

Evidence for Shared Genetic Risk Between Methamphetamine-Induced Psychosis and Schizophrenia

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Methamphetamine (METH) use can provoke psychotic reactions requiring immediate treatment, namely METH-induced psychosis. Although the distinction between METH-induced and primary psychosis is important for understanding their clinical courses, we do not have clear diagnostic procedure by their symptoms. Not only are there similarities between the clinical features of METH-induced psychosis and schizophrenia (SCZ), but there is also epidemiological evidence of a shared genetic risk between 'METH-related' disorders and SCZ, which makes the differentiation of these two conditions difficult. In this study, we conducted a genome-wide association study (GWAS) targeting METH-dependent patients. The METH sample group, used in the METH-dependence GWAS, included 236 METH-dependent patients and 864 healthy controls. We also included a 'within-case' comparison between 194 METH-induced psychosis patients and 42 METH-dependent patients without psychosis in a METH-induced psychosis GWAS. To investigate the shared genetic components between METH dependence, METH-induced psychosis, and SCZ, data from our previous SCZ GWAS (total $N = 1108$) were re-analyzed. In the SNP-based analysis, none of the SNPs showed genome-wide significance in either data set. By performing a polygenic component analysis, however, we found that a large number of 'risk' alleles for METH-induced psychosis are over-represented in individuals with SCZ ($P_{best} = 0.0090$). Conversely, we did not detect enrichment either between METH dependence and METH-induced psychosis or between METH dependence and SCZ. The results support previous epidemiological and neurobiological evidence for a relationship between METH-induced psychosis and SCZ. These also suggest that the overlap between genes scored as positive in these data sets can have higher probability as susceptibility genes for psychosis.

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INTRODUCTION

Illicit drug use, a major concern worldwide, can place a large burden both on individuals and on society. Methamphetamine (METH) use, in particular, is a growing problem; recent evidence from the United Kingdom suggests that

METH is one of the most harmful drugs, with its overall harm (harm to users plus harm to others) ranking fourth out of 20 drugs (Nutt *et al*, 2010). It is of note that harm from METH is mainly associated with harm to the users (self-harm), and one reason for this finding is that METH can provoke psychotic reactions (METH-induced psychosis) requiring immediate medical treatment (Nutt *et al*, 2010).

The distinction between METH-induced psychosis and primary psychosis is critical for understanding the clinical courses of these disorders and planning appropriate treatment; however, we do not fully understand why some

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METH abusers develop schizophrenia (SCZ)-like psychosis (Grelotti *et al*, 2010) and others do not. Moreover, these two conditions are clinically similar partly because some patients do not remit psychotic symptoms for weeks or months after METH exposure, which suggests a specific phenotype induced by METH (ie, 'prolonged type' of METH-induced psychosis) (Ujike and Sato, 2004). Clinical investigators in Japan have long suggested that exposure to METH may cause persistent SCZ-like psychosis, whereas this possibility is discounted in the Western literature: the 'prolonged type' of METH-induced psychosis is recognized as a pre-existing psychotic state, such as SCZ (Callaghan *et al*, 2012).

Not only are there similarities in the clinical features between these conditions, but there are also several epidemiological studies that suggest a shared genetic risk in 'METH-related' disorders (ie, METH use disorder, METH dependence, and/or METH-induced psychosis) and SCZ, which makes the distinction between the two conditions complex. A family study revealed an increased risk of SCZ in the relatives of METH-induced psychosis patients compared with non-psychotic METH abusers or the general population (Chen *et al*, 2005). More recently, although the authors left open the question regarding the clear classification of SCZ and the 'prolonged type' of METH-induced psychosis, an epidemiological survey suggested that METH abuse patients were at the highest risk of developing SCZ compared with the users of other psychoactive drugs (eg, cocaine, alcohol, opioids, and cannabis; Callaghan *et al*, 2012).

In this investigation, we conducted a genome-wide association study (GWAS) of METH dependence to explore the relationship between METH dependence, METH-induced psychosis, and SCZ, by including a re-analysis of the following: (a) the METH data set by dividing it according to the presence of psychosis in each participant and (b) a previously reported Japanese SCZ GWAS (Ikeda *et al*, 2011).

MATERIALS AND METHODS

Samples

A total of 236 patients with METH dependence (185 males, 51 females), most of whom were analyzed in a previous GWAS using the pooling method (Uhl *et al*, 2008), and 864 healthy controls (410 males, 454 females) were included in this study (we will refer to this case-control analysis as the 'METH-dependence GWAS'). These controls had been used as the comparison subjects in other GWASs for narcolepsy (Miyagawa *et al*, 2008), panic disorder (Otowa *et al*, 2009), and SCZ (Hashimoto *et al*, unpublished data).

The METH-dependence GWAS data set was re-analyzed within case samples based on the presence (or absence) of psychotic symptoms (we will refer to this analysis as the 'METH-induced psychosis GWAS'). This METH-induced psychosis sample group consisted of 194 METH-dependent patients with psychosis (METH-induced psychosis: 155 males and 39 females) and 42 METH-dependent patients without psychosis (METH non-psychosis: 30 males and 12 females).

All subjects were unrelated Japanese subjects and were recruited from the same relatively small geographical area of Japan. Consensus diagnoses were made by at least two experienced psychiatrists according to ICD-10 criteria on

the basis of unstructured interviews with patients and their families, as well as a review of medical records. Patients were excluded if they had a history of SCZ, bipolar disorder, or known intellectual disability. The Japan SCZ sample consisted of 560 SCZ cases and 548 controls, and results from the GWAS of this sample were published previously ('SCZ GWAS') (Ikeda *et al*, 2011). Healthy controls reported no personal history of mental disorders, but they were not screened using standard diagnostic procedures.

After providing a complete description of the study to the subjects, written informed consent was obtained. This study was approved by the ethics committees of each university participating in this project.

Genotyping and Quality Control (QC)

Genotyping for the METH-dependence GWAS was performed using the Affymetrix Genome-Wide Human SNP Array 5.0 or 6.0 (Affymetrix, Santa Clara, CA) according to the manufacturer's protocol. Of the 236 subjects with METH dependence, 169 of them (all METH-induced psychosis) were genotyped using the 5.0 chip, whereas 67 subjects (25 METH-induced psychosis and 42 METH non-psychosis) were genotyped using the 6.0 chip. The healthy controls were genotyped using the Affymetrix 6.0 chip. Genotypes were called from the CEL files using the BRLMM-P algorithm for the 5.0 chip and Birdseed v2 for the 6.0 chip implemented in the Genotyping Console software (Affymetrix). To correct for hidden confounding factors introduced by different genotyping platforms, only SNPs that are in common were selected (total of 436 213 SNPs). We then applied the following QC criteria to exclude samples: (1) arrays with a low QC (<86% for 5.0 chip or <0.4 for 6.0 chip) according to the BRLMM-P or Birdseed v2 algorithm ($n=0$) and (2) samples for which <95% of genotypes were called ($n=0$). Next, we excluded SNPs that (1) had low call rates (<0.95), (2) were duplicated, (3) localized to sex chromosomes, (4) deviated from Hardy-Weinberg equilibrium in controls ($P<0.0001$), or (5) had low minor allele frequencies (<0.05). Finally, 244 224 QC-ed SNPs were used in the subsequent analyses.

To test for the presence of genetic structure in the data, we performed a principal component analysis (PCA) using EIGENSTRAT 3.0 (Price *et al*, 2006). Ten Eigenvectors were calculated. Genotype information from the JPT, CHB, CEU, and YRI in HapMap phase III was compared with our data set to check for population stratification (Supplementary Figure S1). All Japanese samples from our case-control sample were in a separate cluster from the non-Japanese HapMap samples; however, two samples lay outside the main Japanese cluster, and those samples were excluded. Therefore, the final analysis consisted of 234 METH-dependent (193 METH-induced psychosis and 41 non-psychosis) subjects and 864 healthy comparison subjects.

The genotyping platform for the Japanese SCZ Study was Affymetrix 5.0, and SNPs were evaluated using the same procedures used in our previous study (Ikeda *et al*, 2011).

Statistical Analysis

To assess the association between individual SNPs, we used genomic control (GC)-adjusted P -values derived from

allele-wise analysis based on median chi-square statistics (Purcell *et al*, 2007).

We performed a polygenic component analysis following the method described by the International Schizophrenia Consortium (ISC) (Purcell *et al*, 2009). This analysis is based on the idea that common SNPs collectively contribute to a substantial proportion of the heritability of complex diseases. To test this hypothesis, in essence, the authors defined sets of putative 'risk' alleles as being those that surpassed more liberal thresholds for association (eg, $P < 0.5$) in a discovery case-control sample set ('discovery' sample). These sets (ie, putative 'risk' alleles) were used to construct polygenic scores, which represent the number of 'risk' alleles carried by individuals in a second test data set ('target' sample). The analysis showed that the cases had on average significantly higher polygenic scores than controls. After discounting the influence of potential sources of bias, the authors in ISC concluded that the findings were best explained by the existence of polygenic component to the disorder comprised of a large number of common 'risk' alleles with small and cumulative effect.

Although several approaches are now available to examine the polygenic effects on the complex diseases/phenotypes (eg, GCTA: Yang *et al*, 2011), the polygenic component analysis which we used in this study is suitable to evaluate the genetic overlap within the same phenotype (eg, in the ISC, they extracted 'risk' from their 'discovery' SCZ GWAS and applied these to the independent 'target' SCZ GWASs to examine whether cases in the target samples had higher polygenic score) or between different diseases (extracted risk from their 'discovery' SCZ GWAS and applied to the 'target' bipolar disorder GWASs). Therefore, we applied this method to evaluate the genetic risk overlap with relaxed thresholds in METH dependence, METH-induced psychosis, and SCZ. The same criteria used by the ISC (Purcell *et al*, 2009) for LD pruning were applied to METH samples (r^2 threshold of 0.25 and window size of 200 SNPs) and 64 815 LD-independent SNPs based on linkage equilibrium were analyzed. The polygenic score was calculated using PLINK ver.1.07 (Purcell *et al*, 2007). Nagelkerke's pseudo R^2 was calculated by logistic regression with covariation for 'non-missing SNPs'. A one-tailed test was applied under a directional hypothesis that expects higher scores to be associated with an increased risk of disease.

We also performed gene-based testing of the associations, because this method can provide more statistical power than single SNP-based analysis (Liu *et al*, 2010). To conduct the analysis, the software package VEGAS (Liu *et al*, 2010) was used by applying individual SNP-based P -values of the GC adjustment. VEGAS can perform analyses by taking into account not only gene size but also linkage disequilibrium patterns based on the HapMap East Asia (JPT and CHB) panel. SNPs were assigned to one or more defined boundaries of autosomal genes by extending the genomic sequence corresponding to each gene by 50 kb in the 5' and 3' directions. Gene-based P -values for all genes were calculated in this analysis, and 17 049 genes were assigned for both disorders (genomic positions were based on hg18). To include genes with nominal associations, we set the type I error rate for the gene-based test to 0.05. The enrichment was assessed by hyper-geometric analysis.

RESULTS

SNP-Based Association Results of 'METH-Dependence' and 'METH-Induced Psychosis' GWASs

The Manhattan plots for the 'METH-dependence' and 'METH-induced psychosis' GWASs are shown in Figure 1, and the Q-Q plots are shown in Supplementary Figures S2 and S3. The GC inflation factors (λ) were 1.024 and 1.016 for the 'METH-dependence' and 'METH-induced psychosis' GWASs, respectively. We did not detect any SNPs with genome-wide significance (5×10^{-8}), which is widely used as a benchmark of association, in either data set. The strongest association with METH dependence was observed for the rs4427170 SNP in the sarcoglycan zeta gene (*SGCZ*) ($P = 3.9 \times 10^{-6}$, two-tailed test; Table 1), and the strongest association with METH-induced psychosis was observed for rs12591257, an intronic SNP in ATP/GTP binding protein-like1 (*AGBL1*) ($P = 3.6 \times 10^{-6}$,

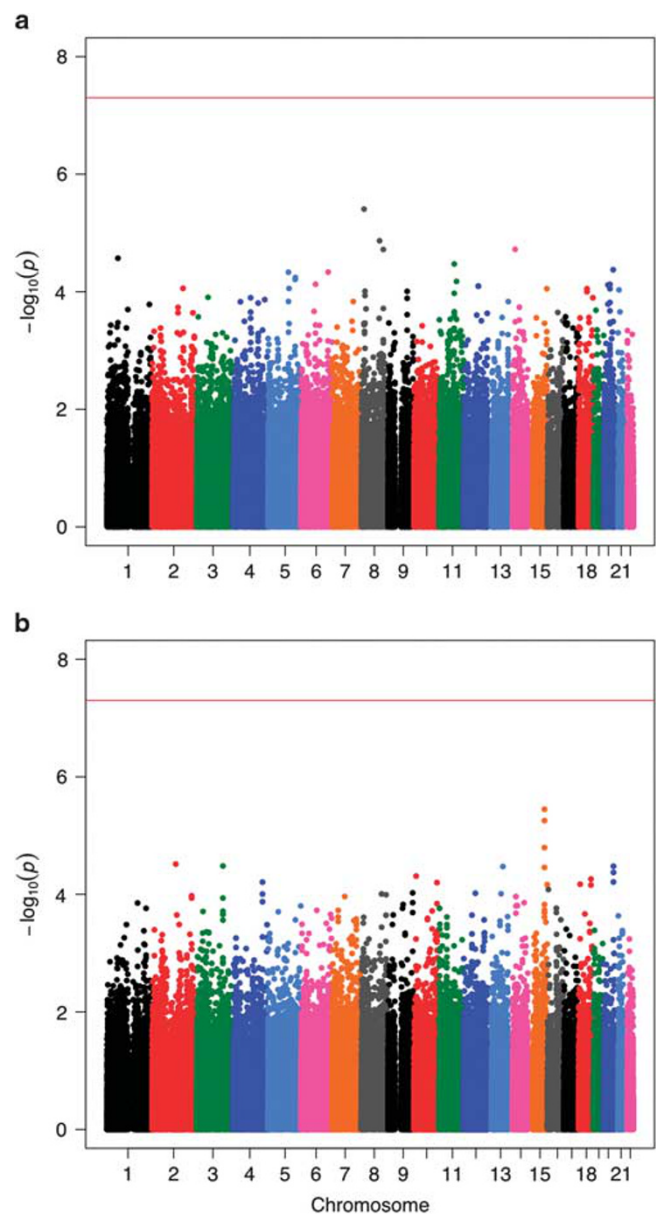


Figure 1 The Manhattan plots for (a) METH dependence and (b) METH-induced psychosis GWASs. METH, methamphetamine.

Table 1 Individual SNP-Based Analyses of METH-Dependence and METH-Induced Psychosis GWASs

Phenotype	SNP	Rank	CHR ^a	BP ^b	AI ^c	Frequency of AI in case	Frequency of AI in control	A2 ^d	OR ^e	P _{GC} ^f	Gene ^g
METH-dependence GWAS	rs4427170	1	8	14853781	T	0.515	0.395	A	1.63	3.9×10^{-6}	SGCZ
	rs7826857	2	8	99436341	A	0.081	0.162	G	0.45	1.4×10^{-5}	KCNS2
	rs12894058	3	14	33532016	A	0.222	0.140	G	1.75	1.9×10^{-5}	NPAS3
	rs2326193	4	8	120029709	A	0.338	0.239	C	1.63	1.9×10^{-5}	
	rs4915748	5	1	61954169	T	0.150	0.242	C	0.55	2.7×10^{-5}	
	rs617231	6	11	84837898	C	0.131	0.070	T	1.99	3.4×10^{-5}	DLG2
	rs6022102	7	20	51425077	C	0.209	0.133	T	1.73	4.2×10^{-5}	
	rs6940190	8	6	148644731	A	0.280	0.383	T	0.63	4.6×10^{-5}	SASH1
	rs2416305	9	5	112483604	G	0.197	0.293	A	0.59	4.7×10^{-5}	MCC
	rs17111695	10	5	150432446	C	0.186	0.115	T	1.77	5.7×10^{-5}	TNIPI
METH-induced psychosis GWAS ^h	rs12591257	1	15	87064089	C	0.041	0.183	A	0.19	3.6×10^{-6}	AGBL1
	rs2346713	2	15	87078337	C	0.067	0.232	A	0.24	5.6×10^{-6}	AGBL1
	rs16977267	3	15	86993464	T	0.073	0.232	G	0.26	1.6×10^{-5}	AGBL1
	rs13414154	4	2	129012073	A	0.145	0.342	G	0.33	3.1×10^{-5}	HS6ST1
	rs6767236	5	3	143758399	G	0.189	0.402	T	0.35	3.3×10^{-5}	
	rs6091985	6	20	53445939	C	0.044	0.171	G	0.22	3.3×10^{-5}	
	rs7333069	7	13	82458858	A	0.394	0.646	C	0.36	3.4×10^{-5}	
	rs8026683	8	15	86825255	A	0.098	0.268	C	0.30	3.5×10^{-5}	AGBL1
	rs6064117	9	20	53458592	G	0.047	0.175	A	0.23	4.2×10^{-5}	
	rs2768428	10	10	12523129	T	0.052	0.183	C	0.24	4.9×10^{-5}	CAMK1D

^aCHR: chromosome.^bBP: base position based on hg19.^cAI: minor allele name based on whole sample.^dA2: major allele name.^eOR: odds ratio (for AI: A2 is reference).^fP_{GC}: P-value-adjusted genomic control (two-sided).^gGene: gene (± 20 kb).^hThis comparison was based on the presence (or absence) of psychotic symptoms in the METH-dependence samples.

two-tailed test; Table 1). The 100 SNPs most associated with these disorders are shown in Supplementary Tables S1 and S2 (Figure 1 and Table 1).

Polygenic Component Analysis and Gene-Based Analysis

In the polygenic component analysis, we detected statistically significant enrichment of alleles scored in the 'discovery' METH-induced psychosis GWAS sample in the 'target' SCZ GWAS sample at P -thresholds (P_{TS}) of <0.3 , 0.4 , and 0.5 ($P_{best} = 0.0090$, Supplementary Figure S4; Figure 2). However, the variances in SCZ liability explained by the 'risk' SNPs of METH-induced psychosis were smaller ($R^2 \sim 0.7\%$, Supplementary Figure S4) than those found in previous studies when only SCZ samples were used in the polygenic component analysis ($R^2 \sim 3\%$) (Purcell *et al*, 2009; Ikeda *et al*, 2011). The reciprocal analysis (discovery/target SCZ/METH-induced psychosis pair) revealed a non-significant P -value of statistical enrichment of the 'risk' SCZ alleles in the 'target' METH-induced psychosis samples ($P_{best} = 0.092$, Supplementary Figure S5). Although statistical evidence was not obtained from this analysis (likely due to the small 'target' sample), it is of note that the variances

explained were higher ($R^2 \sim 1.2\%$, Supplementary Figure S5) than that detected in the discovery/target METH-induced psychosis/SCZ pair, suggesting that larger METH-induced psychosis sample sizes will be essential for obtaining conclusive results. By contrast, no statistical overlap was observed among other combinations of discovery/target pairs (Figure 2, Supplementary Figures S6–S9).

We also performed gene-based testing of the associations, because this method can provide more statistical power than individual SNP-based analysis (Liu *et al*, 2010). Seventy-four of the 17049 genes showed significant associations at $P_{gene} < 0.05$, both in METH-induced psychosis and SCZ, suggesting significant enrichment by hypergeometric analysis ($P = 0.0075$; Supplementary Table S3). Supplementary Table S4 lists the genes that overlapped. Notably, *NOTCH4*, a promising candidate gene for SCZ (Stefansson *et al*, 2009; Ikeda *et al*, 2012) was found to be associated with both disorders (Figure 2).

DISCUSSION

In the current study, we detected shared genetic risk between METH-induced psychosis and SCZ but failed to

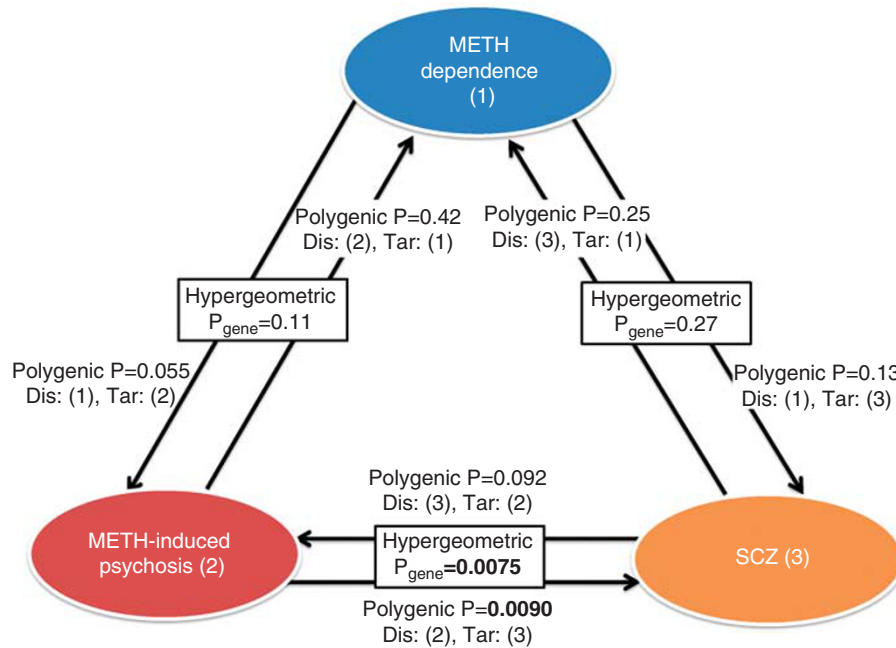


Figure 2 Relationship between METH-dependence (1), METH-induced psychosis (2), and schizophrenia (3). METH, methamphetamine; SCZ, schizophrenia; Dis, Discovery sample; Tar, Target sample. 'Polygenic *P*' indicates the best *P*-value calculated by logistic regression analysis in the polygenic component analysis. 'Hyper-geometric *P*' indicates the *P*-value calculated by hyper-geometric analysis to assess the enrichment of the risk genes that showed significance in both the two conditions (based on gene-based analysis).

detect an overlap between METH dependence and SCZ. These results highlight that the comparison between the 'presence' and 'absence' of psychosis within METH-dependent subjects, in our case, is preferable and important (even for polygenic component analysis) because the effect size of genetic markers associated with drug response (ie, psychosis as a response to METH exposure) is considered to be larger than that expected in the susceptibility to common and complex diseases (ie, SCZ and METH dependence) (Cirulli and Goldstein, 2010). Although the division of the METH-dependent subjects according to psychotic status will result in lowering the statistical power due to the reduced sample size, this type of research, especially in the psychiatry field where substantial disease heterogeneity is assumed, may benefit from the larger effect size following by this pharmacogenetic/genomic concept (Bousman *et al*, 2009; Cirulli and Goldstein, 2010).

However, our SNP-based analysis, even for METH-induced psychosis, did not show any associations with genome-wide significance. The presence of type II errors in this study are inevitable given our sample size; it is of note, however, that *AGBL1* (rs12591257, $P = 3.6 \times 10^{-6}$) showed a trend for an association with METH-induced psychosis. *ABGL1* was one of the candidate genes for SCZ based on the CATIE GWAS (Sullivan *et al*, 2008), as well as for the side effect by antidepressant treatment in the STAR*D study (Clark *et al*, 2012). In addition, several reports suggested an association between SCZ and the genes listed in our top hits, such as *NPAS3* (Pieper *et al*, 2005; Lavedan *et al*, 2009; Pickard *et al*, 2009; Huang *et al*, 2010; Macintyre *et al*, 2010) and *DLG2* (Kristiansen *et al*, 2006; MacLaren *et al*, 2011). Therefore, although we failed to find associations in this study, the non-genome-wide level of statistical significance

should be interpreted with caution and be validated by independent replication study.

To address the issue of the small sample size in the current study, we applied the powerful method of polygenic component analysis described by ISC, which showed that common SNPs collectively contribute to a substantial proportion of the heritability of common complex diseases. Our main finding supports previous epidemiological evidence linking between METH-induced psychosis and SCZ (Chen *et al*, 2005). Nevertheless, the variance-explained connecting these conditions was modest ($R^2 \sim 0.7\%$), and it showed similar magnitude reported in the comparison of SCZ between Japanese and the UK populations ($R^2 \sim 0.8\%$, Ikeda *et al*, 2011). This suggests that at least some of the liberal 'risk' alleles of the METH-induced psychosis GWAS are likely to be SCZ risk alleles, but these disorders have specific risk alleles as well. Furthermore, the results obtained by gene-based analysis, which showed a significant enrichment of the risk genes between these two conditions, are also in agreement with the results of the polygenic component analysis (Figure 2). Therefore our results based on the polygenic component and the gene-based analyses are the first molecular genetic evidence for overlap between METH-induced psychosis and SCZ in humans: this, in turn, supports the proposed role of the METH exposure, where mice treated by METH have been used as a mouse model of SCZ (Machiyama, 1992). In the gene-based analysis, although it involves multiple comparison issues, it is also of note that we detected a significant association of *NOTCH4* (Stefansson *et al*, 2009; Ikeda *et al*, 2012) both with the METH-induced psychosis and SCZ samples. Other overlap genes are possible candidate genes for 'psychosis', thus these genes should be examined with different sets of

samples, especially for SCZ, because our results indicate a higher previous likelihood that these genes are susceptibility genes for SCZ.

Several limitations should be noted to interpret our results. Firstly, the polygenic score aggregates evidence from multiple weakly associated genomic loci, which is important in the situation where most of the true-positive association signals fall below the genome-wide association threshold due to a lack of statistical power. In this context, there are several confounding problems associated with the interpretation of polygenic score analysis results. One critical factor is population stratification. To check for the possibility of this effect, we performed 'discovery/target METH-induced psychosis/SCZ' analysis with the major four principle components included as covariates. In this analysis, however, we still found statistically significant enrichment at $P_T < 0.3$, 0.4, and 0.5, despite the decreased variance described above (Supplementary Figure S10). Another concern is the difference between cases and controls in terms of gender ratio, which is biased substantially towards males in the METH-dependent subjects (>3:1). We have not conducted the analysis of X-linked loci, as there is no gold standard so far established in analyzing the genotypes on chromosome X but included the 'discovery/target METH-induced psychosis/SCZ' analysis using gender-adjusted P -values for discovery statistics (Supplementary Figure S11). Again no large change was observed in this explorative analysis.

In summary, a large number of 'risk' SNPs selected from a METH-induced psychosis GWAS are enriched in individuals with SCZ. This result suggests that the overlap between genes scored as positive in both the data sets can have higher probability as susceptibility genes for psychosis. In the future, the shared genetic risk component between these disorders may provide insights into disease processes and the diagnosis and may open up new avenues for drug development in terms of pharmacological modeling of psychosis. Based on the current study, however, it is difficult to clarify the question of whether the 'transient' type (remitting a psychiatric state immediately or a couple of weeks after METH exposure) or 'prolonged' type of psychosis has more genetic similarity with SCZ. To obtain conclusive results, further studies with much larger samples are required.

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The authors declare no conflict of interest.

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