

Developmental Psychopathology and Wellness

Genetic and Environmental Influences

EDITED BY

James J. Hudziak, M.D.

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PREFACE

In early March 2007 the American Psychopathological Association (APPA) convened its annual conference with the theme of genetic and environmental influences on developmental psychopathology and wellness. The goal of the conference was to present and discuss the remarkable recent advances made in identifying genetic and environmental influences on the development of emotional-behavioral disorders of children and adolescents. The long-term goal of this work is to advance our understanding of the causes of child psychopathology, with an aim toward improving the way we conceptualize and treat child psychiatric illness. This book is a by-product of that meeting. Each of the scientists who participated in the meeting kindly contributed an up-to-date chapter of their important work. This effort is truly international. Authors in this edition hail from a wide variety of places from around the globe, including England, Australia, the Netherlands, and the United States. I am grateful to each of them for their friendship, excellence, and esprit de corps in ensuring that this book could be completed in such rapid fashion. One of the joys of academic life is to meet and work with wonderful people, and each of the scholars who participated in this process is such a person. To each of you, I publicly state my gratitude. It is my contention that this book is written in such a way that it will be useful to families, clinicians, research scientists, and anyone else who has wondered why some children are always well, why some children sometimes suffer and recover, and why others remain worried or sad throughout their lives.

The book contains 13 chapters divided into four parts: Part 1: Basic Principles of Developmental Psychopathology; Part 2: General Concepts of Gene-Environment Interaction on Child Development; Part 3: Disorder-Based Examples of the Study of Gene-Environment Interaction; and Part 4: The Future of the Study of Developmental Psychopathology in Genetics and Clinical Settings.

PART 1: BASIC PRINCIPLES OF DEVELOPMENTAL PSYCHOPATHOLOGY

Part 1 provides the uninitiated and cognoscenti of developmental psychopathology with a primer and an update on the development of the field and how it has been influenced by advances in genomic medicine. Readers will be treated to chapters by the founders of this field. Sir Michael Rutter contributes a brilliant overview of the history of this young field (with its beginnings in the early 1970s) and more importantly provides readers with a road map for the future of the study of gene–environment interaction by defining the developmental perspective. He finishes by outlining the work ahead. Professor Thomas Achenbach coined the phrase “developmental psychopathology” in 1974 in his book of that same name. In the second chapter, he builds on Rutter’s contribution to this volume by detailing the necessity of identifying the contributions of age, gender, informant, and cultural sources of variance on developmental perspective. His chapter is especially focused on the importance of culture in understanding the genetic and environmental influences on children’s and families’ problems. In addition to identifying the problem of how to measure these sources of influence, he has also provided us with a solution. The final chapter in this section is by Professor Ezra Susser and Dana March, who extend and expand on Rutter and Achenbach’s lessons by reminding us all of the importance of social context when considering the measurement of one’s experience (good or bad). Susser and March elegantly point out that one’s experience matters and that the social context in which that experience occurs can vary widely and lead to different outcomes. The net lessons gleaned from these three outstanding chapters will be to introduce families, clinicians, and scientists to or expand their awareness of the importance of the developmental perspective as providing the basis to understand all complex medical illnesses, of which child psychopathology is only one example.

PART 2: GENERAL CONCEPTS OF GENE–ENVIRONMENT INTERACTION ON CHILD DEVELOPMENT

Part 2 includes three chapters presenting the important concepts of personality and temperament, cognition, and sex. Dr. David Rettew provides an overview of the relations between temperament and developmental psychopathology, including findings from genetics and neurobiology. He argues that the continued study of temperamental traits and their close association

to child emotional reactivity and control likely will lead to an understanding of the mechanisms of these relations in a developmentally sensitive perspective. Dr. Margaret Wright, from Professor Nick Martins's group, and colleagues advance the discussion from temperament to personality and cognition. They provide an expert overview of the field and present findings from their molecular genetic investigations on adolescent cognition, temperament, and brain function. Professor Andrian Angold provides a scholarly and important contribution explaining that sex should not be considered as a separate categorical construct, but rather as a developmental process itself. Understanding such a point, he argues, will illuminate sex differences in psychopathology.

PART 3: DISORDER-BASED EXAMPLES OF THE STUDY OF GENE-ENVIRONMENT INTERACTION

Part 3 includes five chapters, beginning with Dr. Joan Kaufman's seminal work on the genetic and environmental modifiers of risk and resilience in maltreated children. Kaufman elegantly describes maltreatment and its relation to other forms of environmental risk, genetic mediation, and reactivity in the presence of maltreatment. She concludes with a terribly important lesson for all of us who care about children's problems: "the negative effects associated with early stress are not inevitable and need not be permanent." As will be evidenced throughout this section, we no longer think of emotional-behavioral illness and wellness as exclusively caused by genetic or environmental factors, but rather their interaction over time. Kaufman's lessons are then extended to the study of anxious depression, attention-deficit/hyperactivity disorder (ADHD), autism and pervasive developmental disorders, and antisocial personality disorders. It is important to our readers to know these lessons have been applied to almost every child psychiatric condition; however, it is simply beyond the scope of this book to address them all. In her chapter on anxious depression, Professor Boomsma and colleagues provide a picture of the genetic architecture of childhood worry from ages 3 to 12. They present data from an extraordinary twin sample of 30,000 pairs that have been followed since birth. Here we learn how genetic and environmental influences vary by the age (and, in some instances, gender) of a child—findings that perhaps give us a clue on how to design interventions for children who worry. Dr. Angela Reiersen (from Professor Richard Todd's group) and colleagues, also using a twin sample, discuss the importance of considering genotypes, environment (in this case, maternal substance use behavior), and co-occurrence of other disorders in a chapter that explores preferential risks (both genetic and environmental) for ADHD and a sub-

type of ADHD in which children also meet the criteria for an autism spectrum disorder (ASD). The discussion of the genetic epidemiology of ASD is elaborated by Drs. John Constantino and Richard Todd, who detail the possibility that ASD is best conceptualized as existing on a severity continuum in which multiple genes of small effect contribute aspects of the overall syndrome. An individual with a few of these genes may have only mild symptoms or in fact be at an advantage. Further, these authors hypothesize, as the genes of risk accumulate, so does the expression of the syndrome. Here we learn that therapeutic interventions that have been unsuccessful in severely affected persons may be useful in less affected individuals. Lastly, Professor Frank Verhulst presents results from a 14-year longitudinal study on the risk for developing antisocial behavior in adulthood. In this chapter he details the advantages of the developmental perspective by revealing that only some of the findings generated on antisocial behavior in studies that ignore the developmental approach are supported in a longitudinal prospective study. Pathways into and out of antisocial personality are identified and hold important clues for the clinician.

PART 4: THE FUTURE OF THE STUDY OF DEVELOPMENTAL PSYCHOPATHOLOGY IN GENETICS AND CLINICAL SETTINGS

For much of the last decade of my career I have been asked two critical questions about child psychiatric genetics: Where can I learn about this stuff (child psychiatric genetics)? and Does it really matter if I can't use it in the clinic? Part 4 of the present volume is a first pass at providing an answer to both questions. Professor Stephen Faraone, arguably the preeminent molecular geneticist in child psychopathology today, gives us the answer to the first question. He has provided us with an excellent primer on the application of statistical and molecular genetic approaches to developmental psychopathology. In addition, he provides some provocative strategies for learning from our own mistakes and those of other fields to move rapidly forward in our search for genes that influence developmental psychopathology. In the final chapter, Dr. Meike Bartels and I attempt to answer the second question: Does it really matter if I can't use it in the clinic? Here we provide a synthesis of what I have learned over my years in this field as a scientist, teacher, and clinician. The chapter summarizes the gene-environment family-based approach I developed for our clinic. In order to bridge the gap between research findings and clinical practice, we argue that much of what you will find in this book is already clinically useful. Critics may object that our approach is too time consuming, economically unrealistic, or eco-

logically invalid. However, on the basis of our knowledge of genetic and environmental influences, I ask you to carefully consider the value of a genetically informed family-based approach.

It is my hope that you will find valuable lessons contained in this book. I use them in my daily practice, teaching, and research. At its best, this work is changing the way the fields of child psychiatry and clinical psychology are conceptualized by debunking and demystifying damaging misconceptions about child psychiatric illness. We are leaving behind the era of false dichotomies—of nature versus nurture and genes versus environment—and are entering a period of progress in which relations between nature and nurture—genes and environment—can be better understood.

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GENETICS OF PERSONALITY AND COGNITION IN ADOLESCENTS

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Disturbances in normal personality and cognitive development underlie much childhood and adolescent psychopathology. It is therefore of value to study these aspects of human behavior in normal adolescents and to try and

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unravel the genetic and environmental factors that contribute to individual differences. Since 1992 we have been conducting a longitudinal study of adolescent twins and their nontwin siblings to estimate the importance of genes and environment in personality and cognition. More recently, we have been using gene mapping techniques to pinpoint the particular genes responsible for variation. In this chapter we describe the study and the methods we are using and present some of the results across the domains of personality and cognition.

METHODOLOGY

Twin Sample

A large sample of adolescent and young adult twins (3,408 individuals) and their nontwin singleton siblings (1,572), constituting 1,703 families, is a common resource for several key studies at the Queensland Institute of Medical Research (QIMR) in Australia (Wright and Martin 2004). The twins were recruited from primary and secondary schools in the greater Brisbane area, by media appeals, and by word of mouth. The sample includes both monozygotic (MZ) and dizygotic (DZ) twin pairs, including opposite-sex twin pairs, the singleton siblings of twins, and the twins' parents. The twins and siblings attend QIMR for testing as close as possible to their 12th, 14th, and 16th birthdays and are measured on a range of phenotypes, with personality being measured at 12, 14, and 16 years and cognition at 16 years. In addition, blood is collected for DNA and various hematological and immunological measures. Where possible, any singleton siblings of the twins who are within 5 years of age of the twins are also recruited and tested on an identical protocol. The benefits of a twin and sibling design include increased statistical power to detect genetic and shared environmental influences on a measured variable and the testing of several assumptions of the classical twin design. Thus, the design provides important information on whether estimates based on twin samples can be generalized to a nontwin population (Posthuma and Boomsma 2000). Also, by adding a sibling, MZ pairs become informative for linkage and within-pair association analysis. (By themselves they are not.) Families of DZ twins also become more informative (Dolan et al. 1999). Parents of twins are not phenotyped, but their DNA is used in error detection of marker genotypes and contributed to identity by descent (IBD; see below) estimation as well as haplotype determination.

For all same-sex twin pairs, zygosity is established by DNA polymorphisms using a commercial kit (AmpFISTR Profiler Plus PCR Amplification Kit, Applied Biosystems, Foster City, CA) and cross-checked with blood group results (ABO, MNS, and Rh) and/or phenotypic data such as

hair, skin, and eye color, giving an overall probability of correct zygosity assignment of greater than 99.99%. For DZ pairs this is subsequently confirmed by genome-wide genotyping for linkage scans. All participants give written, informed consent before participating in the study.

Phenotyping of Personality and Cognition

The personality questionnaire we are using in our adolescent studies is the full 81-item Junior Eysenck Personality Questionnaire (JEPQ) (Eaves et al. 1989; H.J. Eysenck and Eysenck 1975; S.B.G. Eysenck 1972), which assesses the three major dimensions of personality: Psychoticism (17 items), Extraversion (24 items), and Neuroticism (20 items). In addition, the questionnaire contains the 20-item Lie scale, which is a measure of social desirability. The JEPQ is scored on a 3-point scale (yes, don't know, and no), with "don't know" responses recorded as missing.

A broad array of cognitive data is being collected, and the measures have been described in detail elsewhere (Wright and Martin 2004; Wright et al. 2001a). Briefly, psychometric IQ is assessed using the Multidimensional Aptitude Battery and the Digit Symbol Substitution subtest from the Wechsler Adult Intelligence Scale—Revised, which provides a Full Scale IQ score, Verbal and Performance IQ scores, and scores for several specific cognitive abilities (Information, Arithmetic, Vocabulary, Spatial, Object Assembly, Digit Symbol). Processing speed is assessed at multiple levels: inspection time assesses early perception; choice reaction time (2-, 4-, and 8-choice reaction time [RT]) assesses information/response processing; and an event-related brain potential (ERP) measure, P300 latency, assesses stimulus evaluation. Similarly, working memory is assessed by performance accuracy and speed measures on a delayed response task, and ERP P300 amplitude and slow-wave amplitude assess attention and visuospatial processing, respectively. Resting electroencephalogram (EEG) measures—(individual) alpha frequency, EEG power (delta, theta, alpha, beta), and EEG coherence—provide psychophysiological measures of brain processing. In addition, two measures of reading ability, the Cambridge Contextual Reading Test (CCRT) and the Schonell Graded Word Fluency Test (SGWFT), are included. The CCRT is a contextualized adaptation of the National Adult Reading Test, which is widely used as a measure of premorbid IQ (Franzen et al. 1997) because of the correlation of word reading ability with IQ and the greater resilience of word reading performance to neurological insult compared with other cognitive measures. Lastly, the battery includes a measure of academic achievement, the Queensland Core Skills Test (QCST), which the majority of grade 12 Queensland students take in their final year at secondary school (i.e., a Queensland equivalent of the SAT).

Genome Scan for the Purpose of Linkage Analysis

Two separate genome-wide marker scans have been completed on a subset of these families (525 families, 2,123 individuals), one by the Australian Genome Research Facility, Melbourne, and a second by the Center for Inherited Disease Research, Bethesda, Maryland (supported by the National Institutes of Health). Combining the two scans results in 795 microsatellite markers (each of the separate but intercollating scans had approximately 400 markers), including 761 markers on the autosomes and 34 markers on the X chromosome, with an average heterozygosity of 79% and an average inter-marker distance of 4.8 centimorgans (cM).

Locations of markers were determined from the sex-averaged deCODE genetic map (Kong et al. 2002; Leal 2003). For twins/siblings the number of markers ranged from 211 to 790, with an average of 601 (± 192) total markers. Extensive crosschecking and data cleaning included pedigree error checking, genotype error checking via Mendelian error detection, and detection of spurious double recombination events (see Zhu et al. 2004 for a detailed description). Genotype data from approximately 80% of parents also assisted with error detection.

THE PERSONALITY STUDY

Numerous reports based on adult twin data have examined the heritability of personality, in particular for the domains of neuroticism and extraversion. Heritability estimates in the vicinity of 50% have been reported (Eaves and Eysenck 1975; Eaves et al. 1998; Heath et al. 1997; Jinks and Fulker 1970; Kendler et al. 1993; Martin et al. 1979). Given this strong empirical support for genetic contributions to personality, more recently several studies have attempted to locate quantitative trait loci (QTLs) for personality traits (Abkevich et al. 2003; Boomsma et al. 2000; Fullerton et al. 2003; Kirk et al. 2000; Thorgeirsson et al. 2003; Zubenko et al. 2003). These linkage studies have focused on neuroticism, neuroticism-like traits, and genetically related measures of mood and anxiety, and as yet there have been no genome scans for extraversion or psychoticism.

In the next section we summarize our findings of the magnitude of genetic and environmental effects on the multidimensional structure of personality across time (i.e., at ages 12, 14, and 16 years) using genetic simplex modeling (reported in full in Gillespie et al. 2004). We also report our linkage findings for the four domains of personality as assessed by the JEPQ in a subsample of these adolescent twins (see Gillespie et al., in press, for an in depth report).

Genetic Simplex Modeling of Personality in Adolescence

The sample included 670 twin pairs (253 MZ, 417 DZ) at age 12, 578 (216 MZ, 362 DZ) at age 14, and 545 (249 MZ, 296 DZ), at age 16 years. Personality scores were analyzed in the Mx statistical package (Neale et al. 2003) with genetic simplex modeling that explicitly took into account the longitudinal nature of the data. Genetic correlations between personality scores measured at 12, 14, and 16 years were moderate to high (0.61–1.00). Consistent with previous research findings for personality, familial aggregation for each dimension was significant and explained approximately 30%–50% of the total variance at each age. With the exception of the Lie dimension, model-fitting results revealed that familial aggregation was entirely explained by additive genetic effects, accounting for approximately 30%–50% of the total variance at each age, and that large proportions of the additive genetic variance observed at ages 14 and 16 years could be explained by genetic effects present at age 12 years. However, there was evidence for smaller but significant genetic innovations at ages 14 and 16 years for Neuroticism in boys and girls, at 14 years for male Extraversion, at 14 and 16 years for female Psychoticism, and at 14 years for male Psychoticism. These smaller genetic innovations not only suggest that genetic variation is not completely determined by age 12 years but potentially hint at age-specific genetic effects related to developmental or hormonal changes during puberty and psychosexual development.

Genome-Wide Linkage Scan for the Four Dimensions of Personality

Methods

Linkage analysis, using a variance components approach, was based on a subsample of 493 families (1,280 twins and sibs) for whom both genotyping and phenotypic data were available and included only the first twin of a MZ pair. Univariate variance components linkage analysis, parameterized as a function of the variance due to a major QTL, a polygenic component, and unique environment, was performed in Mx, with age and sex specified as a covariate on the means. Estimation of the QTL effect requires the calculation of multipoint IBD probabilities using the software program MERLIN (Abecasis et al. 2002). The covariance of a pair of siblings is modeled according to the extent to which they share alleles IBD at a typed polymorphic marker locus (maximum likelihood, multipoint IBD probabilities: $P[\text{IBD}=0,1,2]$). QTL linkage is present if omission of the QTL from the model causes a significant worsening of fit as evidenced by the χ^2 change. This produces a logarithm of odds ($\text{LOD}=\chi^2/4.6$) score that is compatible

with the parametric linkage analysis index. Linkage was considered significant if LOD scores exceeded 3.6 and suggestive if LOD scores exceeded 2.2 (Lander and Kruglyak 1995).

In addition, to increase the power to detect linkage for each of the personality dimensions, we tested, by means of a multivariate model that included measures at ages 12, 14, and 16 years, with age and sex as a covariate, whether a QTL is responsible for the same amount of phenotypic variation at each age by equating the three QTL factor loadings. From this reduced model, we then tested for linkage by examining whether the (equated) QTL could be set to zero (for a detailed description, see Evans et al. 2004).

Results

Genome-wide linkage results for the four personality dimensions are shown in Figure 5–1, with the cumulative map position (cM) plotted on the x-axis and LOD score on the y-axis. Univariate analyses at 12, 14, and 16 years are superimposed so that it is possible to compare the consistency of results across each measurement occasion, and displayed immediately below in the figure is the multivariate scan where the QTL factor loadings across the three waves are equated ($df=1$). LOD scores greater than 1.5 are presented in Table 5–1. Suggestive linkage, defined as the a priori criterion of a LOD score greater than 2.2, was found for Neuroticism on chromosome 16, Extraversion on chromosomes 2 and 3, and Psychoticism on chromosomes 1, 7, 10, and 13, but no significant linkage peaks ($LOD > 3.6$) were evident. The linkage signal on chromosome 16 was for Neuroticism measured at age 16 years, with no coincident peaks for Neuroticism measured at 12 or 14 years, or for the multivariate analysis. Similarly, the linkage signal on chromosome 2 for Extraversion was specific to age 16 years, as was the signal on chromosomes 10 and 13 for Psychoticism specific to age 12 years. However, there was reasonable consistency for the linkage signal for Extraversion on chromosome 3, with a suggestive LOD score of 2.38 found in the multivariate analysis and overlapping peaks with LODs > 1.5 found for Extraversion measured at 12 and 16 years, with a peak close by at age 14 years. Also, the linkage signals for Psychoticism on chromosomes 1 and 7 were found for more than one measure: on chromosome 1 overlapping peaks were found in the multivariate analysis and at age 12 years, and on chromosome 7 overlapping peaks were found at ages 12 and 14 years, as well as in the multivariate analysis.

Discussion

This is the first genome-wide scan for adolescent Neuroticism and the first in both adolescents and adults for the dimensions of Extraversion, Psychoti-

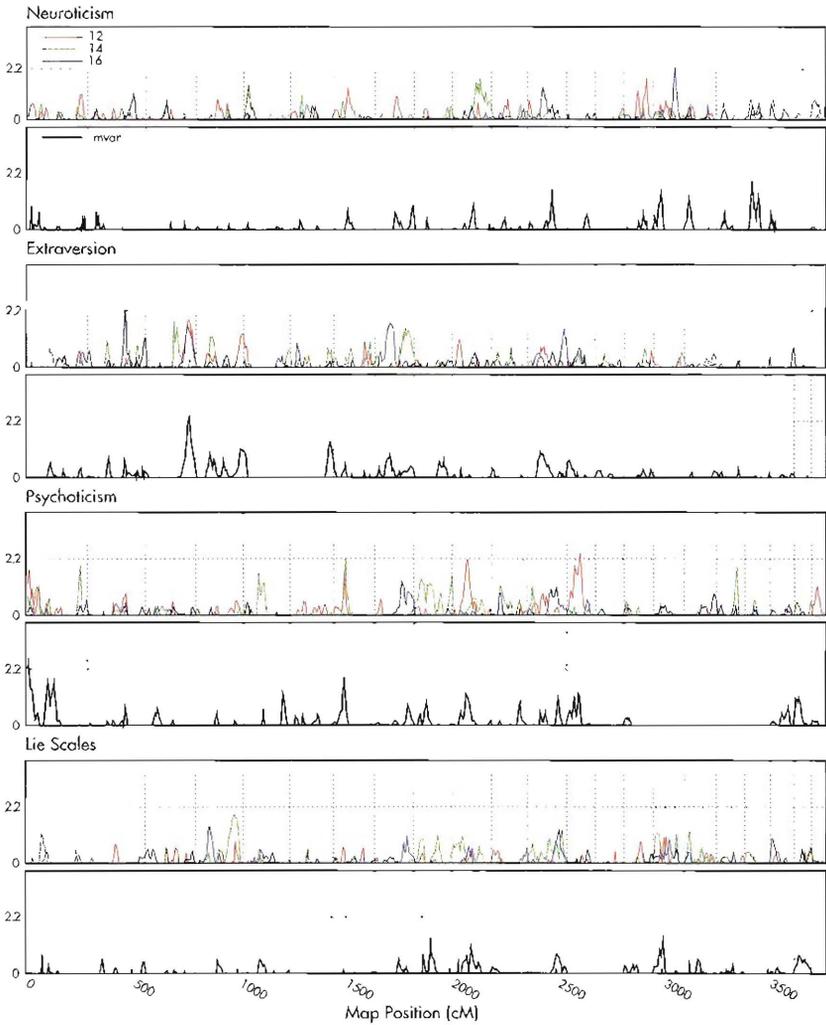


FIGURE 5–1. Genome screen for personality in the Brisbane adolescent twin sample.

Note. Linkage plots displaying the significance (Lod [logarithm of odds] scores [y-axis]) of Neuroticism, Extraversion, Psychoticism, and Lie to regions on chromosomes 1 to 22 (distance in centimorgans [cM] along the x-axis) for the univariate analyses at each of the three time points (ages 12 [red], 14 [green], 16 [blue]) and for the multivariate (mvar [black]) analysis. Suggestive linkage is indicated by a $Lod > 2.2$ (indicated by the horizontal dotted line).

TABLE 5-1. Regions of suggestive linkage (LOD > 2.2; shown in bold) and LODs greater than 1.50 for personality measures

Chromosome	Measure	Position (cM)	Marker	Peak LOD
1	Psychoticism_12	25.713	D1S450	1.77
	Psychoticism_mvar	25.713	D1S450	2.46
	Psychoticism_mvar	116.42	D1S551	1.70
	Psychoticism_14	266.206	D1S2785	2.08
2	Extraversion_16	174.226	D2S2330	2.29
3	Extraversion_12	198.435	D3S1262	1.86
	Extraversion_14	126.31	D3S2460	1.81
	Extraversion_16	198.435	D3S1262	1.73
	Extraversion_mvar	203.567	D3S1580	2.38
4	Lie_14	181.735	D4S2417	1.92
5	Neuroticism_14	15.873	D5S2505	1.51
	Psychoticism_14	64.933	D5S1457	1.71
7	Psychoticism_12	50.565	D7S817	1.81
	Psychoticism_14	54.925	D7S484	2.26
	Psychoticism_mvar	50.565	D7S817	1.88
8	Extraversion_16	69.471	D8S1110	1.73
9	Psychoticism_14	160.92	D9S158	1.58
10	Psychoticism_12	69.072	D10S196	2.20
	Neuroticism_14	126.019	D10S597	1.79
12	Neuroticism_mvar	111.14	D12S393	1.56
13	Psychoticism_12	54.01	D13S788	2.45
15	Neuroticism_12	106.632	D15S130	1.80
16	Neuroticism_16	113.279	D16S516	2.29
18	Psychoticism_14	90.349	D18S68	1.92
19	Neuroticism_mvar	38.55	D19S588	1.90

Note. mvar=multivariate analysis; 12=at age 12 years; 14=at age 14 years; 16=at age 16 years.

cism, and Lie. Although we found no regions that reached the significance criterion of 3.6, several linkage peaks met the suggestive criterion, identifying a number of regions that may contain genes playing a role in the normal variation of personality in adolescence. For some of these linkage peaks there was good congruency across the three ages, in line with our findings of significant additive genetic continuity across the age bands (Gillespie et al. 2004).

The most consistent evidence for linkage was for Extraversion on chromosome 3, with a maximum LOD score of 2.38 near the marker D3S1580 in the multivariate analysis and LOD scores greater than 1.5 in the same region at ages 12 and 14 years and in an overlapping region at age 14 years. However, note that linkage peaks span chromosomal regions of around 20 cM and many hundreds of genes, making it difficult to identify a gene or nucleotide variant that is responsible for the QTL effect. Other regions that emerged for Extraversion were regions on chromosomes 2 and 8, both for age 16 years. The linkage signal on chromosome 2 is interesting given that it is coincident with our linkage peak on chromosome 2 for general cognitive ability that is described below (see also Luciano et al. 2006; Posthuma et al. 2005; Wainwright et al. 2006), with the present sample being a subsample of that used in the cognition study. There has been recent interest in the relationship between intelligence and personality, with extraversion in particular suggested to influence IQ test performance (Wolf and Ackerman 2005).

The next strongest linkage signals were for Psychoticism on the short arm of chromosome 1, with a reasonably strong signal found in the multivariate analysis and a coincident peak at age 12 years. Indeed a number of areas of interest for this dimension of personality were evident, with a linkage peak on chromosome 7 also reaching the suggestive level with a coincident peak at another time point and in the multivariate analysis. Further single peaks at one time point were evident on chromosomes 10 and 13. As this is the first complete genome scan for Psychoticism, there are no studies with which to compare the location of these peaks. However the linkage peak on chromosome 13 is in the vicinity of the *HTR2A* gene located at 13q14.21, which has been implicated in schizophrenia, psychosis, and impulsivity (e.g., Abdolmaleky et al. 2004; Walitza et al. 2002; Williams et al. 1996).

In contrast to the dimensions of Extraversion and Psychoticism, for Neuroticism only one linkage signal on chromosome 16, at age 16 years, met the suggestive threshold. Evidence for linkage to social phobia for a region nearby on chromosome 16 has been identified previously (Gelernter et al. 2004). There was no evidence for linkage on chromosome 1, which has been the most consistently reported linkage region for Neuroticism in adult studies (e.g., see Fullerton 2006; Fullerton et al. 2003; Nash et al. 2004; B.M. Neale et al. 2005).

The findings of this study represent a first step but should be interpreted cautiously given the modest sample size and the fact that linkage signals were only suggestive. Replication in an independent sample will be required in order to assess the potential role of the chromosomal regions identified.

THE COGNITION STUDY

The Search for Genes Influencing Cognition

Individual differences in cognitive functioning, as measured by IQ tests, are to a large extent caused by differences at a genetic level (Bouchard and McGue 1981; Plomin et al. 1994b). Heritability estimates for various other measures of cognitive functioning (including endophenotypes—quantifiable intermediate constructs that index a behavioral trait) also range from moderate (e.g., 0.38 for perceptual speed) to very high (e.g., 0.83 for EEG power), as shown by us (see below) and others (e.g., Rijdsdijk et al. 1998). Despite this evidence for “genes for cognition,” the actual identification of genes has not been easy and progress has been slow because genetic influences on cognitive ability, much as with other heritable quantitatively distributed traits, are caused by the combined action of many genes of small effect (QTLs), a perspective that recently has been reaffirmed (Hill 2005).

Initial efforts to identify genetic variants influencing IQ (the IQ-QTL Project [Daniels et al. 1998; Plomin et al. 1995; Plomin et al. 1994a]) provided some evidence for associations of cognitive ability with various genetic polymorphisms (e.g., insulin-like growth factor 2 receptor marker) (Chorney et al. 1998), none of which were replicated in a genome-wide association analysis technique (using 1,842 genetic markers) applied to groups of average and extremely high IQ participants (Plomin et al. 2001). Most recently, a 10K microarray typed on the pooled DNA of cases with mild mental impairment and control subject, then on low-versus-high IQ samples showed association of four single nucleotide polymorphisms (SNPs) with general cognitive ability at 7 years; this was confirmed by individual genotyping in 6,154 children (Butcher et al. 2005b). These four SNPs, coupled with a fifth SNP identified in a study of 432 functional nonsynonymous SNPs expressed in the brain (Butcher et al. 2005a), form a SNP set that has been found to account for 0.86% of variance in *g* at age 7 years and also predicts variance in general cognitive ability (*g*) as early as age 2 years (Harlaar et al. 2005).

Another approach comes from targeted candidate gene studies, with findings of polymorphisms in genes coding for brain-derived neurotrophic factor, prion protein, and succinate-semialdehyde dehydrogenase to be as-

sociated with normal variation in IQ (Plomin et al. 2004; Rujescu et al. 2003; Tsai et al. 2004). Allelic associations with tasks measuring the specific cognitive processes of cued discrimination, memory, and attention have also been reported for apolipoprotein E and catechol-*O*-methyltransferase Val158Met polymorphisms (Egan et al. 2001; Flory et al. 2000). Other associations include that for the α_2C -adrenergic receptor gene (*ADRA2C*), which has been implicated in learning disability (Comings et al. 1999), and the forkhead box P2 gene (*FOXP2*) on chromosome 7, which is related to severe disruption of speech and language (Lai et al. 2001).

Our study for genes for cognition in adolescent twins includes a range of behavioral and neurophysiological indices of cognitive function in addition to indices of general cognitive ability (IQ) and is part of a collaborative effort with the Netherlands and Japan (Wright et al. 2001a). It was specifically designed to sample cognitive tasks (e.g., information processing speed, working memory, reading ability, academic achievement) that have shown consistent significant correlations with IQ. The rationale for this approach is that cognitive endophenotypes measuring more discrete components of cognition are more upstream and are likely to be influenced by a smaller number of genes. We summarize in the next section our quantitative analyses of IQ and other cognitive phenotypes, including our genome-wide linkage scan of IQ, and report our most recent linkage findings for our information processing and working memory measures.

Genetic Analyses of IQ and Cognitive Endophenotypes

To date we have tested 681 twin pairs and 207 of their nontwin siblings, with a mean age of 16 years, on our cognitive test battery. This is a subsample of the twin sample described previously. As shown in Figure 5–2 we have found pervasive genetic influence on both elementary and higher-order cognitive tasks; high heritability was not just found for the broadest index of cognition (IQ) but also for specific cognitive processes and endophenotypes of cognitive ability. These range from a high of 0.80 for EEG power to a low of 0.40 for inspection time (IT) and slow wave.

In a series of multivariate analyses we have tested whether correlations between the various cognitive phenotypes stem from shared (pleiotropic) genes (pleiotropy occurs when a single gene influences multiple phenotypic traits). We have shown that common genes influence a range of processing speed and working memory indices, and IQ, and established the extent to which genetic (and environmental) sources of covariation explain the phenotypic association between more specific indices of cognitive ability and IQ (Luciano et al. 2001a, 2001b, 2002, 2003, 2004a, 2004b, 2005; Wainwright et al. 2004, 2005a, 2005b; Wright et al. 2000, 2001b, 2002). For ex-

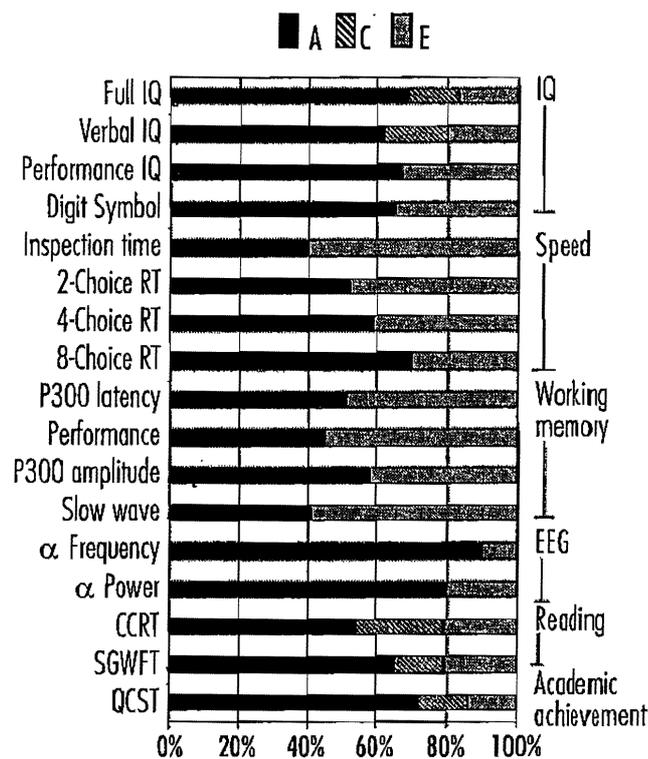


FIGURE 5–2. Heritability of cognitive measures in the Brisbane adolescent twin sample.

Note. A=additive genetic; C=common environment; E=unique environment; CCRT=Cambridge Contextual Reading Test; RT=reaction time; SGWFT= Schonell Graded Word Fluency Test; QCST=Queensland Core Skills Test; EEG = electroencephalogram.

ample, we used direction of causation modeling to show that covariation between IT, which taps perceptual speed, and IQ is best explained by pleiotropic genes that influence individual variation in both IT and IQ (Luciano et al. 2005). However, although we found that a common genetic influence primarily explains the relationship between measures, we also found that “group” genetic factors were important. These may exist because of the mutual reliance of some cognitive measures on processes that are mediated by a different set of genes than general cognitive ability. For example, analysis of the covariance among IT, CRT, and IQ subtests showed that three genetic group factors (verbal, visuospatial, broad speediness) were important, in addition to a single genetic factor influencing all measures (Luciano et al. 2004a). These findings are in agreement with findings from other studies (Martin and Eaves 1977; Petrill et al. 1996; Rijdsdijk et al. 1998; Wainwright et al. 2004) and suggest that it is likely that QTLs exist for these group factors.

Genome-Wide Linkage Scan for IQ

As was reported elsewhere (Luciano et al. 2006), our first whole genome-wide linkage scan on 361 families (2–5 siblings per family) was performed on the scaled Verbal, Performance, and Full Scale IQ scores, three verbal (information, vocabulary, arithmetic) and three performance (Spatial, Object Assembly, and Wechsler Adult Intelligence Scale—Revised [WAIS-R] Digit Symbol) IQ subtests, and two measures of premorbid IQ (CCRT and SGWFT reading tests). We found converging linkage peaks on chromosome 2 for performance IQ and the CCRT, with respective LOD scores of 3.7 and 4.15. (Empirical LOD scores were estimated [with correction for multiple testing], with performance IQ just falling short of the significance criterion of 3.8 and the CCRT just exceeding the significance criterion of 4.14.) Smaller linkage peaks in this same region were found for the performance IQ subtests, Spatial and Object Assembly, and the SGWFT, and also for academic achievement as measured by the QCST in a subsample of twins (Wainwright et al. 2006). Importantly this linkage peak was found in an independent sample from the Netherlands as well as for the combined Australian and Dutch data (Posthuma et al. 2005). Figure 5–3 shows the linkage plots for the cognitive variables showing converging linkage regions on chromosome 2. Our findings suggest that genes in this region influence a breadth of indicators of general cognitive ability. Specific genes potentially implicated include *GAD1*, *NOSTRIN*, *KCNH7*, *TBR1*, *DLX1*, and *DLX2*, with several of these genes involved in glutamatergic neural transmission, and have been discussed in detail by Posthuma et al. (2005) and Luciano et al. (2006).

We have also identified suggestive linkage peaks ($\text{LOD} > 2.2$) on other chromosomes, including a strong peak on the short arm of chromosome 6 for the verbal subtest Arithmetic ($\text{LOD} = 3.05$) as well as Full Scale IQ ($\text{LOD} = 2.24$) (Figure 5–3). This region was identified in the Dutch twin pairs, in the combined linkage analysis of the Australian and Dutch data (Posthuma et al. 2005), and most recently in a linkage analysis of IQ in the collaborative study on the genetics of alcoholism sample (Dick et al. 2006). This region has also been implicated in linkage studies of development dyslexia (Kaplan et al. 2002; Marlow et al. 2003). In addition, a further linkage peak was identified on 6q, with convergence of peaks for verbal test measures (SGWFT, Information, Verbal IQ).

Genome-Wide Linkage for Information Processing and Working Memory

We report here genome-wide linkage findings for information processing measures, including 2-, 4-, and 8-choice RT and inspection time, and for

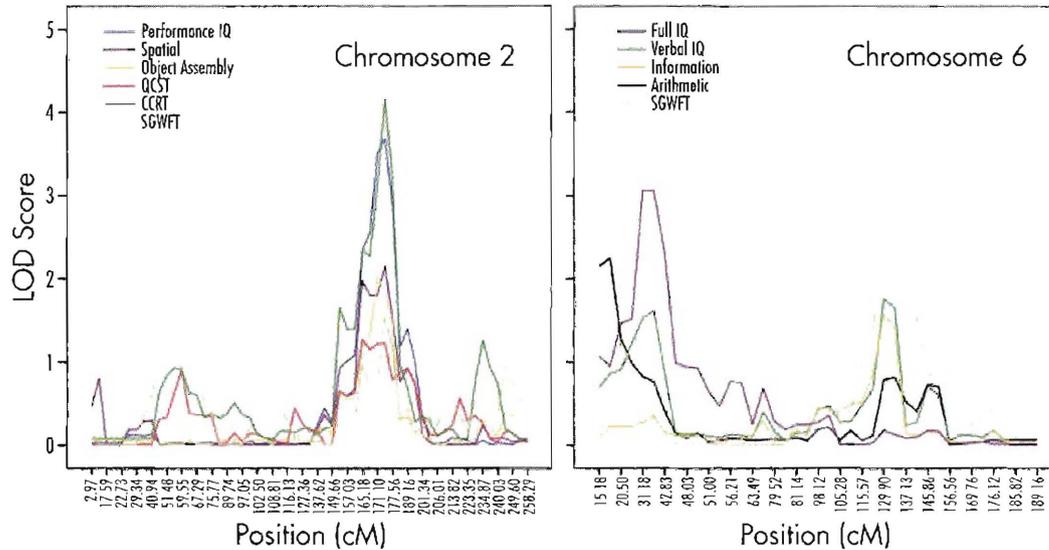


FIGURE 5-3. Converging linkage regions on chromosome 2 and chromosome 6 for IQ measures in the Brisbane adolescent twin sample.

Left. Significant linkage (indicated by a logarithm of odds [LOD] of 3.6) for Performance IQ and the Cambridge Contextual Reading Test (CCRT) on chromosome 2. Overlapping linkage peaks were also evident for the IQ subtests Spatial and Object Assembly, the Schonell Graded Word Fluency Test (SGWFT), and the Queensland Core Skills Test (QCST). Both IQ and reading measures peak in the same region on 2q, suggesting a general cognitive ability gene.

Right. Suggestive linkage on chromosome 6p for the IQ subtest arithmetic with overlapping peaks for full IQ and verbal IQ, and on 6q convergence of peaks for verbal test measures (SGWFT, information, verbal IQ). The x axis indicates position of markers in centimorgans (cM).

Source. Adapted from Luciano et al. 2006.

working-memory behavioral measures during a delayed response (DR) task, including a measure of accuracy, DR spatial (sensory) precision; a speed measure, DR initiation time; and an omnibus measure of working memory performance (including both accuracy and speed), DR performance.

Methods

The sample included all individuals for whom we had both phenotypic and genotypic data available (378 families [2–5 siblings per family] for information processing; 285 families for delayed-response working memory) and was very similar to the sample used in the linkage analyses on IQ reported previously in this chapter. Univariate, multipoint, variance components linkage analysis was performed in the MERLIN software program. As for the linkage analysis of personality traits, the QTL is estimated using the probabilities that siblings share genes IBD, with the QTL effect evaluated by the difference in log₁₀ likelihood of a model that includes the QTL and a model that fixes it to zero. This produces a LOD score that is compatible with the parametric linkage analysis index. Lander and Kruglyak's (1995) criteria for suggestive and significance linkage were adopted but were not corrected for multiple testing because of the exploratory nature of these analyses.

Results

Genome-wide linkage results are shown in Figure 5–4. Suggestive linkage, using the a priori criterion of LOD greater than 2.2, was indicated on the long arm of chromosome 1 for 8-choice RT, with smaller but coincident peaks for both 2- and 4-choice RT (LODs=1.86 and 1.89, respectively). There was also suggestive linkage for 8-choice RT on chromosome 11, for 4-choice RT on chromosomes 8 and 22, and for working memory measures on chromosomes 7 (DR accuracy) and 14 (DR initiation time). Table 5–2 lists the suggestive linkage regions as well as those regions with LODs greater than 1.5 that did not meet the suggestive criteria. These include regions on chromosomes 12 and 18 for inspection time and on chromosome 22 for 4-choice RT, and for working memory measures, a region on chromosome 2 for DR accuracy, and on chromosome 22 for DR initiation time.

Discussion

These new analyses do not corroborate our linkage findings on chromosomes 2 and 6 for general cognitive ability (IQ) described above. They suggest other chromosomal regions that may be involved in more specific cognitive abilities associated with information processing and working memory. Genetic covariance studies of IQ subtests all find a general genetic factor that explains a significant proportion of cognitive measure variability,

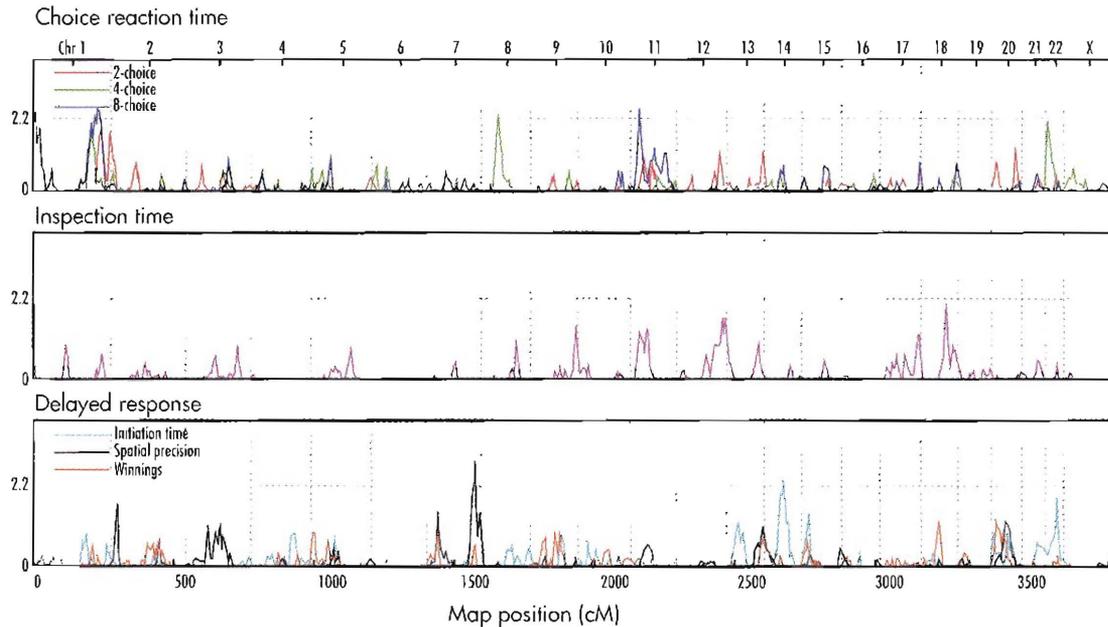


FIGURE 5-4. Genome screen for information processing and working memory measures in the Brisbane adolescent twin sample.

Note. Linkage plots displaying the significance (LOD [logarithm of odds] scores [y axis] of 2-, 4-, and 8-choice reaction time (red, green, and blue, respectively), inspection time, and delayed response measures (initiation time [aqua], spatial precision [black], winnings [brown]) to regions on chromosomes 1–23 (distance in centimorgans [cM] along the x axis) are displayed. Suggestive linkage was defined by a $LOD > 2.2$ and indicated by the horizontal dotted line.

TABLE 5–2. Regions of suggestive linkage (LOD > 2; shown in bold) and LODs greater than 1.50 for the elementary cognitive measures

Chromosome	Measure	Position ^a	1 LOD Drop	Peak LOD
1	2-choice RT	242.13	228.26–244.40	1.86
	4-choice RT	207.07	199.74–219.23	1.89
	8-choice RT	228.26	194.98–244.40	2.50
2	DR spatial precision	19.64	7.60–22.73	1.70
7	DR spatial precision	165.57	159.33–195.13	2.90
8	4-choice RT	54.23	52.74–65.47	2.26
11	8-choice RT	25.69	17.05–42.49	2.50
12	Inspection time	169.54	131.83–169.54	1.67
14	DR initiation time	63.5	36.71–81.46	2.28
18	Inspection time	85.12	77.59–92.54	1.97
22	4-choice RT	2.96	2.96–14.68	2.12
	DR initiation time	37.03	32.92–42.26	1.89

Note. DR=delayed response; RT=reaction time.

^aComings et al. 1999.

but it is apparent that there is also a large proportion of genetic variability accounted for by genetic group and specific factors (Martin and Eaves 1977; Petrill et al. 1996; Rijdsdijk et al. 1998; Wainwright et al. 2004).

The strongest linkage signal was on chromosome 1, in which the linkage peaks for all three levels of the CRT task overlapped. The evidence for linkage was greatest for the 8-choice RT, possibly because this measure had the highest heritability and is the most reliable, as shown by test-retest reliability. As can be seen in Figure 5–4, linkage to this region, albeit nonsignificant, is also observed for IT, and previously we found a small linkage peak (LOD > 1) for the IQ subtest Vocabulary and the IQ subtest Digit Symbol (Luciano et al. 2006). Moreover, we found that the CRT tasks share information processing variance with the IQ subtest Digit Symbol that is greater than that shared with other IQ subtests through a genetic general cognitive ability factor, and that IT is also related to choice RT and Digit Symbol through this genetic information processing factor (Luciano et al. 2004a). Thus, it may be that genes in this region on chromosome 1 influence variation in measures that involve information processing efficiency. Independent support for this notion is the finding of small linkage signals in this region for a number of neuropsychological tests, including Digit Symbol, Block Design, and Trails B of the Trail Making Test, which involve an

information processing component, in the Collaborative Study on Genetics of Alcoholism Sample (Buyske et al. 2006).

All other regions of "suggestive" linkage (defined as $LOD > 2.2$) were for a single measure. The linkage signal on chromosomes 8 and 22 for 4-choice RT was specific to this measure, and these regions were not implicated in our previous analyses of IQ (Luciano et al. 2006) or academic achievement (Wainwright et al. 2006). Similarly, the peak on chromosome 11 for 8-choice RT also appears to be specific, although we note a weak coincident linkage signal for IT and a small peak for 2-choice RT that is overlapping with this region. However, for the DR working memory measures, the peaks on chromosome 7 for DR accuracy and on chromosome 14 for DR initiation time are coincident with suggestive linkage peaks identified on chromosome 7 for verbal IQ, and on chromosome 14 for both the IQ subtest Arithmetic and the SGWFT (Luciano et al. 2006). The region on chromosome 14 is particularly interesting given the finding of suggestive linkage to this region for the WAIS-R Digit Symbol subtest in the Collaborative Study on the Genetics of Alcoholism Sample (Buyske et al. 2006).

Although the results of this study are not sufficiently strong of themselves to firmly implicate any of the regions identified in cognition, they are of interest in that they possibly identify other chromosomal regions, in addition to those on 2 and 6, that may harbor genes for cognition, and are beginning to reveal patterns of genes that have an impact on related cognitive phenotypes.

CONCLUSIONS

In this ongoing work, a long-term aim has been to provide a powerful resource of brain phenotypes and genotypes to test hypotheses of how putative genetic mechanisms influence variation in normal brain function, in particular with respect to personality and cognition. It is hoped that in time this will dovetail with information being gathered from various clinical studies of neurological and psychiatric disorders and will allow for the piecing together of disjointed parts of the literature in powerful and novel ways.

With the award of a medical genomics grant from the National Health and Medical Research Council of Australia for high-density SNP mapping, we will have available over a period of 4 years a genome-wide association scan using the Affymetrix 500K chip with more than 500,000 SNPs for most of the twins and siblings in our adolescent sample. This will provide us with a unique opportunity to examine the association of genetic polymorphisms, spread across the entire genome, with the personality and cognition phenotypes.

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