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Variation in the dysbindin gene and normal cognitive function in three independent population samples

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The association between *DTNBP1* genotype and cognitive abilities was investigated in three population samples (1054 Scottish, 1806 Australian and 745 English) of varying age. There was evidence in each of the cohorts for association ($P < 0.05$) to single nucleotide polymorphisms (SNPs) and haplotypes previously shown to relate to cognition. By comparison with previous findings, these associations included measures of memory, and there was at best equivocal evidence of association with general cognitive ability. Of the SNPs typed in all three cohorts, rs2619528 and rs1011313 showed significant association with measures of executive function in two cohorts, rs1018381 showed significant association with verbal ability in one cohort and rs2619522 showed significance/marginal significance with tests of memory, speed and executive function in two cohorts. For all these SNPs, the direction and magnitude of the allelic effects were consistent between cohorts and with previous findings. In the English cohort, a previously untested SNP (rs742105) located in a distinct haplotype block upstream of the other SNPs showed the strongest significance ($P < 0.01$) for measures of memory but weaker significance for general cognitive ability. Our results therefore support involvement of the dysbindin gene in cognitive function, but further work is needed to clarify the specific functional variants involved and the cognitive abilities with which they are associated.

Keywords: Cognitive ability, *DTNBP1*, haplotypes, memory, normal population

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Dysbindin-1 (*DTNBP1*) is a gene expressed in neurons in varying regions of the brain (e.g. frontal cortex, temporal cortex and midbrain; Weickert *et al.* 2004) but predominantly in mossy fibre synaptic terminals in the cerebellum and hippocampus (Benson *et al.* 2001). *DTNBP1* encodes dystrobrevin-binding protein, which binds to β-dystrobrevin and potentially forms part of the dystrophin protein complex occurring in postsynaptic densities and other brain regions, therefore being important for neuromuscular synapse formation and maintenance (Straub *et al.* 2002). A role for *DTNBP1* in cognition was supported following fine mapping of a region at 6p24-22 linked to schizophrenia (Maziade *et al.* 1997) that identified several variants within *DTNBP1* to be associated with schizophrenia risk (van den Oord *et al.* 2003) and later replicated in several diverse populations (Funke *et al.* 2004; Tang *et al.* 2003). Additional studies suggested that 6p24 was linked to a schizophrenia subtype characterized by pervasive neurocognitive deficit (Hallmayer *et al.* 2005), and Williams *et al.* (2004) found that a haplotype protective against schizophrenia was associated with higher educational achievement among schizophrenic patients. Independent linkage studies of intelligence in normal samples had found significant linkage in the 6p region (between 23.75 and 42.83 cM; Luciano *et al.* 2006; Posthuma *et al.* 2005), suggesting that association of *DTNBP1* in schizophrenia may be related to cognition in the normal population.

Burdick et al. (2006) tested whether *DTNBP1* was related to general cognitive ability, examining associations of *DTNBP1* in samples of patients with schizophrenia or schizoaffective disorder and healthy volunteers. They extracted the common variance from a battery of neuropsychological tests including Wide Range Achievement Test Reading Subtest, Digit Span, Continuous Performance Test-Identical Pairs Version, California Verbal Learning Test, Controlled Oral Word Association Test and Trail Making Tests A and B. This factor was associated with a six-locus haplotype previously shown to be associated with increased schizophrenia risk (Funke *et al.* 2004) and which overlapped with other reported risk haplotypes (van den Oord *et al.* 2003; Straub *et al.* 2002; Tang *et al.* 2003), explaining 3.3% of variance in general cognitive ability in the healthy volunteers; its tagging single nucleotide polymorphism (SNP) rs1018381 was also associated with cognitive ability, although the other individual SNPs were not. Five of these SNPs plus one other identified by Williams *et al.*

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(2004) as a schizophrenia risk allele were tested for their association with Wechsler Adult Intelligence Scale (WAIS) IQ (Zinkstok *et al.* 2007). In the three groups of participants (patients, siblings and controls), three of the SNPs were associated with full-scale IQ, two with verbal IQ and two with performance IQ. A model including only rs760761 captured as much variance in IQ as a model with all SNPs. In another study, which looked at the *DTNBP1* schizophrenia risk haplotype identified by Williams *et al.* (2004), measures of spatial working memory but not attention were associated with the haplotype in a sample diagnosed with schizophrenia or schizoaffective disorder (Donohoe *et al.* 2007).

While there is mounting evidence for involvement of *DTNBP1* in cognition, the studies to date have focused on neuropsychological testing of schizophrenic patients and controls. Additionally, the specific SNP and haplotype relationship to cognition remains unclear. In this paper, three independent cohorts measured on a battery of well-validated cognitive tasks were genotyped on a minimum of five SNPs in the *DTNBP1* gene and tested for their association with individual SNPs and previously identified haplotypes.

Methods

Sample

Scottish cohort

The Lothian Birth Cohort 1936 (LBC1936) comprises 1091 participants of the Scottish Mental Survey 1947 who undertook medical and cognitive testing at the age of 70 years. All participants were Scottish, lived independently in the community and gave written, informed consent before their participation. Ethics permission for the study protocol was obtained from the Multi-Centre Research Ethics Committee and from Lothian Research Ethics Committee. See Deary *et al.* (2007) for full details on participant recruitment and testing schedules. The analysis excluded 13 participants identified as having potential dementia (a score <24 on the Mini-Mental State Examination (MMSE; Folstein *et al.* 1975), one who reported a history of dementia, and another who had incomplete test data. A further 22 individuals did not have any *DTNBP1* genotype data because of the lack of a good quality DNA sample ($n = 13$) or failed genotyping ($n = 9$). The final sample for analysis included 527 women and 527 men, with a mean age of 69.6 $\pm$ 0.8 years.

Australian cohort

This cohort comprised adolescent twins and their non-twin siblings from Brisbane and surrounding regions who were initially recruited as part of ongoing studies of melanoma risk factors and cognition (McGregor *et al.* 1999; Wright *et al.* 2001). Families comprised up to five siblings (including twins) and were 98% Caucasian, predominantly Anglo-Celtic (~82%). Ethical approval for this study was received from the Human Research Ethics Committee of the Queensland Institute of Medical Research. Written informed consent was obtained from each participant and their parent/guardian (if younger than 18 years) prior to phenotype and blood collection. The sample included 1806 individuals (49.1% male) from 878 families. Of the 350 monozygotic (MZ) families, there were 229 with memory data, 266 with IQ data (145 overlapped) and 136 of these families had at least one additional non-twin sibling tested on memory or IQ measures. Of the 546 dizygotic (DZ) families, there were 417 paired twins and 62 unpaired twins with memory data (193 families had at least one additional sibling), and 360 paired twins and 32 unpaired twins with IQ data (91 with at least one sibling). A further 17 families comprised non-twin individuals (3 of these formed sibling pairs) mostly measured on memory. There was 60% overlap between the memory and the IQ DZ samples. The age range of the sample when tested on memory measures was 12–28 years, with a mean age of 19.1 $\pm$ 3.6 years, and for IQ measures was 15–22 years (mean age 16.2 $\pm$ 0.4 years for twins and 17.4 $\pm$ 1.13 years for siblings).

English cohort

The 745 Caucasian volunteers involved in this study form part of the Dyne Steele DNA bank for cognitive genetic studies and comprise 224 males and 521 females. The age range was 41–85 years, with the mean age being 63.1 ($\pm$6.4) years at wave 1 (W1) and 64.9 ($\pm$6.1) years at wave 2 (W2). At the beginning of the study, all volunteers achieved the maximum score on the MMSE. Recruitment and sample composition details are described elsewhere (Rabbitt *et al.* 2004). Volunteers gave written consent for the use of their DNA. Genetics work for the cohort is approved by University of Manchester Research Ethics Committee and Salford and Trafford Local Research Ethics Committee.

Cognitive tests

Scottish cohort

Full details of all cognitive tasks are given in a free-access LBC1936 protocol article (Deary *et al.* 2007). In brief, the MMSE was used to screen for possible dementia (Folstein *et al.* 1975). *General Cognitive Ability* was measured by the Moray House Test No 12 when participants were aged 11 years in the Scottish Mental Survey of 1947 (Scottish Council for Research in Education 1949). It was re-administered in this sample at a mean age of almost 70 years, using the same instructions and the same 45-min time limit. A general cognitive ability factor (*g*) was derived from a principal components analysis of five WAIS-III ^{UK} subtests and Digit Span from the WMS-III ^{UK} (Wechsler 1998). Regression scores were calculated for the first unrotated principal component (explaining 51% of variance) using SPSS 14.0 (SPSS 2005). At the age of 70 years, *Verbal Declarative Memory* was assessed by Logical Memory I (immediate) and II (delayed) and Verbal Paired Associates and *Spatial Memory* by Spatial span forward and backward (WMS-III ^{UK}). A general memory factor (accounting for 46% of variance) was similarly derived for the memory measures from the WMS-III ^{UK}. *Working Memory* was assessed by Letter-Number Sequencing and Backward digit span (WAIS-III ^{UK}). *Fluid-Spatial Ability* was tested by Matrix reasoning and Block design (WAIS-III ^{UK}) and *Processing Speed* by Digit symbol coding and Symbol search (WAIS-III^{UK}). The Verbal Fluency test provided a measure of *executive function* (Lezak 2004). *Verbal Ability* was tested by the National Adult Reading Test (NART; Nelson & Willison, 1991).

The Scottish cohort had the closest range of tests to those used by Burdick *et al.* (2006); therefore, a *g* factor (termed neuropsychological *g*) was derived from the following tests using principal components analysis: Verbal Fluency, NART, Digit Symbol, Digit Span, Verbal Paired Associates and Symbol Search; it (the first unrotated principal component) explained 45% of variance.

Australian cohort

IQ data were collected in the laboratory using the shortened version of the Multidimensional Aptitude Battery (Jackson 1984, 1998), which taps verbal ability (Information, Arithmetic, Vocabulary subtests; Verbal IQ scaled score) and fluid-spatial ability (Spatial, Object Assembly subtests; Performance IQ scaled score). Additional tests of verbal ability included the Cambridge Contextual Reading Test (Beardsall 1998; Nelson & Willison 1991) and the Schonell Graded Reading Test (Schonell & Schonell 1960) as described in Wainwright *et al.* (2004). Full IQ represented the measure of general cognitive ability. Measures of full-scale IQ and *g* have been shown to be strongly correlated (~0.90) in previous research (Jensen 1998). Processing speed was measured by the Digit Symbol subtest (WAIS-R, Wechsler 1981). An overlapping study of language collected relevant measures of immediate memory (Digits Forward) and working memory using the Digits-Backward and Letter-Number Sequencing subtests of the WAIS-III. These measures were available for most of those tested on the IQ battery plus additional younger participants. All variables with the exception of the Schonell reading test – transformed by a reverse, logarithmic function – were normally distributed.

English cohort

Two waves of testing were completed. At W1, tests of general cognitive ability comprised the Alice Heim 4 intelligence tests parts one and two (Heim 1970), and verbal ability tests included the Mill Hill Vocabulary A and B (Raven 1965). One verbal declarative memory measure (Cumulative Recall) was ascertained. The Cumulative recall test comprises of 15 six-letter nouns that are flashed one at a time on a screen at 2-second intervals. The volunteers must write down as many words as they can remember in any order. This is repeated four consecutive times using the same words in the same order. At W2, processing speed was assessed using the Random Letters test, and further tests of verbal declarative memory were administered: semantic memory, immediate verbal recall and delayed verbal recall. A general memory factor was derived from these three memory measures and accounted for 67% of variance. The Cattell Culture Fair test measured *fluid ability* (Rabbitt *et al.* 2004). General cognitive ability factors were extracted, using principal components analysis, from the tests at W1 (explaining 61% of variance) and the tests at W2 (44%), with the regression factor scores used as a measure of *g* (as previously described). Detailed information on the cognitive tests is described elsewhere (Rabbitt *et al.* 2004).

Genotyping

In all cohorts, genomic DNA was isolated from whole blood. Table 1a shows the SNPs investigated in the previous studies of cognition and the present cohorts.

In the Australian cohort, blood was also taken from at least one parent (82%) for blood grouping and DNA extraction, and zygosity of same-sex twins was diagnosed using nine polymorphic DNA microsatellite markers (AmpF1STR Profiler Plus Amplification Kit, ABI, Foster City, CA, USA) and three blood groups (ABO, MNS and Rh), giving a probability of correct assignment greater than 99.99%.

In the Scottish and Australian cohorts, the seven SNPs tested by Burdick *et al.* (2006) were genotyped: rs909706, rs1018381, rs2619522, rs760761, rs2619528, rs3213207 and rs1011313. However, in the Australian cohort, two SNPs (rs760761 and rs3213207) failed genotyping quality controls. The English cohort was typed on the Burdick SNPs (excluding rs909706) plus two SNPs (rs2619539 and rs2619538) tested by Zinkstok *et al.* (2007) and Donohoe *et al.* (2007) and three additional SNPs (rs1047631, rs17470454 and rs742105) to broaden coverage of the 3′ region of the gene.

In the Scottish cohort, the markers were genotyped using a competitive allele specific polymerase chain reaction system (KASPar) by KBiosciences, Herts, UK. In both the Australian and the English cohorts, multiplexing SNP assays were designed using SEQUENOM ASSAY DESIGN software (version 3.0; Sequenom Inc., San Diego, CA, USA). Genotyping was based on Sequenom MassARRAY technology and was carried out in standard 384-well plates with 12.5 ng of genomic DNA used per sample for the Australian cohort and 15 ng of DNA for the English cohort.

Statistical analysis

Association tests were performed for individual SNPs in PLINK (Purcell *et al.* 2007) using the Qfam (total) option for the Australian family data and the regression option for the Scottish and English cohorts. Sex was modelled as a fixed factor and age as a covariate in the Scottish and English cohorts because IQ scores (which are normalized for age) were not used for these cohorts. Sex residualized scores were used in the Australian analyses because the Qfam procedure does not allow modelling of covariates. The 6-SNP haplotype investigated by Burdick *et al.* (2006) was tested in the Scottish LBC1936 cohort, and the 3-SNP haplotype found by Donohoe *et al.* (2007) was tested in the English cohort, both using the PLINK conditional haplotyping function as a specific risk haplotype had already been reported. The statistical power to detect a genetic effect size of 1% (for minor allele frequencies of 0.25) in each of our cohorts was as follows: 91.2% in the Scottish cohort, 97.9% (for total association) in the Australian cohort and 78% in the English cohort. Our power is even greater to detect an effect size of the magnitude (~3%) previously reported, with 100% power in each of the cohorts (Purcell *et al.* 2003). We report a nominal level of two-tailed probability despite there being prior evidence of a directional effect. Alpha-level corrections were calculated by taking into account interdependence of SNPs and cognitive traits for each cohort. Nyholt's (2004) MATSPD program indicated that there were 5, 4 and 10 independent SNPs in the respective Scottish, Australian and English cohorts. An orthogonal principal components analysis of the individual cognitive tests (not including composite or factor scores that are linear combinations of

Table 1: (1a) SNPs typed in the previous *DTNBP1* studies of cognition and in the present study. (1b) Comparison of associated cognitive domain with *DTNBP1* SNPs across the cohorts in the present study

	(1a) Previous studies			Present study			(1b) Present study associations†		
	Burdick *et al.* (2006)	Zinkstok *et al.* (2007)	Donohoe *et al.* (2007)*	Scottish	Australian	English	Scottish	Australian	English
rs1047631						✓			FA
rs17470454						✓			—
rs742105						✓			VDM, GA
rs909706	✓			✓	✓		EF	—	
rs1018381	✓			✓	✓	✓	—	VA	—
rs2619522	✓	✓		✓	✓	✓	VDM, PS	—	PS
rs760761	✓			✓		✓	—		PS
rs2619528	✓	✓		✓	✓	✓	PS	—	PS
rs3213207	✓	✓	✓	✓		✓	—		PS
rs1011313	✓	✓		✓	✓	✓	WM, EF	FD	—
rs2619539		✓	✓			✓			VDM, VA
rs2619538		✓	✓			✓			—

FA, Fluid Ability; FD, Freedom from Distractibility; EF, Executive Function; GA, General Ability; PS, Processing Speed; VA, Verbal Ability; VDM, Verbal Declarative Memory; WM, Working Memory; —, no significant associations.

*Only the haplotype was tested.

†Significant at a nominal alpha level of 0.05.

the individual tests) in each cohort showed that there were three independent cognitive factors – this value was multiplied by the number of independent SNPs to arrive at the overall number of independent tests in each cohort. Bonferroni adjusted one-tailed significance levels of 0.007, 0.008 and 0.003 were estimated for the respective Scottish, Australian and English cohorts.

Results

The *DTNBP1* allele frequencies across the samples are shown in Table 2. An exact test of Hardy–Weinberg equilibrium (HWE) performed in PLINK (Purcell *et al.* 2007) confirmed that in each cohort the SNPs were all in HWE. The linkage disequilibrium (LD) structure of the SNPs typed in the English cohort (i.e. with the largest number of SNPs typed) is presented in Fig. 1; note that the other cohorts showed very similar values of r^2 between SNPs. For the LBC1936, most of the markers were in low-to-moderate LD (r^2 of 0–0.45); rs2619528, rs760761 and rs2619522 displayed r^2 ranging from 0.90 to 0.95 with each other and encompassed rs1018381 in a haplotype block spanning 7 kb. In the English cohort, the same haplotype block was observed with the three SNPs in strongest LD showing r^2 ranging from 0.97 to 1. In the Australian cohort, rs2619528 and rs2619522 showed an r^2 of 0.99, while the other SNPs were in low-to-moderate LD with each other (r^2 of 0–0.37). In the English cohort, a further haplotype block was defined by markers rs17470454, rs742105, rs2619539 and rs3213207 (spanning 104 kb), with the strongest LD (r^2 of 0.91) between rs742105 and rs2619539. The other SNPs showed low-to-moderate LD with each other (r^2 of 0–0.59).

Data were normally distributed for all cognitive variables, and outliers – scores exceeding ± 3 z scores – were removed from analysis. The association results of the individual SNPs in the Scottish, Australian and English cohorts are shown in respective Tables 3, 4 and 5, and a comparison of individual SNP results across cohorts can be found in Table 1b. Of the individual SNPs tested by Zinkstok *et al.* (2007) – two of which (rs760761 and rs2619522) were in Burdick *et al.*'s study – we observed the following associations. Marker rs760761 was significant for Random Letters in the English cohort; consistent with Zinkstok *et al.*'s (2007) finding of higher full-scale IQs for CC homozygotes; C was the increaser allele in both. Marker rs2619522 was significant for Random Letters in the English cohort and marginally significant ($P = 0.05$) for Symbol Search and Logical Memory Immediate in the Scottish cohort; the minor allele decreased performance in both cohorts being consistent with Zinkstok *et al.*'s (2007) report. Marker rs1011313 was significantly associated with Verbal Fluency and Letter-Number Sequencing in the Scottish cohort and with Digits Forward in the Australian cohort (minor allele conferred worse performance in both cohorts). Marker rs2619528 was associated with Symbol Search and marginally associated with Logical Memory Immediate in the Scottish cohort; in the English cohort, it was associated with Random Letters (minor allele decreased performance in both cohorts). In the English cohort, rs3213207 was associated with Random Letters with the minor allele conferring worse performance. Marker rs2619539 (only tested in the English cohort) was associated with Mill Hill A, where the minor allele related to higher verbal ability scores.

The Burdick *et al.*'s (2006) 6-SNP haplotype was tested for association with the cognitive measures in the Scottish cohort (Table 3); the risk haplotype contributed to variance in Logical Memory Immediate ($P = 0.03$). Interestingly, marker rs1018381, which tags the Burdick *et al.* (2006) risk haplotype, approached significance ($P = 0.057$) for this same cognitive measure, with the direction of effect consistent with the risk haplotype. This tagging SNP was not associated with any of the cognitive measures in the English cohort, but in the Australian cohort was associated with the NART ($P = 0.04$) and approached significance for the Schonell ($P = 0.054$), the direction of the effect being consistent with the Scottish cohort. In the English cohort, the Donohoe *et al.*'s (2007) 3-SNP haplotype was strongly associated with Mill Hill A (W1; $P = 0.0006$) and more weakly associated ($P < 0.05$) with Random Letters (W2) and the *g* factor (W1);

Table 2: SNP marker descriptive information, including genetic map position, gene location and minor allele frequency

			Allele		Minor allele frequency		
SNP ID	Position*	Gene location	Major	Minor	Scottish	Australian	English
rs1047631	15631080	UTR	A	G	—	—	0.15
rs17470454	15631427	Exon (Ser272Pro)	G	A	—	—	0.05
rs742105	15681053	Intron	C	T	—	—	0.47
rs2619539	15728834	Intron	G	C	—	—	0.46
rs3213207	15736081	Intron	A	G	0.20	—	0.21
rs1011313	15741411	Intron	G	A	0.09	0.10	0.09
rs2619528	15757808	Intron	G	A	0.20	0.19	0.21
rs760761	15759111	Intron	C	T	0.20	—	0.22
rs2619522	15761628	Intron	T	G	0.20	0.19	0.21
rs1018381	15765049	Intron	C	T	0.09	0.08	0.09
rs909706	15768850	Intron	G	A	0.39	0.37	—
rs2619538	15773188	5′ flanking region	T	A	—	—	0.42

*SNP position on NCBI Build 35.1.

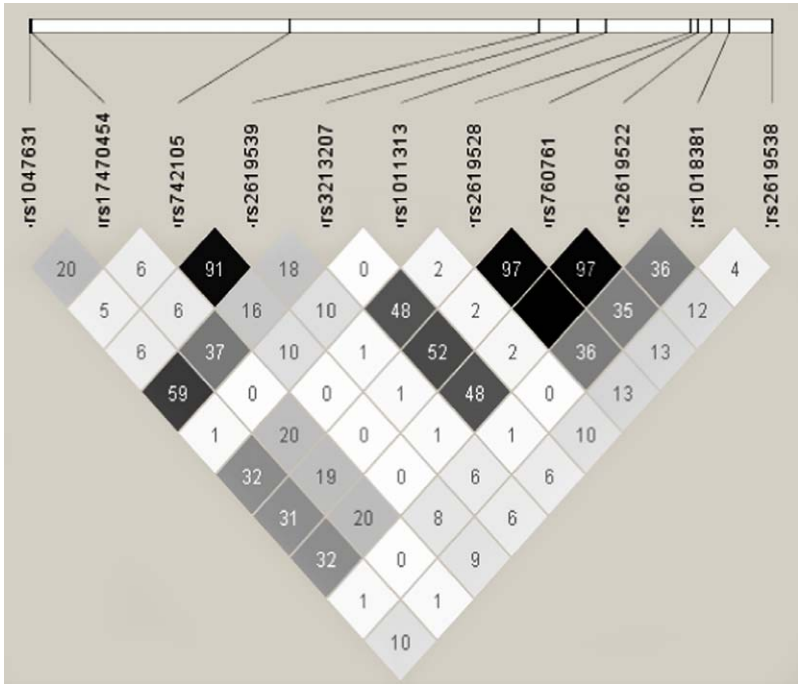

Figure 1: Linkage disequilibrium (r^2) among the *DTNBP1* SNPs genotyped in the English cohort. The only other SNP typed in the Scottish and Australian cohorts, but not shown here, is rs909706 that demonstrated low r^2 (ranging between 0.05 and 0.16) with the other SNPs.

however, the originally reported risk haplotype was associated with better performance on these tests.

An additional two *DTNBP1* SNPs typed in the English cohort but not previously investigated showed significant association with several W2 phenotypes: rs1047631 with the Cattell Culture Fair measure of general ability and rs742105 with Immediate Recall and with both the *g* factor and memory factor, as well as with cumulative recall (W1).

While not meeting the Bonferroni adjusted level of significance, the following markers and measures provided the best evidence for association: rs1011313 with Verbal Fluency ($P = 0.018$; Scottish cohort) and Digits Forward (Australian cohort), rs742105 with Cumulative recall ($P = 0.008$) and Immediate recall ($P = 0.0096$) in the English cohort and the Donohoe *et al.*'s (2007) haplotype with Mill Hill A in the English cohort ($P = 0.00062$). The amount of variance explained by rs1011313 was 0.49% and 0.04% for the respective Verbal Fluency and Digits Forward measures. Marker rs742105 explained 1% of variance in both Cumulative recall and Immediate recall, while the Donohoe *et al.*'s (2007) haplotype explained 2% of variance in Mill Hill A. But note that these estimates of variance are not unbiased as they are dependent on sample size.

Discussion

In three independent cohorts, there was indication of association between cognitive abilities and *DTNBP1* SNPs and haplotypes previously implicated in cognition. Associations differed across study population and cognitive measure but were generally observed for memory traits in the two older cohorts, with additional associations for general ability, that is rs1047631 and rs742105. Previous findings were based on smaller samples ranging from 31 to 126 healthy participants and did not have as diverse range of cognitive tasks as those sampled in this study. In this study, associations were tested for significance at the more conservative two-tailed probability level despite there being prior evidence for directional effects. However, when corrections for multiple testing were applied, only one haplotype remained significantly associated with varied traits. Our findings mostly suggest that *DTNBP1* effects are present in old age and may have their strongest effect on memory and executive function traits.

The original finding linking a 6-SNP *DTNBP1* haplotype with general cognitive ability was supported in schizophrenic patients and a healthy sample in which only 15 individuals carried the risk haplotype (Burdick *et al.* 2006). This haplotype was tested in the Scottish cohort and was significant only for the Logical Memory Immediate phenotype. The tagging SNP (rs1018381) for this haplotype was tested in each of our cohorts and approached significance ($P = 0.06$) for Logical Memory Immediate in the Scottish cohort. In the Australian cohort, this SNP was significantly associated with the NART, a reading test that is strongly correlated with IQ, and approached significance for the Schonell, a similar test of verbal ability. In terms of replicating the original finding, our results confirmed an association of this haplotype with general cognitive ability (as measured by the NART) in the Australian cohort. Verbal declarative memory – an ability that contributed to Burdick's general cognitive ability factor – was associated with this haplotype in the Scottish cohort, and the direction of the effect was the same in our samples. In the English cohort, individuals carrying the rs1018381 minor T allele scored less in the great majority of cognitive tasks, including general cognitive ability and verbal declarative memory. However, the trends did not reach significance, and the reason for the lack of

Table 3: Association results (coefficient *t*-statistic, *P* value) for the seven SNPs typed in the *DTNBP1* gene in the Scottish cohort

	rs3213207	rs1011313	rs2619528	rs760761	rs2619522	rs1018381	rs909706	Burdick's haplotype
Verbal Declarative Memory								
Logical Memory Immediate	−0.16 (0.87)	−0.68 (0.50)	−1.63 (0.10)	−1.84 (0.07)	−1.96 (0.05)	−1.91 (0.06)	0.46 (0.65)	$F_{1,1022} = 4.55$ **(0.03)**
Logical Memory Delayed	−0.49 (0.62)	1.29 (0.20)	0.85 (0.39)	0.72 (0.47)	0.93 (0.35)	1.53 (0.13)	0.82 (0.41)	$F_{1,1023} = 0.69$ (0.41)
Spatial Memory								
Spatial Span Backward	0.34 (0.73)	−1.92 (0.05)	−5.68 (0.79)	0.66 (0.51)	0.09 (0.93)	−0.21 (0.84)	−1.06 (0.29)	$F_{1,1019} = 0.14$ (0.71)
Working Memory								
Letter-Number Sequencing	0.28 (0.78)	−2.14 **(0.03)**	0.94 (0.35)	0.79 (0.43)	0.80 (0.42)	0.91 (0.36)	−0.52 (0.60)	$F_{1,1014} = 0.77$ (0.38)
Executive Function								
Verbal Fluency	0.65 (0.51)	−2.36 **(0.02)**	0.69 (0.49)	0.85 (0.39)	0.52 (0.60)	1.00 (0.32)	−2.25 **(0.02)**	$F_{1,1019} = 1.24$ (0.27)
Processing Speed								
Symbol Search	−0.67 (0.51)	−0.68 (0.49)	−2.28 **(0.02)**	−1.86 (0.06)	−1.93 (0.05)	−1.71 (0.09)	0.45 (0.65)	$F_{1,1017} = 3.29$ (0.07)

Burdick *et al.* (2006) tagging SNP is rs1018381. Eleven variables [including the general cognitive ability (*g*) factor] showing non-significant results for all SNPs ($P > 0.15$) have been omitted. Significant associations at a nominal alpha level of 0.05 are in bold.

Table 4: Association results (pointwise empirical *P* values) for the five SNPs typed in the *DTNBP1* gene in the Australian cohort

	rs1011313	rs2619528	rs2619522	rs1018381	rs909706
Freedom from Distractibility					
Digits Forward	**0.02**	0.96	0.98	0.53	0.60
Fluid Ability					
Spatial	0.11	0.56	0.65	0.57	0.88
Object Assembly	0.21	0.12	0.14	0.26	0.65
Performance IQ	0.09	0.42	0.49	0.44	0.76
Verbal Ability					
NART	0.91	0.71	0.71	**0.04**	0.16
Schonell	0.59	0.43	0.46	0.05	0.61
Information	0.08	0.81	0.83	0.29	0.83
General Ability					
Full IQ	0.10	0.57	0.65	0.39	0.53

Burdick *et al.* (2006) tagging SNP is rs1018381. Test statistic not reported because Qfam procedure uses permutation tests to correct for family structure. Seven variables showing non-significant results for all SNPs ($P > 0.15$) have been omitted. Significant associations at a nominal alpha level of 0.05 are in bold.

association in the English cohort is unclear. The only apparent difference between the English cohort and the two others was its larger age range, so that any moderation of the gene by age might obscure the effect in this sample.

Burdick *et al.* (2006) did not observe association between general cognitive ability with individual SNPs forming their haplotype (with the exception of the tagging SNP). In contrast, Zinkstok *et al.* (2007) reported association between full-scale IQ and three individual SNPs (two of which had been tested by Burdick *et al.*) in 31 control participants. In our much larger study, these two SNPs were significantly associated with Random Letters in the English cohort. For both SNPs, the direction of the effect was consistent with Zinkstok *et al.*'s (2007) report. We also found association with executive and speed tasks – including Verbal Fluency, Letter-Number Sequence, Symbol Search and Random Letters – and some of the non-significant SNPs from Zinstock *et al.*'s study. These SNPs also showed marginal evidence for association with Logical Memory Immediate and Mill Hill A. The fact that Random Letters, Verbal Fluency and Letter-Number Sequencing all rely heavily on central executive function further suggests that *DTNBP1* may be most closely linked with memory and executive tasks rather than to those processes that are common to all cognitive tasks (and hence general ability). Our results differ from Zinkstok *et al.*'s (2007) in that we found little support for association with a general or full-scale IQ factor. Interestingly, the association we did find for general verbal ability (NART) was in the younger Australian cohort, which was of similar age to Zinstock's sample. We predominantly found associations for cognitive abilities more akin to those measured by Burdick *et al.* (2006) and measured in the elderly cohorts. Our finding of association with previously unrelated SNPs by Zinstock *et al.* and Burdick *et al.*

Table 5: Association results (coefficient *t*-statistic, *P* value) for the 11 SNPs typed in the *DTNBP1* gene in the English cohort at W1 and W2

	rs 1047631	rs 17470454	rs742105	rs 2619539	rs 3213207	rs 1011313	rs 2619528	rs 760761	rs 2619522	rs 1018381	rs 2619538	Donohoe haplotype*
Fluid Ability												
Culture Fair (W2)	−2.12 **(0.03)**	0.27 (0.79)	−1.55 (0.12)	−0.09 (0.93)	−1.03 (0.30)	−0.75 (0.45)	−0.22 (0.83)	−0.41 (0.68)	−0.28 (0.78)	0.84 (0.40)	−1.11 (0.27)	$F_{1,703} = 1.39$ (0.24)
Verbal Ability												
Mill Hill A (W1)	−0.04 (0.96)	−0.09 (0.93)	0.70 (0.49)	2.09 **(0.04)**	−0.06 (0.95)	−0.10 (0.92)	−0.60 (0.55)	−0.65 (0.52)	−0.80 (0.42)	−0.81 (0.42)	−0.43 (0.67)	$F_{1,724} = 11.82$ **(<0.001)**
Mill Hill B (W1)	0.22 (0.83)	−0.46 (0.65)	−1.18 (0.24)	0.31 (0.76)	−0.51 (0.61)	0.21 (0.83)	−0.84 (0.40)	−0.89 (0.37)	−1.06 (0.29)	−0.63 (0.53)	−1.25 (0.21)	$F_{1,725} = 2.91$ (0.09)
Verbal Declarative Memory												
Cumulative Recall (W1)	−1.40 (0.16)	−1.46 (0.14)	−2.67 **(0.01)**	−1.43 (0.15)	−1.78 (0.07)	−0.91 (0.36)	−0.83 (0.41)	−0.97 (0.33)	−0.85 (0.39)	0.79 (0.43)	−0.88 (0.38)	$F_{1,692} = 0.67$ (0.41)
Immediate Recall (W2)	−0.20 (0.84)	−0.98 (0.33)	−2.60 **(0.01)**	−1.92 (0.05)	−0.54 (0.59)	−1.30 (0.19)	−0.57 (0.57)	−0.59 (0.55)	−0.46 (0.65)	−0.24 (0.81)	−0.37 (0.71)	$F_{1,695} = 1.71$ (0.19)
Delayed Recall (W2)	−1.18 (0.24)	−0.63 (0.53)	−1.93 (0.05)	−1.14 (0.25)	−1.11 (0.27)	−1.54 (0.12)	−1.16 (0.24)	−1.20 (0.23)	−1.26 (0.21)	−0.46 (0.65)	−0.50 (0.62)	$F_{1,695} = 0.03$ (0.86)
Semantic Memory (W2)	−1.59 (0.11)	−0.42 (0.67)	−1.52 (0.13)	−0.66 (0.51)	−1.21 (0.22)	−1.55 (0.12)	−0.48 (0.63)	−0.56 (0.58)	−0.61 (0.54)	−0.39 (0.69)	−1.06 (0.29)	$F_{1,694} = 0.86$ (0.35)
Memory factor (W2)	−1.03 (0.30)	−0.85 (0.40)	−2.32 **(0.02)**	−1.37 (0.17)	−1.05 (0.29)	−1.79 (0.07)	−0.91 (0.36)	−0.97 (0.33)	−0.95 (0.34)	−0.26 (0.80)	−0.71 (0.48)	$F_{1,692} = 0.01$ (0.90)
Processing Speed												
Random Letters (W2)	−0.86 (0.39)	−0.53 (0.60)	−1.05 (0.29)	0.03 (0.98)	−2.03 **(0.04)**	−0.42 (0.67)	−2.15 **(0.03)**	−2.28 **(0.02)**	−2.14 **(0.03)**	−1.07 (0.29)	−0.39 (0.70)	$F_{1,696} = 4.68$ **(0.03)**
General Ability												
Alice Heim 1 (W1)	−0.75 (0.45)	−0.05 (0.96)	−0.44 (0.66)	0.98 (0.32)	−0.38 (0.70)	−1.15 (0.25)	−0.44 (0.66)	−0.62 (0.54)	−0.36 (0.72)	−0.16 (0.87)	−0.10 (0.92)	$F_{1,728} = 2.82$ (0.09)
Alice Heim 2 (W1)	0.52 (0.60)	0.41 (0.68)	0.44 (0.66)	1.45 (0.15)	−0.13 (0.90)	−0.54 (0.56)	−0.01 (0.99)	−0.31 (0.76)	0 (1)	0.04 (0.96)	−0.56 (0.57)	$F_{1,728} = 3.73$ (0.05)
g factor (W1)	−0.41 (0.68)	0.04 (0.96)	−0.38 (0.70)	1.41 (0.16)	−0.53 (0.59)	−0.73 (0.47)	−0.70 (0.48)	−0.90 (0.37)	−0.80 (0.42)	−0.45 (0.65)	−0.72 (0.47)	$F_{1,688} = 5.67$ **(0.02)**
g factor (W2)	−1.30 (0.19)	−0.42 (0.68)	−2.19 **(0.03)**	−0.83 (0.41)	−1.30 (0.19)	−1.73 (0.08)	−1.13 (0.26)	−1.25 (0.21)	−1.17 (0.24)	−0.35 (0.73)	−0.94 (0.35)	$F_{1,688} = 0.44$ (0.51)

Burdick *et al.* (2006) tagging SNP is rs1018381. Significant associations at a nominal alpha level of 0.05 are in bold.

*rs3213207, rs2619539, rs2619538: risk haplotype ACT.

might be attributed to the increased statistical power in each of our samples.

The 3-SNP haplotype found by Donohoe *et al.* (2007) to be associated with spatial working memory in schizophrenics was tested in the English cohort. At W1, it was associated with Mill Hill A (which withstood the significance correction for multiple testing) and the *g* factor and approached significance for Alice Heim 2 ($P = 0.05$); at W2, it was associated with Random Letters. However, the risk haplotype conferred superior performance in our study. In the original Donohoe *et al.* study, only spatial working memory was associated with this haplotype, but a trend for risk haplotype carriers to perform better on an attentional task was also found. Despite not having measured spatial working memory, our findings are in line with the trend previously reported and suggest that (1) this haplotype is relevant to a wider range of abilities that were not examined in the original report and are generalizeable to a normal population and (2) it has antagonistic pleiotropic effects on diverse cognitive abilities. Most of the associated indices were not measured at W2, so it is difficult to judge how robust these findings are. A study by Bray *et al.* (2005) demonstrated that this haplotype was in phase with a SNP used for allelic expression analysis and that the risk haplotype was associated with significantly reduced *DTNBP1* expression. In light of the functional significance of this haplotype, it is re-assuring that in our study this haplotype showed the most significant (smallest *P* value) association.

An interesting new finding from our study was that rs742105, a marker at the 3′ end of *DTNBP1* and not previously investigated was nominally significant in the English cohort at both W1 (Cumulative recall) and W2 (Immediate recall). It showed lesser significance for the memory and *g* factors at W2 and marginal significance for Delayed recall ($P = 0.05$). As this SNP was not typed in the Scottish or Australian cohorts, it still requires replication in independent samples. Nearby to this marker – and also not previously investigated – is rs1047631, which was associated with the Culture Fair test on W2. A putative microRNA-binding site (hsa-miR377) lies across this marker, so it may be involved in gene regulation.

Our aim was to replicate association with SNPs in *DTNBP1*, and while not all the same SNPs were typed in each of our replicate cohorts, there was evidence of involvement of this gene in cognitive variation. Of the four SNPs that were genotyped in each cohort, rs1018381 showed association in the Australian cohort and marginal association in the Scottish cohort, rs2619522 showed association in the English and Australian cohorts and marginal association in the Scottish, rs2619528 showed association in the Scottish and English cohorts and rs1011313 showed association in the Scottish and Australian cohorts and a trend for association in the English cohort. Thus, there was indication of consistency in results across cohorts for some of the same SNPs tested. While our study was limited by the use of varying cognitive tests between cohorts, the associated measures in the older cohorts were mostly those tapping verbal declarative memory and central executive function. This is in some way consistent with the original study by Straub *et al.* (2002) that found an association between schizophrenia risk and *DTNBP1* (especially rs1011313) because in schizophrenia, the major cognitive dysfunction is in prefrontal brain regions (Pomarol-Clotet *et al.* 2008; Weinberger & Berman 1996), important for working memory and executive processes. The association between prefrontal brain functioning and *DTNBP1* variants has also been shown in healthy subjects whose event related potentials (ERPs) were measured during a continuous performance task (Fallgatter *et al.* 2006). Processing speed was another cognitive function that showed heightened association to *DTNBP1* variation relative to the other cognitive domains in our study. As our speed tasks placed an emphasis on visual stimuli, these results may relate to those in schizophrenics that showed early visual processing deficits (indexed by ERP responses) in *DTNBP1* risk haplotype carriers (Donohoe *et al.* 2008). Our findings raise the possibility of several susceptibility *DTNBP1* markers/haplotypes in which different variants account for variable effects on cognition. In the normal – especially elderly – population, these effects are most significant for those cognitive processes that are predominantly impaired in schizophrenics. Because cognitive decline in schizophrenics has also been associated with *DTNBP1* variation (Burdick *et al.* 2007), it will be useful in the future to investigate *DTNBP1* effects on cognitive change in our elderly cohorts, which have been measured at multiple time-points.

If the effect of *DTNBP1* on cognition mimics that influencing schizophrenia risk, then one possible reason for variation in the cognitive findings to date may relate to differences in genetic and/or environmental influences on *DTNBP1* expression between populations. As mentioned, the *DTNBP1* haplotypes conferring risk of schizophrenia are related with reduced allelic expression of *DTNBP1* (Bray *et al.* 2005), and a genome-wide linkage study of *DTNBP1* expression has shown *cis*-acting and *trans*-acting effects on *DTNBP1* expression that appear to mediate genetic association with schizophrenia at the *DTNBP1* locus (Bray *et al.* 2008). Thus, efforts to model the interaction between genes affecting *DTNBP1* expression and *DTNBP1* allelic variation might be promising directions for future studies of cognition. In the meantime, our study provides further evidence for a role of *DTNBP1* in cognition, despite imprecise replication because of differing SNP sets and cognitive tests used between the cohorts. By presenting results for such a large breadth of cognitive tests, we hope that some of these measures might overlap with those used by other research groups, enabling stricter replication of *DTNBP1*'s effect on cognition, especially with the haplotype in our study that was significant at the corrected probability level.

References

Beardsall, L. (1998) Development of the Cambridge Contextual Reading Test for improving the estimation of premorbid verbal intelligence in older persons with dementia. *Br J Clin Psychol* **37**, 229–240.

Benson, M.A., Newey, S.E., Martin-Rendon, E., Hawkes, R. & Blake,D.J. (2001) Dysbindin, a novel coiled-coil-containing protein that interacts with the dystrobrevins in muscle and brain. *J Biol Chem* **276**, 24232–24241.

Bray, N.J., Preece, A., Williams, N.M., Moskvina, V., Buckland, P.R., Owen, M.J. & O'Donovan, M.C. (2005) Haplotypes at the dystrobrevin binding protein 1 (DTNBP1) gene locus mediate risk for schizophrenia through reduced DTNBP1 expression. *Hum Mol Genet* **14**, 1947–1954.

Bray, N.J., Holmans, P.A., van den Bree, M.B., Jones, L., Elliston, L.A., Hughes, G., Richards, A.L., Williams, N.M., Craddock, N., Owen, M.J. & O'Donovan, M.C. (2008) Cis- and trans- loci influence

expression of the schizophrenia susceptibility gene DTNBP1. *Hum Mol Genet* **17**, 1169–1174.
Burdick, K.E., Lencz, T., Funke, B., Finn, C.T., Szeszko, P.R., Kane, J.M., Kucherlapati, R. & Malhotra, A.K. (2006) Genetic variation in DTNBP1 influences general cognitive ability. *Hum Mol Genet* **15**, 1563–1568.
Burdick, K.E., Goldberg, T.E., Funke, B., Bates, J.A., Lencz, T., Kucherlapati, R. & Malhotra, A.K. (2007) DTNBP1 genotype influences cognitive decline in schizophrenia. *Schizophr Res* **89**, 169–172.
Deary, I.J., Gow, A.J., Taylor, M.D., Corley, J., Brett, C., Wilson, V., Campbell, H., Whalley, L.J., Visscher, P.M., Porteous, D.J. & Starr, J.M. (2007) The Lothian Birth Cohort 1936: a study to examine influences on cognitive ageing from age 11 to age 70 and beyond. *BMC Geriatr* **7**, 28.
Donohoe, G., Morris, D.W., Clarke, S., McGhee, K.A., Schwaiger, S., Nangle, J.M., Garavan, H., Robertson, I.H., Gill, M. & Corvin, A. (2007) Variance in neurocognitive performance is associated with dysbindin-1 in schizophrenia: a preliminary study. *Neuropsychologia* **45**, 454–458.
Donohoe, G., Morris, D.W., De Sanctis, P., Magno, E., Montesi, J.L., Garavan, H.P., Robertson, I.H., Javitt, D.C., Gill, M., Corvin, A.P. & Foxe, J.J. (2008) Early visual processing deficits in dysbindin-associated schizophrenia. *Biol Psychiatry* **63**, 484–489.
Fallgatter, A.J., Herrmann, M.J., Hohoff, C., Ehlis, A.C., Jarczok, T.A., Freitag, C.M. & Deckert, J. (2006) DTNBP1 (dysbindin) gene variants modulate prefrontal brain function in healthy individuals. *Neuropsychopharmacology* **31**, 2002–2010.
Folstein, M.F., Folstein, S.E. & McHugh, P.R. (1975) ''Mini-mental state''. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189–198.
Funke, B., Finn, C.T., Plocik, A.M., Lake, S., DeRosse, P., Kane, J.M., Kucherlapati, R. & Malhotra, A.K. (2004) Association of the DTNBP1 locus with schizophrenia in a U.S. population. *Am J Hum Genet* **75**, 891–898.
Hallmayer, J.F., Kalaydjieva, L., Badcock, J., Dragovic, M., Howell, S., Michie, P.T., Rock, D., Vile, D., Williams, R., Corder, E.H., Hollingsworth, K. & Jablensky, A. (2005) Genetic evidence for a distinct subtype of schizophrenia characterized by pervasive cognitive deficit. *Am J Hum Genet* **77**, 468–476.
Heim, A. (1970) *Intelligence and Personality: Their Assessment and Relationship*. Penguin, Harmondsworth.
Jackson, D.N. (1984) *Manual for the Multidimensional Aptitude Battery*. Research Psychologists Press, Port Huron, MI.
Jackson, D.N. (1998) *Multidimensional Aptitude Battery II*. Sigma Assessment Systems, Inc, Port Huron, MI.
Jensen, A.R. (1998) *The g Factor: The Science of Mental Ability*. Praeger, Westport, CT.
Lezak, M. (2004) *Neuropsychological Testing*. Oxford University Press, Oxford.
Luciano, M., Wright, M.J., Duffy, D.L., Wainwright, M.A., Zhu, G., Evans, D.M., Geffen, G.M., Montgomery, G.W. & Martin, N.G. (2006) Genome-wide scan of IQ finds significant linkage to a quantitative trait locus on 2q. *Behav Genet* **36**, 45–55.
Maziade, M., Bissonnette, L., Rouillard, E. *et al.* (1997) 6p24–22 region and major psychoses in the Eastern Quebec population. Le Groupe IREP. *Am J Med Genet* **74**, 311–318.
McGregor, B., Pfitzner, J., Zhu, G., Grace, M., Eldridge, A., Pearson, J., Mayne, C., Aitken, J.F., Green, A.C. & Martin, N.G. (1999) Genetic and environmental contributions to size, color, shape, and other characteristics of melanocytic naevi in a sample of adolescent twins. *Genet Epidemiol* **16**, 40–53.
Nelson, H.E. & Willison, J.R. (1991) *National Adult Reading Test (NART) Test Manual (Part II)*. NFER-Nelson, Windsor.
Nyholt, D.R. (2004) A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. *Am J Hum Genet* **74**, 765–769.
van den Oord, E.J., Sullivan, P.F., Jiang, Y., Walsh, D., O'Neill, F.A., Kendler, K.S. & Riley, B.P. (2003) Identification of a high-risk haplotype for the dystrobrevin binding protein 1 (DTNBP1) gene in the Irish study of high-density schizophrenia families. *Mol Psychiatry* **8**, 499–510.
Pomarol-Clotet, E., Salvador, R., Sarro, S., Gomar, J., Vila, F., Martinez, A., Guerrero, A., Ortiz-Gil, J., Sans-Sansa, B., Capdevila, A., Cebamanos, J.M. & McKenna, P.J. (2008) Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? *Psychol Med* **38** 1185–93.
Posthuma, D., Luciano, M., Geus, E.J., Wright, M.J., Slagboom, P.E., Montgomery, G.W., Boomsma, D.I. & Martin, N.G. (2005) A genomewide scan for intelligence identifies quantitative trait loci on 2q and 6p. *Am J Hum Genet* **77**, 318–326.
Purcell, S., Cherny, S.S. & Sham, P.C. (2003) Genetic Power Calculator: design of linkage and association genetic mapping studies of complex traits. *Bioinformatics* **19**, 149–150.
Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A., Bender, D., Maller, J., Sklar, P., de Bakker, P.I., Daly, M.J. & Sham, P.C. (2007) PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* **81**, 559–575.
Rabbitt, P., Diggle, P., Horan, M., Pendleton, N., Bent, N., Abson, V., Jones, M. & McInnes, L. (2004) The University of Manchester Longitudinal Study of normal healthy old age 1983 through 2003. *Aging Neuropsychol Cognit* **11**, 245–279.
Raven, J.C. (1965) *The Mill Hill Vocabulary Scale*. HK Lewis, London.
Schonell, F.J. & Schonell, P.E. (1960) *Diagnostic and Attainment Testing*. Oliver & Boyd, Edinburgh.
Scottish Council for Research in Education (1949) *The Trend of Scottish Intelligence: A Comparison of the 1947 and 1932 Surveys of the Intelligence of Eleven-Year-Old Pupils*. University of London Press, London.
SPSS (2005) *SPSS 14.0 for Windows*. SPSS Inc, Chicago, IL.
Straub, R.E., Jiang, Y., MacLean, C.J., Ma, Y., Webb, B.T., Myakishev, M.V., Harris-Kerr, C., Wormley, B., Sadek, H., Kadambi, B., Cesare, A.J., Gibberman, A., Wang, X., O'Neill, F.A., Walsh, D. & Kendler, K.S. (2002) Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. *Am J Hum Genet* **71**, 337–348.
Tang, J.X., Zhou, J., Fan, J.B., Li, X.W., Shi, Y.Y., Gu, N.F., Feng, G.Y., Xing, Y.L., Shi, J.G. & He, L. (2003) Family-based association study of DTNBP1 in 6p22.3 and schizophrenia. *Mol Psychiatry* **8**, 717–718.
Wainwright, M.A., Wright, M.J., Geffen, G.M., Geffen, L.B., Luciano, M. & Martin, N.G. (2004) Genetic and environmental sources of covariance between reading tests used in neuropsychological assessment and IQ subtests. *Behav Genet* **34**, 365–376.
Wechsler, D. (1981) *Wechsler Adult Intelligence Scale – Revised Manual*. The Psychological Corporation, New York, NY.
Wechsler, D. (1998) *WMS-IIIUK Administration and Scoring Manual*. Psychological Corporation, London.
Weickert, C.S., Straub, R.E., McClintock, B.W., Matsumoto, M., Hashimoto, R., Hyde, T.M., Herman, M.M., Weinberger, D.R. & Kleinman, J.E. (2004) Human dysbindin (DTNBP1) gene expression in normal brain and in schizophrenic prefrontal cortex and midbrain. *Arch Gen Psychiatry* **61**, 544–555.
Weinberger, D.R. & Berman, K.F. (1996) Prefrontal function in schizophrenia: confounds and controversies. *Philos Trans R Soc Lond B Biol Sci* **351**, 1495–1503.
Williams, N.M., Preece, A., Morris, D.W. *et al.* (2004) Identification in 2 independent samples of a novel schizophrenia risk haplotype of the dystrobrevin binding protein gene (DTNBP1). *Arch Gen Psychiatry* **61**, 336–344.
Wright, M., De Geus, E., Ando, J., Luciano, M., Posthuma, D., Ono, Y., Hansell, N., Van Baal, C., Hiraishi, K., Hasegawa, T., Smith, G., Geffen, G., Geffen, L., Kanba, S., Miyake, A., Martin, N. & Boomsma, D. (2001) Genetics of cognition: outline of a collaborative twin study. *Twin Res* **4**, 48–56.
Zinkstok, J.R., de Wilde, O., van Amelsvoort, T.A., Tanck, M.W., Baas, F. & Linszen, D.H. (2007) Association between the DTNBP1 gene and intelligence: a case-control study in young patients with schizophrenia and related disorders and unaffected siblings. *Behav Brain Funct* **3**, 19.

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