Epidemiological and genetic data support the notion that schizophrenia and bipolar disorder share genetic risk factors. In our previous genome-wide association study, meta-analysis and follow-up (totaling as many as 18 206 cases and 42 536 controls), we identified four loci showing genome-wide significant association with schizophrenia. Here we consider a mixed schizophrenia and bipolar disorder (psychosis) phenotype (addition of 7469 bipolar disorder cases, 1535 schizophrenia cases, 333 other psychosis cases, 808 unaffected family members and 46 160 controls). Combined analysis reveals a novel variant at 16p11.2 showing genome-wide significant association (rs4583255[T]; odds ratio = 1.08; P = 6.6 × 10⁻¹¹). The new variant is located within a 593-kb region that substantially increases risk of psychosis when duplicated. In line with the association of the duplication with reduced body mass index (BMI), rs4583255[T] is also associated with lower BMI (P = 0.0039 in the public GIANT consortium data set; P = 0.00047 in 22 651 additional Icelanders).

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Keywords: association; bipolar disorder; cross-disorder; schizophrenia; 16p11.2

INTRODUCTION

Two structural variants, a balanced t(1;11) translocation interrupting DISC1 and a microdeletion at 22q11.2, were the first genetic polymorphisms to show compelling evidence of association with schizophrenia. More recently, additional microdeletions and microduplications conferring risk of schizophrenia and, in some cases, bipolar disorder have been uncovered. These copy number variants (CNVs) confer high-to-moderate relative risk, however, because they typically change copy number of multiple genes, and may also affect regulation of genes at their margins, they do not generally implicate individual genes.

Currently, common single nucleotide polymorphisms (SNPs) are convincing risk factors for schizophrenia and bipolar disorder, in addition to structural variants. Common alleles showing genome-wide significant association with at least one of the disorders have been found at more than 20 loci. None of these regions are within structural polymorphisms previously shown to be susceptibility factors for schizophrenia or bipolar disorder. Nevertheless, first principles and data from other disorders predict the existence of common variants conferring risk through the same genes as rare structural alleles. The identification of common risk variants within CNV regions may aid in uncovering the causal gene or genes of a CNV, or help to elucidate other aspects of a CNV's association with disease.

Two loci have been reported to harbor common alleles showing genome-wide significant association with both schizophrenia and bipolar disorder. In addition, several common variants initially displaying genome-wide significant association with one of the disorders have been shown, in subsequent studies, to confer risk of the other. Investigations considering schizophrenia and bipolar disorder as a single phenotype also support shared risk alleles and an overlapping polygenetic component has been described by several studies. These data are consistent with current epidemiological investigations, which predict shared genetic risk factors for schizophrenia and bipolar disorder.

Previously, we carried out a schizophrenia genome-wide association (GWA) study, SGENE-plus, followed by meta-analysis of the top 1500 results with data from the International Schizophrenia Consortium (ISC) and the Molecular Genetics of Schizophrenia (MGS) group. Loci having P-values < 1 × 10⁻⁴ (covered by 39 SNPs located in 33 genomic regions) were followed up in a data set of up to 10 260 schizophrenia cases and 23 500 controls. In this work, we broaden our phenotype of interest to psychosis (schizophrenia, bipolar disorder and related psychoses), examining the same group of follow-up SNPs in a data set augmented by 7469 bipolar disorder cases, 1535 schizophrenia cases, 333 other psychosis cases, 808 unaffected family members and 46 160 controls.

MATERIALS AND METHODS

Samples

The genome-wide typed (SGENE-plus; 2663 cases and 13 498 controls) and meta-analysis (SGENE-plus + ISC + MGS) samples (in total, 7946 cases and 19 036 controls) used here were identical to those used in our previous schizophrenia GWA study and meta-analysis. The primary psychosis follow-up samples employed consisted of follow-up samples from our previous GWA follow-up study (9246 schizophrenia cases and 22 356 controls), plus an additional 9337 psychosis cases (1535 schizophrenia, 7469 bipolar disorder and 333 related psychoses) and 46 968 controls/unaffected family members. The primary follow-up samples were genotyped or imputed for all follow-up markers. The secondary follow-up samples consisted of 1014 cases and 1144 controls from the Göttingen Research Association for Schizophrenia study. These samples, which also had been used for secondary follow-up in our previous GWA follow-up study, were genotyped for SNPs that were genome-wide significant in the combined meta-analysis and primary follow-up samples. Table 1 summarizes the schizophrenia and psychosis data sets used in previous and current work, and Supplementary Table 1 includes details on the individual study groups. The autism samples (3773 cases, 16 103 controls, 4206 family members) derived from the Autism Genome Project, the Autism Genetic Resource Exchange and nine European study groups (Supplementary Table 2). Further information on ascertainment and diagnosis for the psychosis and autism samples is provided in the Supplementary Material.
Genotyping and association analysis

Genotyping was carried out using Illumina (San Diego, CA, USA) and Affymetrix genome-wide arrays (Santa Clara, CA, USA), Nanogen (San Diego, CA, USA) Centaurus assays, Taqmam assays, the Sequenom MassArray iPLEX genotyping system (San Diego, CA, USA) and the Roche LightCycler480 system (Mannheim, Germany) (Supplementary Tables 1 and 2). Quality control and imputation were performed, by study group, as described in the Supplementary Methods. Case–control or family-based association analyses were carried out for each study group. For the case–control analyses, population stratification was controlled for using genomic control or principal components. Summary statistics from the various study groups were combined as described previously.15 Body mass index (BMI) measurements were adjusted for age and sex, and inverse standard normal transformed. Analysis was carried out by regressing the adjusted, transformed data on rs4583255[T] count.

Expression analysis

For the three brain data sets.36-38 expression levels were inverse normal transformed and regressed on the number of rs4583255-T alleles with gender, age at death, post-mortem interval, brain source, expression experiment batch, pH (Colantoni et al.39 only), sample expression level based on the total number of transcripts detected (Webster et al.38 only) and Alzheimer’s disease patient status (Webster et al.38 only) as covariates. To incorporate data from different brain regions (Gibbs et al.40) or different probes (KCTD13 in Colantoni et al.39) derived from the same individual, a mixed-effects model with individual as a random effect was used. Results from the three data sets were combined using inverse-variance weighted meta-analysis. The Dutch whole-blood data set included control samples from two studies.39,40 Analysis was performed using linear regression in Plink41 taking age and gender as covariates. The Icelandic blood data set has been described previously,42 and analysis was carried out as detailed in this work.

RESULTS

We assembled a psychosis (schizophrenia, bipolar disorder and related psychoses) primary follow-up data set made up of 36 study groups containing a total of 18 583 cases, 68 516 controls and 808 unaffected family members (Supplementary Table 1). In each study group, allelic association analysis was carried out for 39 SNPs from 33 genomic regions (these SNPs covered P-values <1 × 10−4 in the SGENE-plus + ISC + MGS meta-analysis at r² = 0.3). Results from the various study groups were combined using inverse-variance weighted meta-analysis.

At 31 of the 33 loci, odds ratios (ORs) in the psychosis follow-up group were in the same direction as in the discovery data set (SGENE-plus + ISC + MGS) (Supplementary Table 3). A similar pattern had been observed in the schizophrenia follow-up set—ORs were in the same direction at 30 of the 33 loci.14 These results indicate that the set of variants chosen for follow-up was enriched for risk alleles (P = 7.0 × 10−7 for schizophrenia; P = 6.5 × 10−8 for psychosis).

Next, we performed a joint analysis of the discovery and psychosis follow-up sets. To account for testing two phenotypes (schizophrenia and psychosis), the genome-wide significance threshold was set at P < (5 × 10−8)/2, or 2.5 × 10−8. Five SNPs, residing at three loci, exceeded this threshold (Supplementary Table 3). Two of the loci—the major histocompatibility complex region and 11q21.2 near NRGN—had been genome-wide significant in the previous schizophrenia analysis; a third locus, in TAOK2 at 16p11.2, was novel (Supplementary Table 3). Following the addition of data from a further 1014 schizophrenia cases and 1144 controls, the variant at the novel locus, rs4583255[T], was associated with psychosis with increased significance (OR = 1.08, P = 6.6 × 10−10, Table 2, Figure 1). rs4583255[T]'s association with psychosis fit the multiplicative test power46,47 and low BMI.47 We obtained large data sets to examine association of rs4583255[T] with both schizophrenia and bipolar disorder (P = 0.0011 and 0.00026, respectively), with OR of 1.06 and 1.08, respectively (independent controls were used for the two analyses; see Supplementary Table 5). We also investigated association with bipolar disorder for variants that had shown genome-wide significant association with schizophrenia in our previous study.14 Following correction for eight tests, rs12807809[T], near NRGN, was significantly associated with bipolar disorder (P = 0.0023) with an OR identical to that of the schizophrenia follow-up samples (OR = 1.09). The remaining schizophrenia susceptibility variants did not show even nominally significant association with bipolar disorder—yet, OR confidence intervals for the two disorders overlapped for at least some variants at all loci (Supplementary Table 5).

Intriguingly, the newly identified SNP is located in a nearby 600-kb region that confers risk of schizophrenia and bipolar disorder when duplicated (Figure 1).5,6,28 Copy number gain of the region also is associated with autism.6,43-45 Reduced head circumference46,47 and low BMI.47 We obtained large data sets to examine association of rs4583255[T] with both autism and BMI. Based on 3773 cases, 16 103 controls and 4206 unaffected family members from the Autism Genetic Resource Exchange, the Autism Genome Project and nine European study groups (Supplementary Table 2), we found no evidence of association with autism spectrum disorder (ASD), strict autism or multiplex ASD (ASD, OR = 1.00, P = 0.98; strict autism, OR = 1.02, P = 0.66; multiplex ASD, OR = 1.07, P = 0.22; Supplementary Table 6), although power

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Table 1. Schizophrenia and psychosis data sets used in previous and current work

<table>
<thead>
<tr>
<th>Data set</th>
<th>Case phenotype</th>
<th>Markers examined</th>
<th>N</th>
<th>Initial use</th>
<th>Overlap with other sets</th>
</tr>
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<tr>
<td>SGENE-plus GWAS</td>
<td>SZ</td>
<td>314 868</td>
<td>2663</td>
<td>Stefansson15</td>
<td>Includes SGENE-plus GWAS</td>
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<td>1500</td>
<td>7946</td>
<td>Stefansson15</td>
<td>No</td>
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<tr>
<td>Primary schizophrenia follow-up</td>
<td>SZ</td>
<td>39</td>
<td>9246</td>
<td>22 356</td>
<td>Steinberg14</td>
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<tr>
<td>Primary psychosis follow-up</td>
<td>SZ, BP, other psychosis</td>
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<td>18 583</td>
<td>69 324</td>
<td>This work Includes primary schizophrenia follow-up</td>
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<td>Secondary follow-up</td>
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<td>1014</td>
<td>1144</td>
<td>Steinberg14</td>
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</tbody>
</table>

Abbreviations: BP, bipolar disorder; GWAS, genome-wide association study; ISC, International Schizophrenia Consortium; MGS, molecular genetics of schizophrenia; SZ, schizophrenia.

*Eight markers were examined in this set in the previous work,14 and an additional marker is genotyped in the current work.
to detect association at the OR found in the follow-up psychosis samples was modest (at a 0.05 significance level, power was about 57% for ASD, 42% for strict autism and 23% for multiplex ASD). In contrast, we found significant association of rs4583255[T] with lower BMI in the published GIANT consortium GWAS data set of 123,865 individuals $^{48}$ ($P = 0.0039$) and in 22,651 Icelanders who were not included in the GIANT study ($P = 0.00047$).

Recently, a study examining the effect of altered expression of 16p11.2 CNV region genes on zebrafish head size identified KCTD13 as the major driver of head size change, with MAPK3 and MVP named as possible modifiers. $^{49}$ These results motivated us to examine association of rs4583255[T] with expression of KCTD13, MAPK3 and MVP in human brain. Using data from three publicly available data sets with at least 50 European-ancestry adult brains each (total $N = 565$), $^{36-38}$ we found that rs4583255[T] was significantly associated with expression of MAPK3 (effect $= 0.12$ s.d.; $P = 0.011$), but not significantly associated with expression of KCTD13 or MVP (Supplementary Table 7). We also investigated association of rs4583255[T] with gene expression in blood using data sets from Iceland ($N = 972$)$^{62}$ and the Netherlands ($N = 437$). $^{39,40}$ Consistent with the brain results, rs4583255[T] was significantly associated with higher expression of MAPK3 (for Iceland, $P = 9.4 \times 10^{-15}$; for the Netherlands, $P = 0.014$ for probe 3870601, and $P = 0.042$ for probe 234040), but not significantly associated with expression of KCTD13 or MVP.

**DISCUSSION**

In this study, we uncovered a novel variant at 16p11.2, rs4583255[T], showing genome-wide significant association with psychosis (OR $= 1.08$; $P = 6.6 \times 10^{-11}$). In follow-up samples, ORs were similar for schizophrenia and bipolar disorder (OR $= 1.06$ and $1.08$, respectively), and association was significant for both ($P = 0.0011$ and $0.00026$, respectively). Thus, rs4583255[T] is a compelling example of a genetic variant that confers risk across traditional diagnostic boundaries.

Among the variants that showed genome-wide significant association with schizophrenia in our previous study, $^{14}$ only rs12807809[T] showed significant association with bipolar disorder in the current work. Nevertheless, OR confidence intervals for schizophrenia and bipolar disorder overlapped for most risk alleles. Very large data sets will be necessary to establish conclusively where these variants fall on the spectrum of conferring risk of one disorder, exclusively, to conferring equal risk of either.

To our knowledge, this is the first case in which a common risk allele showing genome-wide significant association with psychosis has turned out to be located within a CNV that had been previously associated with psychosis. Both copy number gain and loss of the 16p11.2 region are associated with multiple phenotypes. Duplication is associated with psychosis, $^{5,6,28}$ both copy number gain and loss are associated with autism and developmental delay, $^{63-65}$ and duplication and deletion lead to

<table>
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<tr>
<th>Study group</th>
<th>OR (95% CI)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGENE-plus + ISC + MGS</td>
<td>1.10 (1.05, 1.15)</td>
<td>2.5 $\times 10^{-5}$</td>
</tr>
<tr>
<td>Primary psychosis follow-up</td>
<td>1.07 (1.04, 1.10)</td>
<td>9.2 $\times 10^{-7}$</td>
</tr>
<tr>
<td>Secondary follow-up</td>
<td>1.10 (0.97, 1.24)</td>
<td>0.14</td>
</tr>
<tr>
<td>Combined</td>
<td>1.08 (1.05, 1.10)</td>
<td>6.6 $\times 10^{-11}$</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ISC, International Schizophrenia Consortium; MGS, Molecular Genetics of Schizophrenia; OR, odds ratio.
reduction and enlargement, respectively, of head circumference and BMI.46,47

In this work, we found that rs4583255[T] also confers risk of reduced BMI (P = 0.0039 in GIANT; P = 0.00047 in additional Icelanders). This result supports the suggestion, made previously,37 that the effects of duplication on psychosis and BMI have a single origin, presumably in the brain. We did not find evidence of association of rs4583255[T] with autism, although we were somewhat underpowered to detect an effect of the same size as in psychosis, especially, for sub-phenotypes.

We found that rs4583255[T] was associated with increased expression in adult brain and blood of MAPK3, one of the 16p11.2 genes identified and involved in causing head-circumference changes in zebrafish.49 Caution is required in interpretation of this result, however, as the significance in brain is not overwhelming and, furthermore, gene expression in the pre-adult brain may be more relevant for the development of psychosis. Data from only extremely small numbers of European-ancestry brains at pre-adult stages were available, precluding investigation of the association of rs4583255[T] with gene expression at these stages.

In conclusion, in this work, we broadened our phenotype of interest to psychosis, identifying a new common risk allele, rs4583255[T], with similar ORs for schizophrenia and bipolar disorder. The novel variant is located within a duplication previously associated with psychosis, and, in line with the duplication's effects, also is associated with lower BMI. In the future, knowledge of this common variant association may prove useful to studies aimed at further understanding the mechanism through which the duplication exerts its effects on neurodevelopmental and anthropomorphic phenotypes.

CONFICT OF INTEREST
The authors declare no conflict of interest.

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10 Vacic V, McCarthy S, Malhotra D, Murray F, Chou HH, Peoples A et al. Psychosis variant at 16p11.2 of Mental Health to Clara M Lajonchere (PI). Seventh, the Autism Genome Project Consortium* and the participating AGRE families. The AGRE is a program of Autism and related phenotypes. BioInformatics (AGRE Consortium) and the participating AGRE families. The AGRE is a program of Autism Speaks and is supported, in part, by grant U24MH081810 from the National Institute of Mental Health to Clara M Lajonchere (PI). Seventh, the Autism Genome Project (AGP) data sets used for the analysis described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/gap through dbGaP accession number, phs000267.v1.p1. Submission of the data to dbGaP was provided by Dr Bernie Devlin on behalf of the AGP. Collection and submission of the data to dbGaP were supported by a grant from the Medical Research Council (G0601030) and the Wellcome Trust (075491/Z/04), Anthony P Monaco, PI, University of Oxford. This work was also supported by the European Union (grant numbers LSHTM-CT-2006-037761 (Project-Dream), PIAP-GA-2008-1812851 (Project PsychGene), HEALTH-F4-2009-223423 (Project PsychCNCs), HEALTH-F4-2009-242257 (Project ADAMS) and IMI-JU-New Meds); the National Genome Research Network of the German Federal Ministry of Education and Research (BMBF) (grant numbers 01GS08144 (MoodNet5-SF) and 01GS08147 (NGNPhlps)); the National Institute of Mental Health (ROI MH78075, and N01 MH90001, MH074027 to the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project); the Centre of Excellence for Complex Disease Genetics of the Academy of Finland (grant numbers 213506 and 129680; the Biocentrum Helsinki Foundation and Research Program for Molecular Medicine, Faculty of Medicine, University of Helsinki; the Stanley Medical Research Institute; the Danish Council for Strategic Research (grant number 2101-07-0059); H Lundbeck A/S; the Research Council of Norway (grant number 163070/550); the Danish Medical Research Council; the South-East Norway Health Authority (grant number 2004-123); the Medical Research Council; Ministerio de Sanidad y Consumo, Spain (grant number P0181522 to JC); Xunta de Galicia (grant number 08CSA005208PR to A Carracedo); the Swedish Research Council; the Wellcome Trust (Wellcome Trust grants 085475/B/08/Z and 085475/Z/08/Z as part of the Wellcome Trust Case Control Consortium 2); the Max Planck Society; Saarland University (grant number T6 10 00-000005/08); and the Netherlands Foundation for Brain Research (Hersenstichting) (grant number 2008)134 to M Poot); and Eli Lilly and Company (genotyping for CATIE and part of the TOP sample). For further acknowledgements, see the Supplemental Material.


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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

APPENDIX

GENETIC RISK AND OUTCOME IN PSYCHOsis (GROUP)

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