OXFORD

*International Journal of Neuropsychopharmacology* (2019) 22(3): 186–193

**doi:10.1093/ijnp/pyy103**
Advance Access Publication: December 20, 2018
Regular Research Article

REGULAR RESEARCH ARTICLE

# Peripheral Biomarkers in Schizophrenia: A Meta-Analysis of Microarray Gene Expression Datasets

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## Abstract

**Background:** Schizophrenia is a severe psychiatric disorder with a complex pathophysiology. Given its prevalence, high risk of mortality, early onset, and high levels of disability, researchers have attempted to develop early detection strategies for facilitating timely pharmacological and/or nonpharmacological interventions. Here, we performed a meta-analysis of publicly available gene expression datasets in peripheral tissues in schizophrenia and healthy controls to detect consistent patterns of illness-associated gene expression. We also tested whether our earlier finding of a downregulation of *NPTX2* expression in the brain of schizophrenia patients replicated in peripheral tissues.
**Methods:** We conducted a systematic search in the Gene Expression Omnibus repository (https://www.ncbi.nlm.nih.gov/gds/) and identified 3 datasets matching our inclusion criteria: GSE62333, GSE18312, and GSE27383. After quality controls, the total sample size was: schizophrenia (n=71) and healthy controls (n=57) (schizophrenia range: n=12–40; healthy controls range: n=8–29).
**Results:** The results of the meta-analysis conducted with the GeneMeta package revealed 2 genes with a false discovery rate <0.05: atlastin GTPase 3 (*ATL3*) (upregulated) and arachidonate 15-lipoxygenase, type B (*ALOX15B*) (downregulated). The result for *ATL3* was confirmed using the weighted Z test method, whereas we found a suggestive signal for *ALOX15B* (false discovery rate<0.10).
**Conclusions:** These data point to alterations of peripheral expression of *ATL3* in schizophrenia, but did not confirm the significant association signal found for *NPTX2* in postmortem brain samples. These findings await replication in newly recruited schizophrenia samples as well as complementary analysis of their encoded peptides in blood.

**Keywords:** biomarker, biostatistics, meta-analysis, pathway analysis, psychosis, transcriptomics

**Received:** September 9, 2018; **Revised:** December 7, 2018; **Accepted:** December 19, 2018

## Significance Statement

Schizophrenia is a severe psychiatric disorder caused by the interplay of genetic and nongenetic (environmental) factors. Typically, individuals become ill in the late teens to early twenties, and most of them spend their remaining lifespan with severe clinical symptoms that cause a significant decline in their functioning. Thus, it is key to identify at-risk subjects before the illness manifests entirely. In this study, we take advantage of sophisticated bioinformatics approaches to put together publicly available data on the expression of genes in peripheral tissues of individuals with schizophrenia. We found that the expression of a gene, the atlastin GTPase 3 (*ATL3*), was increased in schizophrenic subjects compared with healthy controls. These findings, although encouraging, should be considered as preliminary and await replication in larger samples and newly recruited patients.

## Background

Schizophrenia (SCZ) is a severe psychiatric disorder affecting about 0.5% of the population worldwide (Saha et al., 2005). The incidence rate of SCZ has been estimated at around 0.015%, with peaks during the second and third decades of life (McGrath et al., 2004). The diagnosis of SCZ has a high prospective stability (Fusar-Poli et al., 2016), and affected individuals face a remaining lifespan of chronic active illness substantially impacted by high levels of disability (Świtaj et al., 2012), high rates of medical (Hert et al., 2011) and psychiatric comorbidities (Buckley et al., 2009), and an increased risk of mortality (Saha et al., 2007)—with about 14.5 years of life lost on average (Hjorthoj et al., 2017)—compared with the general population. On top of this, one-third of cases show unresponsiveness to psychopharmacological treatments (Meltzer, 1997), resulting in an even higher burden on the public healthcare system as well as on the entire society.

Thus, researchers have attempted to develop early detection strategies for facilitating early pharmacological and/or nonpharmacological interventions, possibly even in the early stages of SCZ (Sommer et al., 2016). These approaches have been based on the identification of clinical (behavioral, motor, neurocognitive, and psychopathological) (Welham et al., 2009), and neurobiological (Millan et al., 2016) antecedents and have led to the formulation of staging hypothesis in SCZ.

Ideally, predictive models of the longitudinal trajectory of SCZ should be based on readily and easily obtainable markers such as those detectable through a blood sample. Genetic markers pertain to this group. For instance, polygenic risk scores for SCZ, derived from genome-wide association studies, were associated with the manifestation of negative symptoms and anxiety in a large cohort of adolescent followed-up from the age of 12 to 18 years (Jones et al., 2016). Another strategy consists in the analysis of peripheral gene and/or protein expression levels with the aim to develop panels of markers that might distinguish, for instance, unaffected individuals from patients at clinical risk for SCZ (Chan et al., 2015). Although promising, this approach should rely on markers for which association with illness status is statistically significant, biologically validated, and consistently replicated, a scenario at the moment nonexistent in SCZ (Belbasis et al., 2018).

In this context, the exploratory analysis of publicly available datasets can lead to the identification of molecular targets testable in vivo. Using a rigorous meta-analytical methodology, we have shown the consistent and highly statistically significant downregulation of neuronal pentraxin 2 (*NPTX2*) gene in datasets from human-induced pluripotent stem cell-derived neurons and postmortem brain tissue of SCZ patients compared with healthy controls (HC) (Manchia et al., 2017). Of interest, this gene was recently implicated in the pathogenesis of Alzheimer's disease (Cummings et al., 2017) and anxiety (Chang et al., 2018).

In light of these considerations, here we aimed at performing a meta-analysis of publicly available dataset gene expression in peripheral tissues in SCZ and HC to detect consistent patterns of illness-associated gene expression. As an aside, we tested whether our finding of a down-regulation of *NPTX2* expression in the brain of SCZ patients was replicated in peripheral tissues.

## Methods

### Systematic Search of Microarray Expression Profiling Datasets From Peripheral Tissues

We conducted a systematic search in the Gene Expression Omnibus (GEO) repository (https://www.ncbi.nlm.nih.gov/gds/) using the following search terms: filters were "Homo sapiens" and "Expression profiling by array" and keywords were "Schizophrenia" and "Blood." We obtained a total of 23 datasets. A dataset was incorporated in the analysis if the following inclusion and exclusion criteria were satisfied: (1) used a case-control study design; (2) obtained with a noncustom Affymetrix microarray platform; (3) derived from blood or other peripheral tissues; (4) associated with a reference published in Medline; (5) excluded cases with specific genomic rearrangements or variants. After each dataset was checked independently by 2 authors (ISP and MM), we obtained a final list of 3 datasets, which were included in the meta-analysis.

### Datasets Included in the Meta-Analysis

We downloaded raw data of the 3 different microarray RNA expression profiling datasets selected: 1 of skin-derived fibroblasts (GSE62333) and 2 including expression profiling from peripheral blood samples matching the inclusion and exclusion criteria (GSE18312 and GSE27383), all publicly available in the GEO repository (https://www.ncbi.nlm.nih.gov/gds/). The dataset GSE62333 (Cattane et al., 2015) consisted of RNA expression profiling obtained with the Affymetrix Human Gene 1.1 ST array of skin-derived fibroblasts from 20 SCZ subjects and 20 HC. The patients from this study were unrelated, Caucasian and with Italian descent for at least 2 generations. They satisfied the DSM-IV (APA, 2000) criteria for SCZ, and diagnoses were confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (First, 1997). The control samples were unrelated healthy volunteers screened for DSM-IV Axis I disorders by expert psychologists using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Further details are reported in the original study (Cattane et al., 2015).

The dataset GSE18312 (Bousman et al., 2010) consisted of RNA expression profiling obtained with the Affymetrix Human Exon 1.0 ST array of peripheral blood from 13 SCZ subjects and 8

HC. The patients and controls were recruited from the University of California, San Diego and diagnosed using the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994). All details about exclusion and inclusion criteria are reported in Bousman et al. (2010).

The dataset GSE27383 (van Beveren et al., 2012) consisted of RNA expression profiles obtained with Affymetrix Human Genome U133 Plus 2.0 Array of peripheral blood from 43 SCZ subjects and 29 HC. The patients were all males and recruited at the Department of Psychiatry of the Erasmus University Medical Center, Rotterdam, the Netherlands. They were recent onset patients (<5 years) and aged between >15 and <36 years, diagnosed according to DSM-IV criteria after a Comprehensive Assessment of Symptoms and History interview (Andreasen et al., 1992) and by consensus between 2 senior psychiatrists who were blind to the expression results at the time of diagnosis. Clinical symptom severity was assessed with the Positive and Negative Syndrome Scale (Kay et al., 1989). The controls were also recruited at the ECM. Further details about the inclusion and exclusion criteria for cases and controls are reported in van Beveren et al. (2012).

### Quality Control

For all datasets, the following analytical framework was applied. Raw intensity signals (*.CEL files) were normalized using the Robust Multi-Array Average algorithm (Irizarry et al., 2003) using the R-package *affy* (Gautier et al., 2004). Quality controls (QC) were conducted using the R-package *ArrayQualityMetrics* (Kauffmann et al., 2009), inspecting heatmaps of inter-array expression distances, Principal Component Analysis, and MAplot, the latest including the log-intensity ratios (M-values) vs log-intensity averages (A-values). Samples classified as outliers in 2 of the 3 metrics in the first round of QC runs were removed from the dataset. Then, the raw data without outliers were normalized again and used for the downstream analysis. The datasets were annotated with the R Bioconductor packages *hgu133plus2.db*, *hugene10sttranscriptcluster.db*, and *hgu133a.db*, depending to the platform. Filtering was performed using the *GeneFilter* R-package (Gentleman et al., 2018). We excluded nonannotated and duplicated probes, and low expressed probes using the interquartile method (variance cutoff = 0.50).

### Microarray Gene Expression Meta-Analysis

We used 2 different meta-analytic approaches. The main method was developed by Choi et al. (2003), where an overall ranked gene list is produced based on the false discovery rate (FDR) of each gene. The second method is based on the *P* value combination from the differential expression analyses using the Fisher Z weighted test (Zaykin, 2011).

When we applied the method of Choi et al. (2003), the input consisted of the matrix of Robust Multi-Array Average normalized expression values for the common genes. The analysis was conducted with the R package *GeneMeta* (Lusa et al., 2018) using the Random Effect Model to account for heterogeneity among studies as implemented in the function "Zscore." The FDR for each gene was obtained with the function "ZscoreFDR" using 100 000 permutations. The genes were considered significant for FDR < 0.05.

Further corroboration of our findings came from the method based on *P* values combination (Zaykin, 2011). In this case, the input consisted of the *P* values obtained from the differential expression analysis. We conducted the differential expression analysis for the 3 datasets separately, using a linear model as implemented in the R-package *Limma* (Ritchie et al., 2015), including sex and age as covariates (when available) to minimize the sources of variability among studies. The significance was assessed with the moderated *t* test and the *P* values were corrected for multiple testing using the FDR method (Benjamini and Hochberg, 1995). Since the Fisher Z weighted test assumes 1-tailed *P* values, we converted the 2-tailed nominal *P* value to 1-tailed *P* value using the following formula when the Log2 fold change was >0: $P_{1Tailed} = P_{2\text{-}Tailed}/2$. Otherwise, we used the following formula: $P_{1Tailed} = 1 - (_{P2Tailed/2})$. The uncorrected *P* values were weighted using the sample sizes of the 3 datasets and combined using the *combine.test* function with the "*Z.method*" option included in the R-package *survcomp* (Schroder et al., 2011). Finally, the combined 1-tailed *P* values were converted in 2-tailed *P* values and corrected with the FDR method.

We compared the results between this meta-analysis and our previous study (Manchia et al., 2017) computing the Spearman correlation coefficient between overlapping genes detected in both studies (using the Zscore from the GeneMeta results). Moreover, we investigated the relationship of the same genes across different tissues using the RNA sequencing data available in the Genotype-Tissue Expression (GTEx) database (GTEx Consortium, 2015) from whole blood and brain cortex. We used the transcript per million counts, with a log2 transformation for both graphical representation and analysis. We computed the Spearman correlation coefficient between whole blood and brain areas, and the expression levels were compared using the Mann–Whitney U test.

### Pathway-Based Microarray Meta-Analysis

We conducted a meta-analysis for pathway enrichment (MAPE) using the method developed by Shen and Tseng implemented in the R-Package Metapath (Shen and Tseng, 2010). We used the integrated method (MAPE_I), which combines and exploits the advantages of the meta-analytic approach at the gene level (MAPE_G) with the meta-analytic approach after pathway analysis (MAPE_P). The input for the analysis consisted of the complete microarray datasets, including overlapping and nonoverlapping genes. We conducted the analysis using the conservative statistics max*p* to identify consistent biomarkers across the different studies, and the Kolmogorov-Smirnov statistics for the enrichment (Shen and Tseng, 2010). The results were corrected using the FDR method (Benjamini and Hochberg, 1995). As a reference database for the enrichment, we used the Molecular Signatures Database "hallmark" gene set. This gene set was developed using a hybrid approach combining computation with manual expert imputation. The advantage is a reduction of redundancy and the production of more robust enrichment results (Liberzon et al., 2015).

## Results

### Quality Controls

We removed 1 outlier from the SCZ group in the dataset GSE62333, obtaining a final dataset of 19 SCZ and 20 HC samples. The dataset GSE18312 consisted originally of 13 SCZ and 8 HC. One outlier in the SCZ group was detected, with a final sample size comprised of 12 cases and 8 HC. The dataset GSE27383 was comprised of 43 SCZ and 29 HC. The SCZ group was composed of 22 "acutely remitted" and "remitted." After removal of 3 outliers

in the patients group, the final dataset was comprised of 40 SCZ and 29 HC.

### Differential Gene Expression Analysis

We conducted the differential gene expression analysis for each dataset separately to obtain the *P* values for the meta-analysis based on Fisher's Z weighted test. The complete results for the 3 datasets are reported in supplementary Tables 1 (GE62333), 2 (GSE18312), and 3 (GSE27383). After QC, the dataset GSE62333 had 9241 probes, with 13 of them statistically significant after correction for multiple testing and 976 significant before correction (supplementary Table 1). The dataset GSE18312 had 7238 different probes. After correction for multiple testing, we did not obtain statistically significant results. However, 517 probes were significant before multiple test correction (supplementary Table 2). For dataset GSE27383, we analyzed 10 096 different probes. After correction for multiple testing, we obtained 313 probes statistically significant (supplementary Table 3), with 1747 significant before correction. The overlap of the differentially expressed genes among datasets is reported in the Venn diagram (Figure 1). There were no overlapping genes after adjustment for multiple testing. We detected 2 genes significant before adjustment across the 3 datasets: *DNAJC13* and *IL18R1*. However, *IL18R1* showed a discordant log2 (FC) in the dataset GSE18312.

### Microarray Gene Expression Meta-Analysis

We combined the 3 datasets, obtaining a total of 2641 common genes used as input in the meta-analysis. The results of the meta-analysis conducted with the *GeneMeta* package revealed 2 genes with FDR < 0.05: atlastin GTPase 3 (*ATL3*) (upregulated; FDR = 0.048) and arachidonate 15-lipoxygenase, type B (*ALOX15B*) (downregulated; FDR = 0.049) (Table 1). A detailed report of this analysis is outlined in supplementary Table 4, while the box plots of *ATL3* and *ALOX15B* gene expression are shown in supplementary Figure 1.

As a validation method, we combined the nominal *P* values obtained in the differential gene expression analysis using the Fisher's weighted z test, correcting the results with the FDR method (supplementary Table 5). In this analysis, we obtained 37 genes significant after correction for multiple testing. Interestingly, the *ATL3* gene also showed a significant upregulation as observed with the GeneMeta analysis (adj *P* = 4.8E-02), whereas *ALOX15B* confirmed to be downregulated, albeit with only a suggestive association signal (adj *P* = 5.3E-02).

We compared our results with our previous study, but *ATL3* and *ALOX15B* were not present in the datasets, probably removed during QC steps. We did not detect any other overlap when we compared the results obtained using both methods.

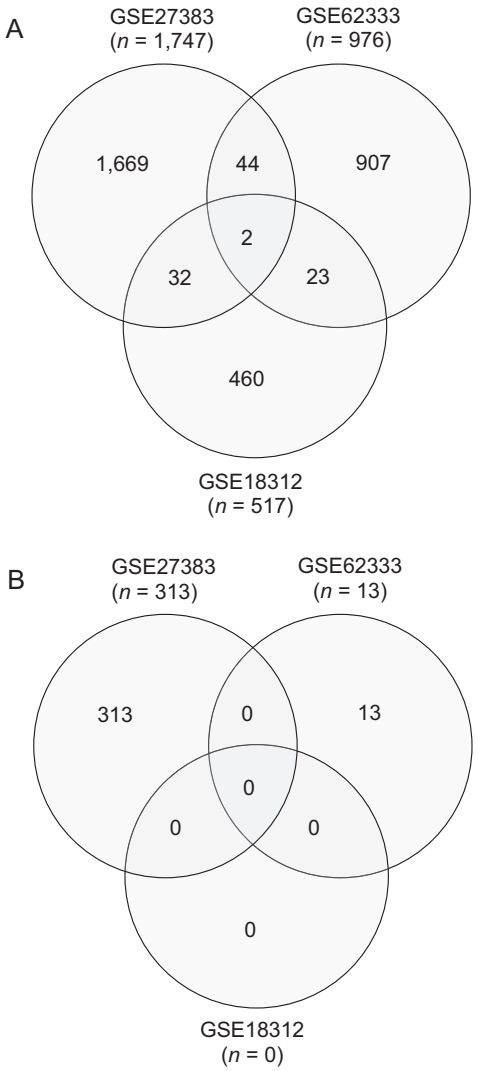


**Figure 1.** Venn diagram showing the overlap of differentially expressed genes among included datasets. (A) Before adjustment for multiple testing; (B) after adjustment for multiple testing.

### *NPTX2* Expression Level

In light of the results obtained in our previous study (Manchia et al., 2017), we checked the expression levels of the *NPTX2* gene in the analyzed datasets. The gene was not present in all datasets. Then, we reanalyzed the data without filtering out the low variance probes, detecting *NPTX2* in GSE62333 and GSE27383, but not in GSE18312. The gene was nonsignificantly downregulated in the other 2 datasets, which showed weak *NPTX2* expression (Table 2). We combined the 2 datasets with the 2 meta-analytic methods, obtaining in

**Table 1.** Significant Results for the Meta-Analysis Conducted With the GeneMeta Package

| | GSE62333 | | GSE18312 | | GSE27383 | | Combined | |
|---|---|---|---|---|---|---|---|---|
| Genes | z | FDR | z | FDR | z | FDR | z | FDR |
| *ATL3* | 1.460 | 0.573 | 1.925 | 0.545 | 2.830 | 0.084 | 3.630 | 0.048 |
| *ALOX15B* | −1.529 | 0.545 | −1.918 | 0.538 | −2.692 | 0.102 | −3.566 | 0.049 |

**Table 2.** Expression Levels of *NPTX2* in GSE62333 and GSE27383

| Dataset | Probe ID | log2 FC | Average Expression | *t* | B | *P* | Adjusted *P* |
|---|---|---|---|---|---|---|---|
| GSE62333 | 8134463 | −0.060 | 4.836 | −0.739 | −5.576 | .464 | .830 |
| GSE27383 | 213479_at | −0.051 | 4.086 | −1.014 | −5.506 | .314 | .700 |

The gene was not detected in the dataset GSE18312. All *P* values are 2 sided. FC, fold-change.

both cases nonsignificant results: z = −1.326 and adj *P* = .700 with *GeneMeta*, and adj *P* = .637 with the Weighted z test (not adjusted *P* = .216).

### Comparison of Brain and Peripheral Gene Expression Data

We compared the RNA profiling results obtained in this study with the results from our previous study (Manchia et al., 2017) in brain tissue. We used the "*GeneMeta*" results, computing a nonparametric correlation between the z scores of the 2 analyses, representing the final effect size for each meta-analysis. We found 692 overlapping genes, and the correlation was not significant (ρ=0.010; *P*=.783) (supplementary Figure 2). Further, we used the GTEx data to assess the correlation between 665 of the 692 overlapping genes we found in GTEx. We compared the log2-transformed transcript per million counts available on GTEx between whole blood and cortex, frontal cortex (BA9), and anterior cingulate cortex (BA24). In all regions, we obtained significant and positive correlations (ρ ranging from 0.261 to 0.299; *P*<1E-12). The scatterplot with the correlation for Cortex is reported in supplementary Figure 3. We also compared the expression levels among these brain regions and whole blood observing significant lower expression values in the latter tissue compared with brain regions (Mann–Whitney U test: *P*<2.2E-16) (supplementary Figure 4).

### Pathway-Based Microarray Meta-Analysis

The meta-pathway analysis conducted with MetaPath using the Molecular Signatures Database Hallmark gene set did not identify biological processes significantly perturbed after FDR correction, but 3 nominally significant processes (supplementary Table 6).

## Discussion

### Findings From Gene Expression Microarray Meta-Analysis

In this study, we performed a meta-analysis of publicly available gene expression datasets from peripheral tissues in the attempt to identify biological targets associated with SCZ. In addition, we tested whether the finding of a highly significant alteration in *NPTX2* gene expression in the brain of SCZ patients (Manchia et al., 2017) was consistently (downregulation) or discordantly (upregulation) replicated in peripheral tissues. *ATL3* was significantly upregulated using both meta-analytical methods (adj *P*<.05), whereas *ALOX15B* (downregulated) was marginally significant in one case but showed a suggestive signal (adj *P*<.10) in the second method. Finally, we were not able to detect a significant association signal for *NPTX2* gene expression.

### Comparison With Previous Evidence

The *ATL3* gene is located on chromosome 11 in the cytogenetic band q13.1 and is comprised of 15 exons. This chromosomal region has not been previously implicated in the genetic architecture of SCZ by linkage analysis (Mulcrone et al., 1995) or genome-wide association studies (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014). Of interest, however, is the presence in *ATL3* genomic neighborhood of the gene encoding for a member of the neurexin family, neurexin 2. Although the involvement of neurexin family in SCZ is mainly led by evidence on neurexin 1 (Kirov et al., 2009), there are findings in animal models supporting a possible role of neurexin 2 in SCZ (Dachtler et al., 2015).

The *ATL3* gene encodes for a protein, atlastin-3, described in 2008 (Rismanchi et al., 2008) that is part of a family of human GTPases involved in the pathogenesis of hereditary sensory neuropathy (Kornak et al., 2014). Of note, atlastin-3 protein is widely expressed in peripheral tissues (Rismanchi et al., 2008) but also in the brain (Fagerberg et al., 2014). Its localization is predominantly in the endoplasmic reticulum (ER) membranes and serves as a key element of the structure and functioning of the ER (Kornak et al., 2014). This aspect is of great relevance in SCZ. Indeed, alterations in posttranslational protein modifications regulating protein targeting, trafficking, synthesis, and function, which take place in the ER, have been linked to SCZ pathophysiology (Patel et al., 2017; Kim et al., 2018). Although in the absence of a direct mechanistic link, it is plausible that a disruption in the *ATL3* gene, resulting in the perturbation of physiological ER function, might play a role in the pathophysiological underpinnings of SCZ.

The gene *ALOX15B* has 14 exons and is located on chromosomal area 17p13.1 (Krieg et al., 2001). The encoded product is the arachidonate 15-lipoxygenase, isoform B, a member of lipoxygenase family that converts arachidonic acid exclusively to 15S-hydroperoxyeicosatetraenoic acid (Droege et al., 2017). Of note, this eicosanoid pertains to the family of lipoxins, which, instead of promoting inflammation, exerts an anti-inflammatory effect (Aliberti et al., 2002). Evidence appears to support a biological link with SCZ. First, the presence of a downregulation of *ALOX15B* gene expression in peripheral tissue seems consistent with the neuroinflammatory hypothesis of SCZ (Müller, 2018). Indeed, a low level of arachidonate 15-lipoxygenase, isoform B implies a reduction in the synthesis of 15S-hydroperoxyeicosatetraenoic acid, an antiinflammatory lipoxin, with an overall increase in inflammation in SCZ patients. Recently, support for the neuroinflammatory hypothesis has come from the recent study of Sekar et al. (2016) that dissected the association signal in the most significant association region for SCZ, which lies among genetic markers in the major histocompatibility complex locus (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In fact, these authors found that this highly significant association involved several common, structurally distinct alleles of the gene encoding for complement 4 (C4) that affected expression of C4A and C4B, key components of immune response and inflammation, in the brain (Sekar et al., 2016). Overexpression of these proteins might lead to an excess of synaptic pruning (Sekar et al., 2016), possibly causative of detrimental effects at brain level.

Second, using fine mapping, Shlien et al. (2010) found a common deleted region that includes *ALOX15B* in patients with pervasive developmental disorder, bipolar disorder, aggressive behavior, and severe cognitive impairment.

Finally, there is evidence that the product of Disrupted in Schizophrenia 1 gene, strongly implicated in the genetic architecture of SCZ, regulates neuronal migration, neurite outgrowth, signal transduction, cyclic adenosine monophosphate signaling, cytoskeleton modulation, and translational regulation, by interacting with, among the others, nudE neurodevelopment protein 1 like 1, whose gene is in the same cytogenetic band downstream of *ALOX15B*.

### Comparison With Our Previous Findings

In this study, we were not able to detect the association signal for *NPTX2* previously found in our meta-analysis using RNA profiling from brain tissue. We were also not able to find an overall correlation between studies using the overlapping genes detected. However, the same genes showed a strong correlation between whole blood and brain in the GTEx data and a significantly lower expression in whole blood. The absence of correlation between studies can be explained in light of the following: (1) lower expression levels of overlapping genes in whole blood than in brain, with a consequent less reliable quantification and decreased power in this type of tissue; (2) the absence of a significant correlation between brain and whole blood expression data could be caused by the fact that the same genes might be specifically altered in brain tissue of affected subjects, but not in normal controls (as in GTEx); (3) the lack of a correlation might depend on the different samples used in the meta-analysis. An ideal situation for this type of comparison would be to conduct the study in whole blood and brain of the same individuals.

### Limitations

Our findings should be considered in light of a series of limitations. First, the lack of a biological validation limits the relevance of our findings. Secondly, the FDR method tends to be less stringent in controlling for the rate of Type 1 error compared with other approaches. Further, it should be noted that all transcriptomic changes that were nominally significant in each dataset did not replicate when analyzed across all three. Third, our results do not present correlation with relevant clinical outcomes in SCZ, such as, for instance, cognitive deterioration or severity of negative symptoms. Fourth, we were not able to adjust for duration of illness or for the presence of medical comorbidities, both factors that might influence the expression of genes, particular those related to inflammatory pathways. Fifth, since available datasets were collected cross-sectionally, our findings represent association but do not imply causality, that is, we were not able to assess whether alterations of gene expression anteceded or were consequent to the onset of the illness. Sixth, it is plausible that the lack of a correlation between brain and whole blood expression data might also depend on the different samples used in the meta-analysis. As explained in the previous section, this type of comparison should be ideally conducted in the whole blood and brain samples of the same individuals. Finally, the total sample size was small, also because of the limited availability of datasets to include in the meta-analysis. This is reflected in the low level of significance of our results. The inclusion of new studies (when available) will improve the statistical power of the meta-analysis.

In summary, using a systematic search of publicly available gene expression datasets and 2 different meta-analytical approaches, we found a consistent and statistically significant upregulation of *ATL3* gene and a downregulation of *ALOX15B* gene in peripheral tissues of SCZ patients. These data await replication in newly recruited SCZ samples as well as complementary analysis of their encoded peptides in blood to confirm their potential as reliable biomarkers of illness status in SCZ. It remains to be established whether these alterations in the pattern of gene expression might have predictive value in unaffected subjects at clinical risk for SCZ.

## Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

## Acknowledgments

This study makes use of data publicly available in the Gene Expression Omnibus (GEO) repository: GSE62333, GSE18312, and GSE27383. We thank the authors of the dataset-related publications for sharing their data.
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. J.L.K. and C.C.Z. were supported by a grant from the Canadian Institutes of Health Research. M.M. was supported by a grant funded by “Fondazione di Sardegna” and “Regione Autonoma della Sardegna”, L.R. 7/2007, year 2016 – DGR 28/21 of the 17/05/2015.

## Interest Statement

All the authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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