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A Linkage Study of Academic Skills Defined by the Queensland Core Skills Test

Mark A. Wainwright,[1,2,3] Margaret J. Wright,[1] Michelle Luciano,[1] Grant W. Montgomery,[1] Gina M. Geffen,[2] and Nicholas G. Martin[1]

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This study used genome-wide linkage analysis to detect Quantitative Trait Loci (QTLs) implicated in variation in general academic achievement as measured by the Queensland Core Skills Test (QCST) (Queensland Studies Authority, 2004). Data from 210 families were analysed. While no empirically derived significant or suggestive peaks for general academic achievement were indicated a peak on chromosome 2 was observed in a region where Posthuma *et al*. (2005) reported significant linkage for Performance IQ (PIQ) and suggestive linkage for Full Scale IQ (FSIQ), and Luciano *et al*. (this issue) observed significant linkage for PIQ and word reading. A peak on chromosome 18 was also observed approximately 20 cM removed from a region recently implicated in reading achievement. In addition, on chromosomes 2 and 18 peaks for a number of specific academic skills, two of which were suggestive, coincided with the general academic achievement peaks. The findings suggest that variation in general academic achievement is influenced by genes on chromosome 2 which have broad influence on a variety of cognitive abilities.

KEY WORDS: Academic achievement; cognitive abilities; genome-wide linkage; twins.

INTRODUCTION

The focus of this paper is to investigate linkage for general academic achievement measured by the Queensland Core Skills Test (QCST) (Queensland Studies Authority, 2004), which assesses academic achievement in year 12 (final year of secondary schooling) students. This study complements the linkage study of psychometric IQ of Luciano *et al*. (this issue), using a subsample of 210 twin families drawn from the larger sample of 361 families in that study.

Academic achievement is a phenotype closely related to IQ and multivariate genetic analyses have indicated that a common genetic factor influences academic outcomes and IQ measures (Plomin, 2003). As such, linkage analysis of academic achievement may implicate genes in the same regions that have recently been identified for IQ measures (Luciano *et al*., this issue; Posthuma *et al*., 2005). While a variety of linkage and association studies have been published for reading (e.g., Cardon *et al*., 1994; Kaplan *et al*., 2002) to our knowledge there are no published linkage or association studies for academic achievements other than reading.

General cognitive ability (*g*) is a higher order construct which emerges from factor analyses of diverse measures of cognitive abilities, and is well captured by Full Scale IQ (FSIQ). It is considered to reflect mental processes, particularly the eduction of relations and correlates (Jensen, 1998), that underlie the observed positive correlations among these diverse measures. The pervasive effects of *g* are evident in a very large number of studies which suggest that, on average, IQ correlates about 0.5 with

[1] Queensland Institute of Medical Research, Post Office Royal Brisbane Hospital, Herston, Brisbane, QLD, 4029, Australia.
[2] Cognitive Psychophysiology Laboratory, School of Psychology, University of Queensland, Brisbane, Australia.
[3] To whom correspondence should be addressed at Queensland Institute of Medical Research, Post Office Royal Brisbane Hospital, Herston, Brisbane, QLD, 4029, Australia. Tel.: +61-7-3362-0272; Fax: +61-7-3362-0101; e-mail: Mark.Wainwright@qimr.edu.au

academic achievement (Bartels *et al*., 2002; Jensen, 1998; Petrill and Wilkerson, 2000). Standardised tests of academic achievement tend to correlate more highly with IQ than school grades (See Baade and Schoenberg, 2004), most probably because of the greater reliability of standardised tests (Jensen, 1998). Notably, when specifically analysing the relationship between *g* (independent of specific abilities) and academic achievement, Thorndike (1984) reported that virtually all predictable variation in achievement is attributable to *g*.

Not surprisingly then, the distinction between achievement and IQ tests has been disputed (Ceci, 1994). We have reported strong phenotypic correlations between general academic achievement and Verbal IQ (VIQ) (0.81) and Performance IQ (PIQ) (0.57) (Wainwright *et al*., 2005a), which are comparable with reported correlations between other achievement tests and IQ measures (See Baade and Schoenberg, 2004). The primary distinction is that achievement tests assess knowledge and skills acquired within a circumscribed set of learning experiences and limited time frame (e.g., senior education), while IQ tests assess abilities and knowledge developed/acquired more generally (Murphy and Davidshofer, 1994). We recognise the conceptual distinction between achievement and IQ tests while acknowledging that they engage similar if not identical mental processes (i.e., the eduction of relations and correlates), with the strong phenotypic and genetic correlations between achievement measures and IQ reflecting this commonality. The dilemma in this regard is not limited to our study but one that cognitive and educational psychology has not fully confronted or resolved.

Recent analysis from our laboratory showed that a common genetic factor explained virtually all genetic variation in the five *a priori* designated specific academic achievement skills of the QCST. This common factor also principally influenced genetic variation in VIQ and PIQ (Wainwright *et al*., 2005b). We interpreted this factor as genetic *g*—a latent genetic factor with pervasive influence on cognitive abilities. Consequently, our primary interest is in linkage analysis for general academic achievement (total QCST score—sum of the five academic achievement skills scores) which should best reflect the influence of genetic *g*. Nevertheless, we present linkage results for the five specific academic skill achievements, as we believe it is informative to present how these five specific measures, which evidence strong genetic correlations (Wainwright *et al*., 2005b) are implicated in linkage signals for general academic achievement.

Difficulty in locating QTLs that influence variation in cognitive abilities suggests that cognitive measures reflect complex traits, with multiple genes of small effect likely to be implicated in brain functioning, and consequently in subtest score variation (Plomin, 2003). Nevertheless, there has been some encouraging work in this area. The most consistent success has been for reading disability with multiple reports identifying the regions 6p22.3–6p21.3 (e.g., Cardon *et al*., 1994; Deffenbacher *et al*., 2004; Gayán *et al*., 1999) and 15q21 (e.g., Grigorenko *et al*., 1997; Smith *et al*., 1991) as relevant to reading difficulties. Fisher *et al*. (1999) using DNA pooling reported initial significant association for 11 markers on chromosome 4 for general cognitive ability, with replicated significant association using independent samples for three of these markers (D4S2943, MSX1, and D4S1607). More recently, studies looking at targeted candidate genes have shown polymorphisms within a brain-derived neurotrophic factor, prion protein, and succinate-semialdehyde dehydrogenase genes to be associated with normal variation in IQ (Plomin *et al*., 2004; Rujescu *et al*., 2003; Tsai *et al*., 2004).

For general cognitive ability a more wide-ranging approach than targeting candidate genes was undertaken by Plomin *et al*. (2001) by applying a genome-wide association analysis technique using separate groups made up of either of average or exceptionally high IQ ($> +3$ SDs) individuals. While associations with 108 markers were detected at stage 1 of analysis (case–control DNA pooling), replication at all five stages was not achieved. Luciano *et al*. (this issue) using genome-wide linkage reported significant peaks (LODs > 3.6) for the Cambridge Contextual Reading Test (CCRT – a proxy measure of IQ; Nelson, 1982) and PIQ on chromosome 2 in the regions bounded by D2S2313 and D2S335, and D2S142 and D2S1391 respectively. Suggestive peaks (LOD > 2.2) on chromosome 6 were also found for Full-Scale IQ (FSIQ) and the Arithmetic subtest from the Multidimensional Aptitude Battery (MAB) (Jackson, 1984) and for the Schonell Graded Word Reading Test (SGWRT) (Schonell and Schonell, 1960). Additional suggestive peaks for cognitive measures were also observed on chromosomes 7, 11, 14, 21 and 22.

Using a larger sample, combining participants from the study by Luciano et al. (this issue) with participants from the Netherlands, Posthuma *et al*.

(2005) also have reported a significant linkage for PIQ on chromosome 2 in the region 2q24.1–2q31.1 and suggestive linkage for VIQ and FSIQ on chromosome 6 in the region 6p22.3 – 6p21.31. Importantly, there was evidence of linkage on chromosomes 2 and 6 for both the Dutch and Australian samples when analysed independently, although the signals from the Dutch sample were somewhat weaker, presumably due to their smaller sample size. Thus while the search for QTLs for cognition is challenging due to the large number of genes that are potentially implicated and the fact that linkages will often involve weak effects there is evidence that both targeted and wide-ranging approaches can be fruitful, with replication and meta-analysis being essential in engendering confidence in findings (Cardon and Bell, 2001, Lander and Kruglyak, 1995).

In general, linkage studies are characterised by low power (Plomin, 2003), a limitation which is particularly pertinent to the present study given the small sample size. However, the advantage of the approach lies in permitting identification of chromosomal regions that may contain genes of large effect without the genetic markers being either the functional polymorphisms, or necessarily being extremely closely located to the causative genes (Vink and Boomsma, 2002). Moreover, the aggregation of small QTL effects in a region may yield a signal of larger effect (Legare *et al*., 2000; van Wezel *et al*., 1999; Yalcin *et al*., 2004).

METHODS

Participants

All participants were drawn from a continuing study of cognition, the Brisbane Memory, Attention and Problem Solving (MAPS) twin study (Wright *et al*., 2001; Wright and Martin, 2004). Potential participants were excluded if parental reports indicated either twin had a history of significant head injury, neurological or psychiatric illness, substance abuse or dependence, or current use of medication with known effects on the central nervous system (not including previously concluded short-term treatment). Participants had normal or corrected-to-normal vision (> 6/12 Snellen equivalent).

Data were analysed from 210 families who had been genotyped and had QCST data available. Nineteen of these families were composed of MZ twins with one or two siblings. One family had two siblings that were not twins. Thirty five families were composed of DZ twins with one or two siblings, and 155 families had only DZ twins. Genotype data were available from both parents for 152 families, from one parent for 35 families, and neither parent for 23 families. Participants sat the QCST in their final year of education (17.3 years ± 0.39SD).

Zygosity and Genotyping

Blood was obtained from twins, siblings and 80% of parents for blood grouping and DNA extraction. Details regarding determination of zygosity can be obtained from Wainwright *et al*. (2005a). The Australian Genome Research Facility (AGRF, Melbourne) and the Centre for Inherited Disease Research (CIDR, Baltimore) conducted genotyping. Only a synopsis of genotyping is provided here as Zhu *et al*. (2004) have provided comprehensive detail on data cleaning, genotyping procedures, and overlap between markers typed at different facilities. In all, 796 microsatellite markers (761 autosomal markers, and 34 on the X chromosome) were typed across the entire genome at approximately equal intervals of 4.8 cM, with locations determined from the sex-averaged DeCODE map (Kong *et al*., 2002; Leal, 2003) Genetic distances for unmapped markers were interpolated from the physical map. Marker heterozygosity ranged between 0.49 and 0.94.

Measures

Queensland Core Skills Test

The QCST is composed of five *a priori* academic achievement skill scores which are summed to give a total score (general academic achievement). Comprehend & Collect entails comprehension of facts from a broad range of stimuli, and utilisation of information to display meaning (e.g., interpretation of data presented in tables). Structure & Sequence incorporates the selection, sorting, sequencing, and organisation of information, and discernment of complex patterns and relationships (e.g., visualisation and manipulation of spatial relationships). Analyse, Assess & Conclude involves deduction and induction among relationships, identifying the essential elements and merits of complex arguments, and the drawing of conclusions (e.g., inferring meaning from text). Create & Present captures use of written language which is effectively structured and clearly develops relevant ideas. Apply Techniques & Proce-

dures represents skills in making calculations and mathematical problem solving (e.g., applying principles of proportionality to solve practical problems). Further detail regarding the QCST are included in Wainwright *et al.* (2005a) and additional information including copies of past assessment papers, annual reviews, and assignment of questions to specific achievement skills is available from the QSA website (Queensland Studies Authority, 2005).

The most recent evidence that the QCST is an appropriate measure of academic achievement is provided by reports published by the QSA showing that in 2003 total QCST score correlated 0.73 with a Within-School Measure (WSM) which is an estimate of a student's overall achievement based on teacher-decided rank order information in school-based assessment. A correlation of 0.73 between QCST total score and actual level of achievement based on school grades is also reported for 2003 (Queensland Studies Authority, 2003). These correlations are consistent with reports from previous years.

Procedure

Full details of how QCST data were obtained, including consent procedures for phenotypic data may be found in Wainwright *et al.* (2005a). Also, written consent to examine genotypic data in conjunction with phenotypic data was obtained from participants, and their guardians (if participants <18 years old). Data for 8 years (1996 – 2003) were obtained for analyses reported here. For the QCST the maximum score obtainable varied according to year. For this reason, general academic achievement score and the five specific achievement skills scores in each year were standardised using the means and standard deviations (SD) of the entire enrolment of candidates within each year (ranging from 28,225 individuals in 1996 to 31,099 individuals in 2000) This allowed data across 8 years to be pooled and analysed together. Because there was a limited number of twin participants and different items were used each year we were unable to conduct our own factor analysis on the data and thus used the *a priori* designations provided by the QSA.

Descriptive Analysis

Moderate to strong phenotypic and genetic correlations among general academic achievement and IQ, and specific academic achievement skills and IQ are reported elsewhere (Wainwright *et al.*, 2005a, b). Heritabilities for general academic achievement, Comprehend & Collect, Structure & Sequence, Analyse, Assess & Conclude, Create & Present, and Apply Techniques & Procedures are 0.68, 0.55, 0.73, 0.60, 0.44 and 0.73 respectively (Wainwright *et al.*, 2005b).

Due to mean score differences between males and females for Structure & Sequence, Create & Present, and Apply Techniques & Procedures (Wainwright *et al.*, 2005b), sex was included as a covariate for the linkage analysis for these variables. For total academic achievement there is no sex difference in mean score (Wainwright *et al.*, 2005b). As siblings had not been included in previous analyses, equality of means between twins and siblings for general academic achievement and the five specific academic achievement skills were tested using methods previously described (Wainwright *et al.*, 2005a).

Linkage Analyses

Linkage analysis for the 22 autosomal chromosomes was conducted using the Merlin-Regress program (Abecasis *et al.*, 2002). Like other Merlin procedures, Merlin-Regress does not model common environment in the correlation between pairs of relatives, although this does not substantively influence QTL effect size estimates (Abecasis, personal communication). The method is an extension of the original Haseman–Elston procedure (Haseman and Elston, 1972) and derives linkage information by regressing estimated identical-by-descent (IBD) sharing between pairs of relatives on to trait squared-sums and differences. The method combines the simplicity of regression based approaches with the power of variance-component (VC) modelling. An advantage of the method is that it permits samples with biased ascertainment to be easily analysed provided that the population means, variances and heritability can be reasonably specified. This approach is appropriate to our QCST data which has mild ascertainment bias (Wainwright *et al.*, 2005a). Sham *et al.* (2002) provide a detailed description of the regression method as implemented here.

Population means of zero, standard deviations of one, and heritabilities reported above were stipulated for QCST variables in the Merlin-Regress modelling. However, it should be noted that these are the means for the population that sit the QCST and do not incorporate that part of the birth cohort that do not sit the QCST. As such, while specification of these parameters corrects for our sample being a biased ascertainment from the total QCST sample, it may not wholly account for the QCST population being a biased sample from the birth cohort.

Kosambi map units, derived from the deCODE map were transformed to Haldane map units and subsequently back transformed to Kosambi map units for reporting of linkage results. Empirically derived LOD scores were also calculated for the measures using Merlin-Regress simulation. One thousand simulations per marker were performed, in which the phenotype was matched with an alternative genotype (having the same allele frequencies, marker spacings and missing data patterns). The highest LOD per chromosome (to ensure independence of LOD scores) per simulation was retained giving 22000 LOD scores in total, which were ranked in descending order. A score for empirical significance was set at the 50th highest simulation-derived LOD score, which represented a probability of 0.05 for the entire genome scan (i.e. 50 per 1000 complete genome scans). Likewise a simulation-derived suggestive linkage criterion was set at the 1000th highest simulation-derived LOD (i.e., occurring once per genome scan).

RESULTS

Siblings obtained significantly higher scores for general academic achievement ($p < 0.005$), Comprehend & Collect ($p < 0.005$), Structure & Sequence ($p < 0.05$), Analyse, Assess & Conclude ($p < 0.05$), and Create & Present ($p < 0.005$). As such, sibling status (sibling versus member of a twin pair) was also included as a covariate for these variables. As Merlin-Regress does not permit inclusion of covariates when analysing samples with ascertainment bias (Abecasis, 2004), sex and sibling status were regressed out of the relevant QCST scores in SPSS 13.0 and analyses were conducted on the residuals.

Empirically generated thresholds for significant and suggestive LODs were as follows, general academic achievement, 2.74 and 1.57, Comprehend & Collect, 2.84 and 1.59, Structure & Sequence, 2.96 and 1.70, Analyse, Assess & Conclude, 2.96 and 1.64, Create & Present, 2.88 and 1.61, and Apply Techniques & Procedures, 2.85 and 1.63.

Figure 1 shows results of linkage analyses for general academic achievement and the five specific achievement skills scores. No significant or suggestive peaks using genome-wide empirical significance levels were found for general academic achievement. The highest LODs for general academic achievement of 1.26 and 1.25 were observed on chromosomes 2 (D2S142) and 18 (D18S976) respectively. Overlap-

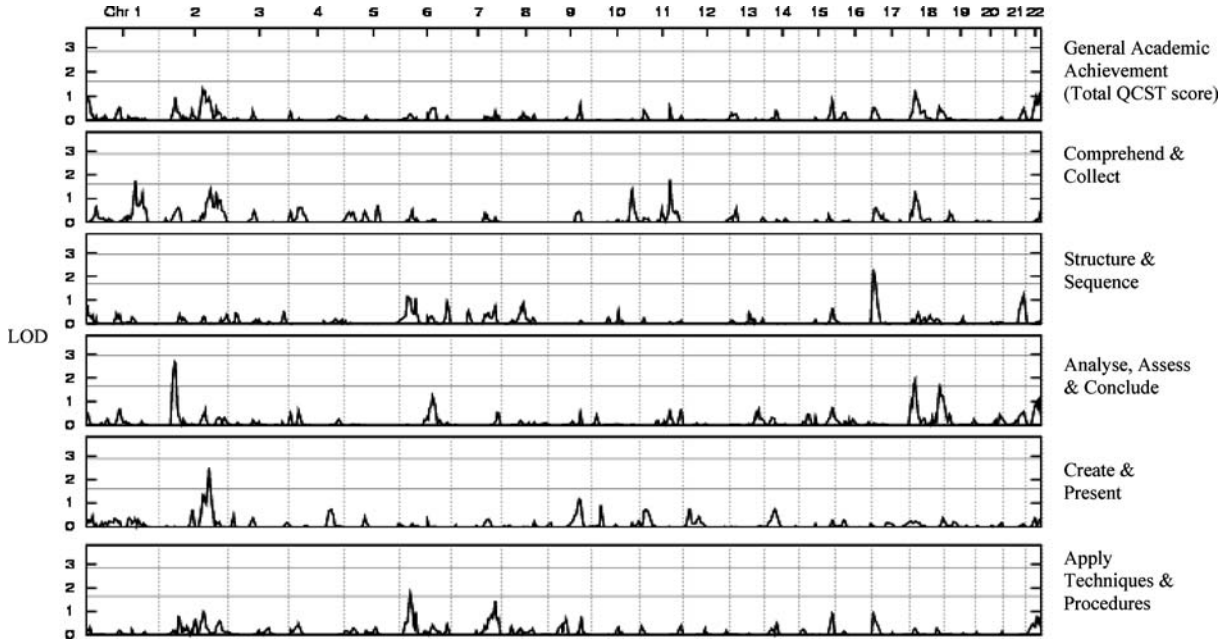

Fig. 1. Linkage plots with genetic distances in Kosambi units displaying LOD scores for general academic achievement and the five specific academic achievement skills for chromosomes 1 to 22. Negative LOD scores are not shown. The horizontal bars indicate empirically derived LOD cut-offs for significance and suggestiveness. The peaks on chromosome 2 for general academic achievement, Comprehend & Collect, Create & Present, and Apply Techniques & Procedures span a region between D2S142 and D2S117. Peaks on chromosome 18 for general academic achievement, Comprehend & Collect, and Analyse Assess & Conclude span a region between D18S63 and D18S452.

ping peaks among general academic achievement and specific academic skills scores in a region spanning approximately 30 cM between D2S142 and D2S117, were observed for Comprehend & Collect (LOD = 1.37 at D2S117), Create & Present (suggestive LOD = 2.51 at D2S1391), and Apply Techniques & Procedures (LOD = 0.97 at D2S1353). Overlapping peaks on chromosome 18 (at D18S976) were evident for Analyse, Assess & Conclude (suggestive LOD = 1.9) and Comprehend & Collect (LOD = 1.32). In addition, peaks which met empirical suggestive criteria were observed for Comprehend & Collect on chromosome 1 (LOD_{max} = 1.75 at D1S518 and chromosome 11 (LOD_{max} = 1.80 at D11S1391), for Structure & Sequence on chromosome 17 (LOD_{max} of 2.30 at D17S849), for Analyse, Assess & Conclude on chromosome 2 (LOD_{max} = 2.66 at D2S367), and for Apply Techniques & Procedures on chromosome 6 (LOD_{max} = 1.77 at D6S289). Table I shows LOD scores above 1.5.

DISCUSSION

The highest obtained LODs of 1.26 and 1.25 for general academic achievement on chromosomes 2 and 18 did not meet empirically derived significance levels for suggestiveness. However, the region on chromosome 2 for which a peak LOD was observed is consistent with the linkage finding for IQ from our laboratory (with the present sample being a subsample of that used in the IQ study) (Luciano *et al*., this issue), and importantly, with an independent sample from the Netherlands, as well as for the combined Australian and Dutch data (Posthuma *et al*., 2005).

The peaks on chromosome 2 reported by Posthuma *et al*. (2005), which are coincident with our peak for general academic achievement, were for FSIQ and PIQ. Interestingly, PIQ shows a lower phenotypic correlation with general academic achievement than VIQ (Wainwright *et al*., 2005a), and an overlap between general academic achievement and VIQ may be more expected. In line with this, Luciano and colleagues (this issue) do report significant linkage in this region for the CCRT (Nelson, 1982), a proxy measure of vocabulary which is more strongly correlated with VIQ than PIQ (Wainwright *et al*., 2004), in addition to peaks for FSIQ, PIQ (and PIQ subtests). Importantly, general academic achievement as indexed by total QCST score incorporates assessment of verbal skills not typically measured by IQ tests (e.g., comprehension of prose, essay writing) as well as mathematical problem solving (not captured by PIQ), with PIQ indexing fluid spatial abilities. As such, the results here dovetail neatly with those of Posthuma *et al*. (2005) and Luciano and colleagues (this issue) to reflect influence from chromosome 2 on a breadth of indicators of general cognitive ability. Specific genes potentially implicated in these effects have been discussed by (Posthuma et al., 2005) and Luciano *et al*. (this issue).

In addition to general academic achievement, linkage results are presented for the five specific academic achievement skills indicating how these constituent measures are implicated in linkage. We note a generalised inconsistency of peak locations among the five specific achievement skills measures, although reasonable consistency is evident on chromosome 2, and to a lesser extent on chromosome 18. However, as phenotypic correlations range from 0.56 to 0.80 among these measures (Wainwright *et al*., 2005b) this means that between 36% and 69% of variation in the specific academic achievement skills is unexplained by covariation and thus not attributable

Table I. LOD Scores Greater than 1.50 for Each of the Specific Academic Achievement Scores. Where Multiple Adjacent Peaks with LODs >1.5 Occur, only the Peak with the Highest LOD is Shown

Chromosome	Kosambi distance	Region	Academic Skill	LOD
1	188.02	D1S518	CC	1.75
2	57.89	D2S367	AAC	2.66
2	189.15	D2S1391	CP	2.51
6	34.61	D6S289	ATP	1.77
11	109.66	D11S1391	CC	1.80
17	0.63	D17S849	SS	2.30
18	16.16	D18S976	AAC	1.90
18	110.57	D18S1371	AAC	1.63

Note: No LOD scores >1.50 were obtained for Total QCST score. CC = Comprehend & Collect, SS = Structure & Sequence, AAC = Analyse, Assess & Conclude, CP = Create & Present, ATP = Apply Techniques & Procedures.

to shared genetic influences. Also, Carey (1992) has demonstrated that while genetic correlations may indicate genes in common it is also possible that high genetic correlations may be observed despite limited pleiotropic influences, which implies that linkage peaks need not overlap despite substantial genetic correlations.

Not surprisingly, the two strongest LOD scores for general academic achievement which are observed on chromosomes 2 and 18 are in regions where peaks are overlapping for at least two of the more specific achievement skills measures. As can be seen, stronger and weaker linkage signals for specific skills tend to average out for general achievement. Presumably, the general academic achievement measure incorporating information from multiple indicators is a more reliable measure and thus provides a more reliable linkage signal.

The peak on chromosome 18 for general academic ability occurs in a region that has been implicated in myopia (Young *et al*., 2001) which has been suggested to share pleiotropic influences with general cognitive ability (Jensen, 1998). Also Fisher *et al*. (2002) reported evidence of genes implicated in dyslexia at a locus (D18S53) approximately 20 cM from the peak observed here on chromosome 18. Interestingly, Luciano *et al*. (this issue) show peaks (not suggestive) in this region for the Information and Vocabulary subtests of the MAB. However, a strong signal was not observed for VIQ or FSIQ. At present we suggest that the results for chromosome 18 are not sufficiently strong of themselves, or buttressed adequately by other studies to clearly implicate this region in variation in general academic achievement.

In the Posthuma *et al*. (2005) and Luciano *et al*. (this issue) studies evidence for linkage was also reported on chromosome 6 in a region spanning D6S942 to D6S422 for FSIQ and VIQ. Luciano and colleagues (this issue) also report a peak particular to arithmetic in this region. No evidence of linkage is observed in this region for general academic achievement. However, suggestive linkage is evident for the Apply Techniques & Procedures skill which particularly assesses mathematical problem solving. This region does appear to be pertinent to variation in cognitive abilities as it has also been consistently implicated in reading achievement (e.g., Cardon *et al*., 1994; Deffenbacher *et al*., 2004; Gayán *et al*., 1999), and for a composite quantitative trait (reflecting general cognitive ability) that was used to index neurocognitive deficits among patients with schizophrenia (or schizophrenia spectrum disorders) and their first degree relatives (Hallmayer *et al*., 2003).

Other suggestive peaks were observed on chromosomes 1, 11, and 17 for particular academic achie-vement skills measures. However, these did not correspond with notable LODs for general academic achievement, and there was a general lack of correspondence for these peaks across the different academic achievement skills measures suggesting that they may not be meaningfully interpreted. Nevertheless, should subsequent research implicate regions on these chromosomes consistent with peaks observed here, we note that the regions on chromosomes 1 and 17 have been implicated in neural development and brain size (Bond *et al*., 2002; Ledbetter *et al*., 1992).

In conclusion, consistent with studies showing strong genetic correlations between academic achievement and IQ measures, our findings suggest that there is commonality among genes implicated in variation in general academic achievement and IQ measures. The results are of additional interest because, while strongly indexing general ability, the QCST uses items not typically found in IQ tests (eg., interpretation of graphs, cartoons, and poetry, comprehension of prose, and written expression) and lends further weight to the notion that genes on chromosome 2 have pervasive influence across cognitive tasks.

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