Table 1 Demographic and clinical characteristics of high-risk individuals with different genotypes

SNP8NRG243177	*T/T*	*T/C*	*C/C*
Number of participants carrying the genotype	25	12	30
Number of participants with psychosis	25	4	2
Male/female	14/11	8/4	14/16
Age at the time of entry into the study	21.3 (4.2)	20.2 (3.8)	21.5 (2.9)
Socioeconomic status	2.2 (0.6)	1.8 (0.8)	1.9 (0.8)
IQ	97.2 (11.9)	105.4 (10.0)	107.4 (10.6)
GAF	51.4 (9.1)	57.5 (5.8)	60.3 (7.1)

Abbreviations: GAF, global assessment of functioning; IQ, Wechsler adult intelligence scale, revised.
Data are mean (s.d.). The measure of the socioeconomic status (Hollingshead Four-Factor Index) was a categorical variable (3, low class; 2, middle class; 1, high class). For the sake of simplicity, this value also is expressed as mean (s.d.). Mann–Whitney *U*-tests revealed no significant differences across 3 groups ($P > 0.1$).

SNP8NRG221533, rs10096573, rs4268090, rs4452759, rs4733263, rs4476964, SNP8NRG241930, SNP8NRG 243177, rs7819063, rs4733267, rs11783236 and rs7000831; see Addington *et al.*[7] and http://www.hapmap.org/).

The primary measure was threshold cycle (C_t value). We adapted the comparative method with double-dye oligonucleotides (TaqMan probes, Applied Biosystems, Foster City, CA, USA) of Bubner and Baldwin.[8] We found no evidence for hemizygosity in our sample.

The distribution of the genotypes deviated from the Hardy–Weinberg equilibrium. Since genotyping errors were controlled, this may be due to the fact that the participants were recruited on the basis of 'at-risk' mental states, which may have resulted in a biased enrichment for people with the T/T risk genotype. In this respect, the small sample size is a critical factor, which is a general problem in the research of 'at-risk' mental states. Two other possible confounding factors related to excessive homozygosity (population stratification and hemizygosity) also were excluded.

NRG1 is one of the most important candidate genes, playing a crucial role in many aspects of the pathophysiology of schizophrenia (neuronal development, synaptic plasticity, glutamatergic neurotransmission and glial functioning). The SNP8NRG243177 variant is of special relevance. Using a bioinformatic approach, Law *et al.*[9] showed that this variant affects the binding of transcription factors to the 5′ promoter region of the gene and is associated with the expression of a newly described isoform of the protein. Further studies are necessary to elucidate how this variant leads to pathological processes that increase the risk of psychosis, and how this genetic trait may interact with environmental factors. Given that this study confirms and extends an earlier report,[1] it is tempting to speculate on use in psychosis risk prediction, especially in clinically high-risk populations.

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Bias in genetic association studies and impact factor

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Studies reporting correlations between genetic variants and human phenotypes, including disease risk as well as individual differences in quantitative phenotypes such as height, weight or personality, are notorious for the difficulties they face in providing robust evidence.[1] Notably, in many cases an initial finding is followed by a large number of attempts at replication, some positive, some negative.[2–5] Although there has been debate over the statistical arguments concerning the strength of evidence in association studies,[1] there has been less interest in understanding why it is that some genetic associations

generate such large literatures of inconclusive results. We wondered whether one source of the difficulties in the interpretation of genetic association studies might lie with the journal that published the initial finding. Studies published in journals with a high impact factor typically attract considerable attention. However, it is not clear that these studies are necessarily more robust than those published in journals with lower impact factors.

We used data from three meta-analytic reviews of gene–disease associations in the psychiatric genetics literature, resulting in a total of $k=81$ studies published between 1990 and 2008. We divided the individual study odds ratio (OR) by the pooled OR, to arrive at an estimate of the degree to which each individual study over- or underestimated the true effect size, as estimated in the corresponding meta-analysis. We have recently used this method to identify a biasing effect of research location and resources.[6] Additional data on the impact factor of the journal in which each individual study was published were collected, using 2006 data. These data were unavailable in the case of two studies, resulting in a final sample of $k=79$ studies.

Data were analysed using meta-regression of individual study bias score against journal impact factor. This indicated a significant correlation between impact factor and bias score ($R^2=+0.13$, $z=4.27$, $P=0.00002$). Our results are presented graphically in Figure 1. We also note that journals with high impact factors tend to publish studies with high bias scores and small sample sizes (as indicated by the smaller circles in the figure).

Genetic association studies offer the advantages of being numerous and highly comparable, allowing analyses of the kind described here. Our results indicate that genetic association studies published in journals with a high impact factor are more likely to provide an overestimate of the true effect size. This is likely to be in part due to the small sample sizes used and the correspondingly low statistical power that characterizes these studies. Initial reports of genetic association published in journals with a high impact factor should therefore be treated with particular caution. However, although we cannot necessarily generalize our findings to other research domains, there are no particular reasons to expect that genetic association studies are unique in this respect.

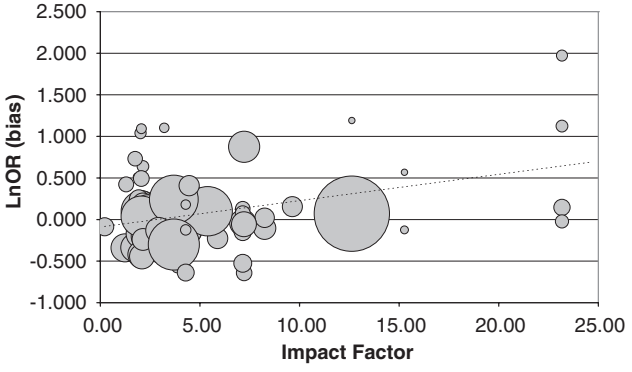

Figure 1 Meta-regression of individual study bias score and journal impact factor. Bias score is plotted against the 2006 impact factor of the journal in which the study was published. Meta-regression indicates a positive correlation between journal impact factor and bias score ($R^2=+0.13$, $P=0.00002$), suggesting that genetic association studies published in journals with a high impact factor are more likely to provide an overestimate of the true effect. Circles, representing individual studies, are proportional to the sample size (that is, accuracy) of the study. *Source*: Thomson Scientific.

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The Met allele of the BDNF Val66Met polymorphism is associated with increased BDNF serum concentrations

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The brain-derived neurotrophic factor (BDNF) hypothesis of depression postulates that a loss of BDNF function is directly involved in the pathophysiology of depression and its restoration may underlie the therapeutic efficacy of antidepressant treatments (for recent review see Groves[1]). The hypothesis is in line with observations that BDNF concentrations in humans are decreased in major depressed patients and healthy humans with depression-related personality traits and are increased after antidepressant treatment.[2,3]

A common single nucleotide polymorphism in the human BDNF gene (c.196G>A, dbSNP: rs6265) has been identified causing an amino-acid substitution