiatrists to consider nature as well as nurture. Schizophrenia was known to run in families, with a risk of 13% for offspring of schizophrenic parents, 13 times the population rate of about 1% (*3*). Adoption experiments allow a determination of whether schizophrenia runs in families for reasons of nature or of nurture. In a classic study, Heston (*4*) examined the offspring of schizophrenic mothers who had been adopted at birth and compared their rate of schizophrenia to a control group of adopted offspring. Of the 47 adopted-away offspring of schizophrenic mothers, 5 were diagnosed as schizophrenic, as compared to none of the 50 control adoptees. Indeed, the risk of schizophrenia for the adopted-away offspring of schizophrenic mothers is the same as the risk for individuals reared by a schizophrenic parent.

These findings implicating substantial genetic influence in schizophrenia have been replicated and extended in other adoption studies, and they confirm the results of twin studies that show greater concordance for identical twins (about 45%) than fraternal twins (about 15%) (*3*). This twin method is a natural experiment in which the phenotypic resemblance for pairs of genetically identical individuals [identical, monozygotic (MZ) twins] is compared to the resemblance for pairs of individuals whose coefficient of genetic relationship is only 0.50 [fraternal, dizygotic (DZ) twins].

The convergence of evidence from family, twin, and adoption designs—each with distinct assumptions—provides the most convincing argument for the importance of genetic factors in behavioral traits.

Behavioral disorders. Evidence for genetic influence has been found for nearly all behavioral disorders that have been investigated (*5*). Figure 1 summarizes the results

of twin studies for some of the best studied disorders. Genetic influence is substantial for schizophrenia, Alzheimer's disease, autism, major affective disorder, and reading disability (6). Not all behavioral disorders are influenced to the same degree by genetic factors. For example, diagnosed alcoholism has been assumed to be highly heritable, but new twin studies show only modest genetic influence for males and negligible genetic influence for females. Interestingly, the amount of alcohol consumed shows greater genetic influence than diagnosed alcoholism (7). In contrast to diagnosed alcoholism, autism, which until the 1970s was assumed to be environmental in origin, appears to be among the most heritable psychiatric disorders.

In addition to the examples in Fig. 1, the following disorders have also shown some evidence of genetic influence: specific language disorder, panic disorder, eating disorders, antisocial personality disorder, and Tourette's syndrome. Some behavioral disorders such as mild mental retardation have not yet been analyzed by genetic research.

Figure 2 summarizes results from twin studies for some of the best studied common medical disorders. Like behavioral disorders, some medical disorders show substantial genetic influence—rheumatoid arthritis, peptic ulcers, and idiopathic epilepsy. Others show more modest genetic influence, such as hypertension and ischemic heart disease. Several common medical disorders show negligible genetic influence. For example, twin studies suggest negligible heritability for breast cancer as a whole in the general population, even though a rare early onset familial type is linked to markers on chromosome 17 (8). By comparing Figs. 1 and 2, it appears that behavioral disorders on average show greater genetic influence than common medical disorders.

Behavioral dimensions. Data on behavioral variability within the normal range also indicate widespread genetic influence. Figure 3 summarizes results of twin studies for personality (neuroticism and extraversion), vocational interests, scholastic achievement, and cognitive abilities (memory, spatial reasoning, processing speed, verbal reasoning, and general intelligence). For quantitative dimensions, the size of the genetic effect can be estimated roughly by doubling the difference between MZ and DZ correlations. This estimate is called heritability, which is a statistic that describes the proportion of phenotypic variance in a population that can be attributed to genetic influences. Heritabilities range from about 40 to 50% for personality, vocational interests, scholastic achievement, and general intelligence. For specific cognitive abilities, heritabilities are also in this range for spatial reasoning and verbal reasoning but lower for memory and processing speed. Recent research also suggests genetic influence for other cognitive measures such as information processing, electroencephalographic evoked potentials, and cerebral glucose metabolism (9). Examples of recently studied noncognitive behaviors that show genetic influence are self-esteem (10), social attitudes (11), and sexual orientation (12). Little is known about genetic effects for perception and learning and for many health-related behaviors (for example, responses to stress, exercise, and diet).

Beyond heritability. Quantitative genetic research has gone beyond merely demonstrating the importance of genetics for complex human behaviors. Three new techniques are especially useful for this advancement, as can be seen most clearly in research on cognitive abilities, the most studied domain of behavior. First, developmental genetic analysis monitors change in genetic effects during development. For cognitive ability, genetic factors become increasingly important for general intelligence throughout the lifespan, reaching heritabilities as high as 80% later in life (13). This is the highest heritability reported for any behavioral dimension. In addition, with longitudinal genetic designs, it is possible to investigate the etiology of age-to-age change—that is, to what extent do genetic effects at one age overlap with genetic effects at another age? For general cognitive ability, longitudinal genetic analyses during childhood suggest that genetic effects do not completely overlap from age to age, indicating changes in genetic effects, especially at the early school years (14).

A second advance is multivariate genetic analysis, which assesses genetic contributions to covariance among traits rather than to the variance of each trait considered separately. Multivariate analyses of specific cognitive abilities suggest that genetic influences on all specific cognitive abilities overlap to a surprising degree, although some genetic effects are unique to each ability (15). This finding implies that genes associated with one cognitive ability are likely to be associated with other cognitive abilities as well. Multivariate analyses also indicate that genetic effects on scholastic achievement overlap completely with genetic effects on general cognitive ability (16). Such techniques can also be used to address the fundamental issues of heterogeneity and comorbidity for psychiatric disorders, contributing to a nosology at the level

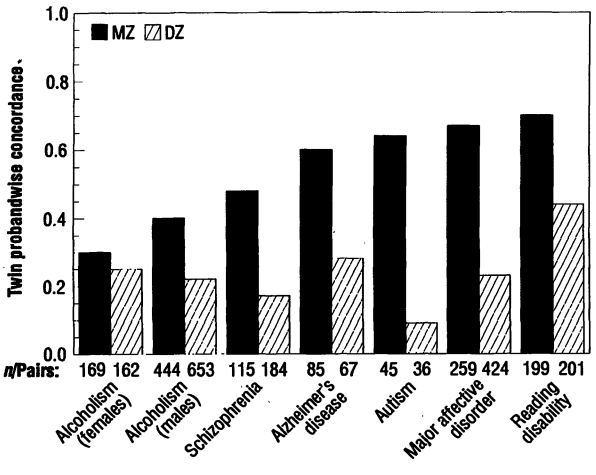

Fig. 1 (left). Identical twin [monozygotic (MZ)] and fraternal twin [dizygotic (DZ)] probandwise concordances for behavioral disorders. Average weighted concordances were derived from the references in (*60*).

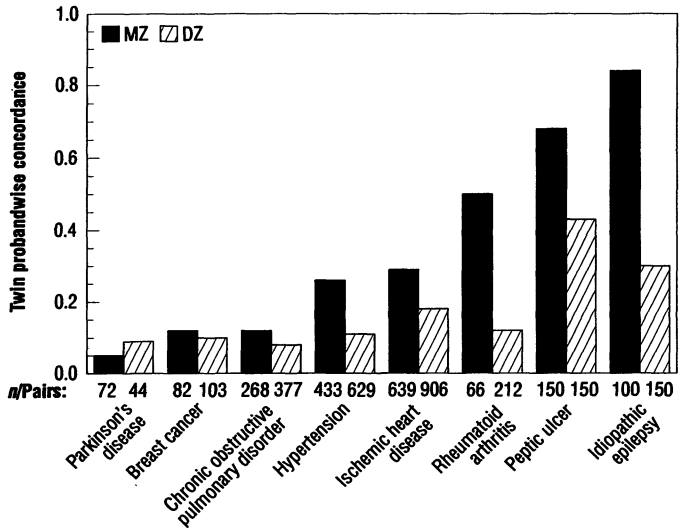

Fig. 2 (right). MZ and DZ probandwise concordances for common medical disorders. Average weighted concordances were derived from the references in (*61*).

of genetic effects rather than at the level of symptoms. Longitudinal and multivariate approaches have been facilitated by advances in analysis that test the fit between a model and observed data (*17*).

The third example, called extremes analysis, addresses genetic links between normal and abnormal behavior. If, as seems likely, multiple genes are responsible for genetic influences on behavioral dimensions and disorders, a continuum of genetic risk is likely to extend from normal to abnormal behavior. For example, is major depressive disorder merely the extreme of a continuous dimension of genetic and environmental variability? A quantitative genetic technique developed during the past decade investigates the extent to which a disorder is the etiological extreme of a continuous dimension (*18*). Preliminary research with this approach suggests that some common behavioral disorders such as depressive symptoms (*19*), phobias (*20*), and reading disability (*21*) represent the genetic extremes of continuous dimensions.

Nurture as well as nature. Another way in which genetic research has gone beyond merely documenting genetic influence is to focus on the implications of genetic research for understanding environmental influences. Genetics research provides the best available evidence for the importance of nonheritable factors. Usually genetic factors do not account for more than about half of the variance for behavioral disorders and dimensions. Most of the disorders and dimensions summarized in Figs. 1 and 3 show as much nonheritable as heritable influence. The current enthusiasm for genetics should not obscure the important contribution of nonheritable factors, even though these are more difficult to investigate. For environmental transmission, there is nothing comparable to the laws of hereditary transmission or to the gene as a basic unit of transmission. It should be noted that the "environmental" in quantitative genetics denotes all nonheritable factors, including nontransmissible stochastic DNA events such as somatic mutation, imprinting, and unstable DNA sequences (*22*).

Two specific discoveries from genetic research are important for understanding environmental influences. First, the way in which the environment influences behavioral development contradicts socialization theories from Freud onward. For example, the fact that psychopathology runs in families has reasonably, but wrongly, been interpreted to indicate that psychopathology is under environmental control. Research shows that genetics generally accounts for this familial resemblance. Environmental influences on most behavioral disorders and dimensions serve to make children growing up in the same family different, not similar (*23*). This effect, called nonshared environment, leads to the question of how children in the same family experience such different environments. For example, what are the nonshared experiences that make identical twins growing up in the same family so often discordant for schizophrenia?

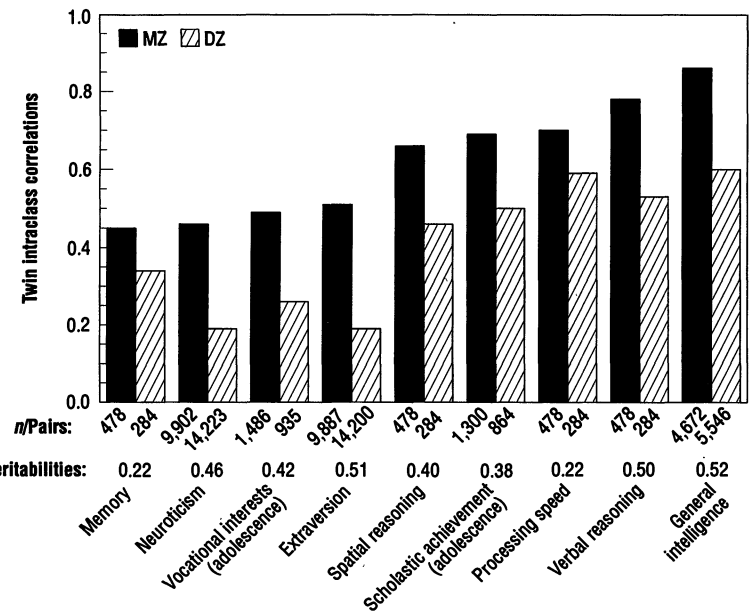

Fig. 3. MZ and DZ twin intraclass correlations for personality (neuroticism and extraversion), vocational interests in adolescence, scholastic achievement in adolescence (combined across similar results for English usage, mathematics, social studies, and natural science), specific cognitive abilities in adolescence (memory, spatial reasoning, processing speed, verbal reasoning), and general intelligence. Average weighted correlations were derived from the references in (*62*).

The second genetic discovery about the environment concerns what has been called the nature of nurture (*24*). Many widely used measures of the environment show genetic influence in dozens of twin and adoption studies. Research with diverse twin and adoption experimental designs has found genetic influence on parenting, childhood accidents, television viewing, classroom environments, peer groups, social support, work environments, life events, divorce, exposure to drugs, education, and socioeconomic status (*25*). Although these results might seem paradoxical, what they mean is that ostensible measures of the environment appear to assess genetically influenced characteristics of individuals. To some extent, individuals create their own experiences for genetic reasons (*26*). In addition, genetic factors contribute to the prediction of developmental outcomes from environmental measures (*25*). For example, genetics is part of the reason why parenting behavior predicts children's cognitive development and why negative life events predict depression.

Quantitative genetics and molecular genetics. Quantitative genetic research is needed to inform molecular genetic research. Most fundamentally, quantitative genetic research can steer molecular genetic research toward the most heritable syndromes and combinations of symptoms. Genes are less likely to be identified for complex behaviors that show little genetic influence in the population unless some aspect of the trait can be found that is more highly heritable, as in the case of breast cancer. Although genetic influence has been detected for many behavioral disorders and dimensions (Figs. 1 and 3), little is known about the most heritable aspects within these domains.

Even more useful is quantitative genetic research that goes beyond heritability to take advantage of new techniques mentioned above. For example, developmental genetic research shows that genetic influence increasingly affects cognitive abilities throughout the life-span. This suggests that molecular genetic research on cognitive abilities is most likely to be successful later in life when phenotype better represents genotype. Multivariate genetic research indicates that genes associated with one cognitive ability are likely to be associated with other cognitive abilities. The clue here is that molecular genetic research will profit from focusing on what cognitive abilities have in common. Quantitative genetic research suggests that common disorders represent the quantitative extremes of continuous dimensions. This suggests that genes associated with disorders can be found by investigating continuous dimensions and

vice versa. Finally, quantitative genetic research suggests that nongenetic factors generally account for as much variance as genetic factors, that behavior-relevant environmental factors generally operate in a nonshared manner to make children growing up in the same family different, not similar, and that genetic factors play a role in individuals actively creating their own experience. Molecular genetic research will benefit from incorporating environmental measures, especially measures of nonshared environment.

Molecular Genetics

Quantitative genetic research leaves little room for doubt about the importance of genetic influence in behavior. The next step is to begin to identify some of these genes. This is obviously a more difficult step, especially in the case of complex traits, and some of the initial steps in this direction have faltered. However, the difficulty of identifying specific genes underlying complex traits should not obscure the evidence for the importance of genetic influence.

Many rare disorders such as Huntington's disease show simple Mendelian patterns of inheritance for which defects in a single gene are the necessary and sufficient cause of the disorder. Linkage analysis and the rapidly expanding map of the human genome guarantee that the underlying genes will be mapped and eventually cloned, as has already happened for scores of single-gene disorders. The new frontier for molecular genetics lies with common and complex dimensions, disorders, and diseases. The challenge is to use molecular genetic techniques to identify genes involved in such complex systems influenced by multiple genes as well as multiple nongenetic factors, especially when any single gene is neither necessary nor sufficient. Because this challenge is the same for complex behaviors as for common medical disorders, their futures will be intertwined.

One gene, one disorder? Complex traits that show no simple Mendelian pattern of inheritance are unlikely to yield simple genetic answers. For this reason, it has often been assumed that complex disorders consist of a concatenation of several disorders, each caused by a single gene, or at least a gene of major effect that largely accounts for genetic influence. Indeed, one definition of the word "complex" is a composite of distinguishable constituents. This could be called the one gene, one disorder (OGOD) hypothesis. The OGOD hypothesis is more than a simple single-gene hypothesis. It does not look for a single gene for complex traits, but rather assumes that complex traits comprise several subtraits each influenced by a single gene. Even if single genes corresponding to subtypes of a disorder cannot be found throughout the population, the hope is that by analyzing linkage in large pedigrees, it may be possible to find a single gene responsible for a family's particular version of the disorder.

The OGOD strategy has already been successful for some complex behavioral disorders, especially severe mental retardation. A classic example is the distinct type of mental retardation, phenylketonuria (PKU), caused by recessive mutations in the phenylalanine hydroxylase (PAH) gene on chromosome 12 (*27*). Although its incidence is low (fewer than 1 in 10,000 births), PKU accounted for about 1% of institutionalized mentally retarded individuals before diets low in phenylalanine were implemented.

Recently, another distinct type of mental retardation was discovered, fragile X, which is caused by an unstable expansion of a CGG repeat in the *FMR-1* gene on the X chromosome (*28*). Its incidence is 1 in 1250 males and 1 in 2500 females, making it the single most important cause of mental retardation after Down syndrome. Another fragile site on the X chromosome has been linked to a less common form of mental retardation (*29*). In addition to these defects in single genes necessary and sufficient to develop distinct forms of mental retardation, more than 100 other rare single-gene disorders include mental retardation among their symptoms (*30*).

Another example of the success of the OGOD approach for behavior involves a common syndrome, dementia, which is marked by progressive memory loss and confusion. Dementia of the Alzheimer's disease (AD) type includes a rare, familial dementia that appears in middle age, shows a dominant Mendelian pattern of inheritance, but which accounts for fewer than 1% of AD cases. Mutations in the amyloid precursor protein gene on chromosome 21 segregate with the disease in some families with autosomal dominant AD (*31*). The majority of such cases are linked to chromosome 14 (*32*), although the gene is not yet identified.

An example of a successful OGOD approach outside the cognitive realm of retardation and dementia involves a particular type of violence. A point mutation in the monoamine oxidase A (MAOA) gene, which disrupts MAOA activity, has been linked to impulsive violence in one Dutch family (*33*).

The well-known false positive linkage results for bipolar affective disorder and schizophrenia (*34*) and the more recent failure to replicate reported X-linkage for bipolar affective disorder (*35*) were caused by procedural and interpretative problems rather than by faults with the analytic technology itself. If a single gene is responsible for genetic influence on a trait, linkage can detect it. Although the entire genome has not yet been screened for linkage with these disorders, it is possible that there are no genes of major effect to be found despite clear twin and adoption evidence for genetic influence. Conventional linkage analysis of extended pedigrees is unlikely to have sufficient power to detect a gene unless the gene accounts for most of the genetic variance. Newer linkage methods such as "affected-relative-pair" linkage designs are more robust than traditional pedigree studies because they do not depend on assumptions about mode of inheritance (*36*). These newer methods may be able to detect genes of somewhat smaller effect size if large samples (for example, several hundred sibling pairs) are used. They can also incorporate quantitative measures (*37*). Nonetheless, linkages found with these methods imply that a single gene explains most of the genetic effects on the trait, especially if sample sizes are not large.

Two behavioral examples involve linkages reported for sexual orientation and reading disability. For sexual orientation, linkage has been reported with markers on the X chromosome in a study of 40 homosexual brothers selected for pedigrees consistent with maternal transmission (*38*). Reading disability has been linked to markers on chromosome 15 and possibly to chromosome 6 in a family pedigree linkage analysis (*39*) as well as sib-pair linkage analyses of sibling pairs in these same families (*40*), although later reports show less evidence for chromosome 15 linkage.

Quantitative trait loci. Quantitative geneticists assume that genetic influences on complex, common behavioral disorders are the result of multiple genes of varying effect size. These multiple-gene effects can contribute additively and interchangeably, like risk factors, to vulnerability to a disorder. In this case, the word "complex" means "complicated" in the sense of multigenic and multifactorial rather than a composite of OGOD constituents. Any single gene in a multigene system is neither necessary nor sufficient to cause a disorder. In other words, genetic effects involve probabilistic propensities rather than predetermined programming.

Genes that contribute to genetic variance in quantitative traits are called quantitative trait loci (QTL) (*41*). One implication of a multigene system is that genotypes are distributed quantitatively (dimensionally) even when traits are assessed phenotypically by dichotomous diagnoses. For this reason, the term QTL is apropos for the liability to diagnosed disorders, not just quantitative traits. The term QTL re-

places the word "polygenic," which literally means "multiple genes" but has come to connote many genes of such infinitesimal effect size that they are unidentifiable. QTL denote multiple genes of varying effect size. The hope is to be able to detect QTL of modest effect size. "Oligogenic" is another word that has been used as a substitute for polygenic, but it presupposes that only a few ("oligo") genes are involved.

QTL examples have been detected by allelic association, often called linkage disequilibrium. Allelic association refers to a correlation in the population between a phenotype and a particular allele, usually assessed as an allelic or genotypic frequency difference between cases and controls. Allelic association has often been used to pin down a single-gene effect, but it also provides the statistical power to detect small QTL effects, as discussed below. Allelic associations involving small genetic effects in multiple-gene systems could be called QTL associations. The best QTL example for a common medical disorder is provided by the associations between apolipoprotein genes and risk for cardiovascular disease, accounting for as much as a quarter of the genetic variance (*42*).

Two recent QTL associations from medical research are especially noteworthy in relation to complex behaviors. A deletion polymorphism in the angiotensin-converting enzyme (ACE) gene is associated with cardiovascular disease independent of effects on lipid metabolism (*43*). The frequency of individuals homozygous for the *ACE* deletion was 32% for patients with myocardial infarction and 27% for controls. This slightly increased relative risk of 1.3, which accounts for less than 1% of the liability for the disorder, is significant statistically because the sample was extremely large (610 cases and 733 controls). The second example involves longevity, which is only modestly heritable. Significant associations with longevity have recently been reported for both the *ACE* deletion and allele 4 of the apolipoprotein E (Apo-E) gene (*44*). Allelic frequencies for 325 centenarians differed from 20- to 70-year-old controls for the *ACE* deletion (62% as compared with 53%) and for *Apo-E4* (5% as compared with 11%). Again, these modest allelic frequency differences are statistically significant because the sample size was so large. In addition, *Apo-E2* was associated with increased longevity.

The best QTL example for a behavioral disorder is the recently discovered association between late onset AD and *Apo-E4* (*45*). Unlike the rare, early onset, autosomal dominant form of dementia discussed above, the prevalence of AD increases steeply with age from less than 1% at age 65 years to 15% in the ninth decade (*46*). The frequency of the *Apo-E4* allele is about 0.40 in individuals with AD as compared with 0.15 in control populations. The odds ratio, or approximate relative risk, is 6.4 for individuals with one or two *Apo-E4* alleles (*47*). The *Apo-E4* allele is neither necessary nor sufficient to develop the disorder: Many individuals with AD do not possess an *Apo-E4* allele, and many individuals with an *Apo-E4* allele do not develop AD. It has been estimated that *Apo-E4* contributes approximately 17% to the population variance in liability to develop the disorder (*47*). Although this is a large effect for a QTL, it is much too small to qualify as a single-gene effect. A linkage study of 32 pedigrees found only relatively modest evidence of linkage for the *Apo-E4* region of chromosome 19 (*48*). A QTL of this magnitude may be near the lower limit of detection by linkage analysis with realistic sample sizes, as discussed below.

We predict that QTL associations will soon be found for other complex human behaviors. For example, a weak association has been suggested for paranoid schizophrenia in seven of nine studies with the *A9* allele of human leukocyte antigen (HLA), yielding a combined relative risk of 1.6, which accounts for about 1% of the liability to the disorder (*49*). Severe alcoholism (*50*) and other forms of drug abuse (*51*) have been reported in several studies to be associated with the *A1* allele of dopamine receptor D_2, but the association remains controversial (*52*). A QTL association study of general cognitive ability has found two suggestive but as yet unreplicated associations for DNA markers in or near neurally relevant genes (*53*). Thyroid receptor–β gene has been associated with symptoms of attention deficit–hyperactivity disorder (*54*). However, because this allelic association was found in individuals hospitalized for resistance to thyroid hormone, it is possible that symptoms of hyperactivity were due to the disease itself.

As illustrated in Fig. 4 for mental retardation, both the OGOD and QTL approaches are likely to contribute to the elucidation of the genetic basis of complex behaviors. Although we have emphasized the distinction between the OGOD and QTL approaches, we recognize that in fact there is a continuum of varying effect sizes. The relative contributions of single-gene effects at one end of the continuum and undetectably small effects at the other end are unknown. If genetic effects on complex behaviors are single-gene effects, traditional linkage approaches will detect them. If effects are infinitesimal (for example, accounting for less than 0.1% of the variance), they will never be detected. In the middle of the continuum, QTL of large effect size (for example, genes accounting for 10% of the variance) might be detected by the newer linkage strategies. In the example of *Apo-E* and AD, linkage analysis suggested the possibility of a gene in this

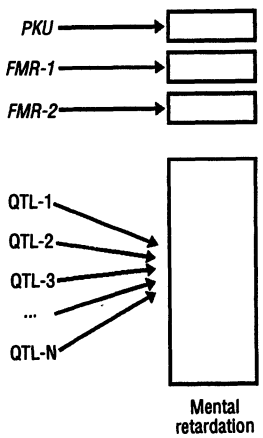

Fig. 4. Complex behaviors such as mental retardation are likely to involve single genes, each responsible for a distinct subtype of the disorder, as well as QTL that contribute probabilistically and interchangeably to genetic risk.

Table 1. Reported linkages and associations with complex behaviors.

Behavior	Gene, chromosome	Reference
Mental retardation		
Phenylketonuria	*PAH*, 12	(*27*)
Fragile X-1	*FMR-1*, X	(*28*)
Fragile X-E	*FRAX-E*, X	(*29*)
Alzheimer's disease		
Early onset, dominant	*APP*, 21	(*31*)
	?, 14	(*32*)
Late onset	*Apo-E*, 19	(*43*)
Violence	*MAOA*, X	(*33*)
Hyperactivity	Thyroid receptor–β, 3	(*54*)
Paranoid schizophrenia	*HLA-A*, 6	(*49*)
Alcoholism, drug abuse	Dopamine receptor–D_2, 11	(*50, 51*)
Sexual orientation	?, X	(*38*)
Reading disability	?, 15	(*39, 40*)

region of chromosome 19, and association analysis identified the gene. QTL of small effect size (for example, genes accounting for 1% of the variance) cannot be detected by linkage. Allelic association can detect such QTL, as in the example of *ACE* and myocardial infarction.

Of the few loci that have been implicated to date for complex behaviors (Table 1), most are genes of major effect rather than QTL, especially the indisputable linkages for PKU, fragile X, and early onset, dominant dementia. This may be the result of reliance on linkage approaches that are only able to detect genes of major effect. The replicated association between *Apo-E4* and AD makes it likely that more systematic association studies will be undertaken to identify QTL with modest effects on complex behaviors.

Allelic association. The advantage of linkage approaches is that they can identify genes without a priori knowledge of pathological processes in a systematic search of the genome by using a few hundred highly polymorphic DNA markers. Such systematic screens of the genome can also exclude the presence of genes of major effect. However, they cannot exclude small QTL effects, at least when realistic sample sizes are used. We predict that failure to find major gene effects by exclusion mapping for complex behaviors will by default provide the best evidence for QTL. The disadvantage of traditional linkage designs is that they are only able to detect single genes or genes largely responsible for the trait.

Although linkage remains the strategy of choice for detecting single-gene effects and for identifying the largest QTL effects, other strategies are needed to detect QTL of smaller effect size. Most likely, new techniques will soon be developed to reach this goal. For the present, allelic association represents an increasingly used strategy that is complementary to linkage (*55*). Allelic association can provide the statistical power needed to detect QTL of small effect size. As in the examples of allelic associations between myocardial infarction and the *ACE* deletion polymorphism and between longevity and *ACE* and *Apo-E*, statistical power can be increased to detect small QTL associations by increasing sample sizes of relatively easy-to-obtain unrelated subjects. Such small QTL effects could not be detected by linkage analysis with realistic sample sizes.

As noted above, allelic association refers to a correlation between a phenotype and a particular allele in the population. Loose linkage between two loci does not result in allelic associations in the population because alleles on the same chromosome at all but the tightest linked loci are separated by recombination with sufficient frequency that both sets of alleles quickly return to linkage equilibrium in the population. When allelic association depends on linkage disequilibrium between a DNA marker and the trait locus, the marker must be very close to the trait locus and both must have low rates of mutation. For example, when the marker and trait locus are separated by about one million base pairs (that is, a recombination fraction of 0.01), an allelic association would return halfway to equilibrium in about 70 generations or about 2000 years (*56*). For this reason, allelic association research on complex traits can use markers in or near relevant genes, because the markers are likely to be in linkage disequilibrium with any functional polymorphism in the gene.

Linkage disequilibrium is not the only cause of allelic association between a marker and a trait. Allelic association can also occur because the marker itself codes for a functional polymorphism that directly affects the phenotype (pleiotropy). Use of such functional polymorphisms greatly enhances the power of the allelic association approach to detect QTL (*57*). It is noteworthy that both the *Apo-E4* and *ACE* deletion markers show direct physiological effects. The new generation of complementary DNA markers and techniques to detect point mutations in coding sequences are rapidly producing markers of this type.

Another distinction between linkage and allelic association involves the issue of dimensions and disorders. As mentioned earlier, complex behaviors in multigene systems are likely to be distributed as continuous quantitative dimensions rather than as qualitative dichotomies. Quantitative dimensions cannot be easily analyzed by linkage, which is based on cosegregation between a DNA marker and a disorder, although a newly developed sib-pair linkage technique for use with quantitative measures employing interval mapping is promising (*37*). In contrast, allelic association is as easily applied to quantitative dimensions as to qualitative disorders.

Limitations of allelic association analysis include ethnic stratification and chance positive results when many markers are examined. The possibility that an allelic association might be the result of ethnic differences can be investigated by using within-family controls (*58*). False positives can best be addressed by replication (*59*). The major limitation to the use of allelic association analysis is that a systematic search of the genome would require thousands of DNA markers separated by about 500 kb or less and would detect only QTL with low mutation rates.

Until such massive genotyping is feasible, allelic association will be limited to screening functional polymorphisms or DNA markers in or near possible candidate genes. For complex behaviors, the problem is that few candidate genes are known that are as specific as the apolipoprotein genes associated with cardiovascular disease. Nonetheless, many genes expressed in the brain are likely to make very small contributions to the genetic variance for complex behaviors, which can be detected with large samples. A single very large representative sample could be used to screen functional polymorphisms for a multitude of common behavioral as well as medical dimensions and disorders. Inclusion of sib pairs would permit sib-pair linkage analyses as well as provide within-family control groups for allelic association analyses. Such a sample could serve as a cumulative and integrative resource for QTL allelic association research.

The goal of the genome project is to sequence the entire human genome. However, there is no single human genome. We need to determine the variability of genes between individuals and then to determine how this variation contributes to phenotypic differences between individuals. For complex traits (including behavior), this will be facilitated by a merger between quantitative genetics and molecular genetics.

Conclusions

Most of what is currently known about the genetics of complex human behavior comes from quantitative genetic research. Twin and adoption studies have documented ubiquitous genetic influence for most reliably measured behavioral dimensions and disorders. More quantitative genetic research is now needed that goes beyond merely documenting the presence of genetic influence. This will guide molecular genetic research by identifying the most heritable domains of behavior and the most heritable dimensions and disorders within domains. New quantitative genetic techniques can also track the developmental course of genetic contributions to behavior, identify genetic heterogeneity, and explore genetic links between the normal and abnormal. The same quantitative genetic data that document significant and substantial genetic influence for complex behavior also provide the best available evidence for the importance of nongenetic factors. Possible environmental factors need to be investigated in the context of genetically sensitive designs to follow up on the far-reaching findings of nonshared environment and genetic influences on experience and to explore the developmental processes of genotype-environment correlation and interaction by which genotypes become phenotypes. This research will in turn facilitate molec-

ular genetic attempts to identify specific genes that contribute to genetic variance in complex behaviors. The confluence of quantitative genetics and molecular genetics will be synergistic for the elucidation of complex human behaviors.

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