Schizophrenia is a highly polygenic brain disorder. The main hypothesis for disease etiology in schizophrenia primarily focuses on the role of dysfunctional synaptic transmission. Previous studies have therefore directed their investigations toward the role of neuronal dysfunction. However, recent studies have shown that apart from neurons, glial cells also play a major role in synaptic transmission. Therefore, we investigated the potential causal involvement of the 3 principle glial cell lineages in risk to schizophrenia. We performed a functional gene set analysis to test for the combined effects of genetic variants in glial type–specific genes for association with schizophrenia. We used genome-wide association data from the largest schizophrenia sample to date, including 13,689 cases and 18,226 healthy controls. Our results show that astrocyte and oligodendrocyte gene sets, but not microglia gene sets, are associated with an increased risk for schizophrenia. The astrocyte and oligodendrocyte findings are related to astrocyte signaling at the synapse, myelin membrane integrity, glial development, and epigenetic control. Together, these results show that genetic alterations underlying specific glial cell type functions increase susceptibility to schizophrenia and provide evidence that the neuronal hypothesis of schizophrenia should be extended to include the role of glia.

Key words: GWAS/PGC/gene set analysis/psychiatric disease/glia/genome-wide association

Introduction

Schizophrenia is a debilitating brain disease affecting up to 1% of the population. It is characterized by delusions, hallucinations, disordered speech, and deficits in emotional and social behavior. It is highly familial with heritability estimated at 81% and thought to be influenced by thousands of common alleles of small effects. Most efforts in understanding the cellular basis of schizophrenia have focused on the role of neurons. This has led to findings of alterations in neuronal transmission and synapse cytoarchitecture as well as reports of putative neuronal susceptibility genes. Nevertheless, recent insights have implicated glial cells in several brain functions that are highly relevant to neurological disorders. Accordingly, for each of the 3 principal glial cell types, altered gene expression has been found in brains of schizophrenia patients. Furthermore, oligodendrocytes have been implicated by diffusion tensor imaging studies showing disruption of white matter tracts in schizophrenia, and both astrocytes and microglia are associated with neuroinflammatory processes in several brain regions of schizophrenia patients. However, it still remains to be investigated whether glial perturbations in schizophrenia represent primary glial-genetic deficits and not merely secondary responses to disturbances in neuronal functioning.

Genetic association studies based on single nucleotide polymorphisms (SNPs) can be used to gain more insight...
into primary genetic processes that are potentially disease causing. Typically, genome-wide association studies (GWAS) have been used for this but require large samples in order to identify the typically small genetic effects underlying complex diseases as schizophrenia.\(^5\)\(^\text{21-24}\) Moreover, single SNP associations will not necessarily lead to insights in underlying molecular or cellular mechanisms.\(^25\)\(^\text{26}\) Alternatively, pathway analysis or functional gene set analysis involves testing for the combined effect of multiple SNPs in functionally related genes that individually have small effect sizes that do not reach significance. This approach thus takes into account genetic contributions that may only be observed if the appropriate combination of genes is tested.\(^25\)\(^\text{29}\)

Here, we used gene set analysis to obtain genetic evidence for primary roles of specific glial cell type functions and pathways in schizophrenia. Lists of nonoverlapping genes for astrocytes, oligodendrocytes, and microglia, obtained by means of a detailed literature study, were subdivided into glial functional gene sets based on Gene Ontology (GO) annotations and expert glial knowledge. Using the largest schizophrenia GWAS sample to date, including 13 689 schizophrenia cases and 18 226 controls, we found a significant association with schizophrenia for highly specific gene sets of astrocytes and oligodendrocytes, and no association with any of the microglia gene sets.

Subjects and Methods

**Generation of Glial Cell Type–Specific Gene Lists and Functional Gene Sets**

A flowchart of the steps taken for generating the glial gene lists and subsequent functional gene sets is shown in figure 1. More detailed information is provided in supplementary methods. Briefly, we conducted an in-depth literature study to select glial genes based on microarray gene expression patterns,\(^30\)\(^\text{38}\) and gene symbols and names were converted into human Entrez Gene IDs to assemble astrocyte, oligodendrocyte, and microglia gene lists.

Next, to strengthen the association of genes in these lists with specific astrocyte, oligodendrocyte, or microglia functioning, genes were removed if found in more than one of these cell types or if present in a curated exclusion list of general neuronal genes (supplementary figure 1; see supplementary methods for more information and exceptions). An enrichment analysis using GO biological processes was performed on the final, filtered astrocyte, oligodendrocyte, microglia, and neuronal lists to see if processes associated with specific cell type functions were uniquely enriched within each list. For each step, gene lists and gene IDs can be obtained from the corresponding authors.

For each glial cell type (oligodendrocytes, astrocytes, and microglia), functional gene sets were created based on GO biological process annotations. Importantly, gene sets were built according to the hierarchical structure of GO (ie, higher level parental nodes were subdivided into more specific child nodes), resulting in an organization of related gene sets over a maximum of 3 levels and substantial overlap of genes between gene sets (table 1; for detailed information, criteria, and used software\(^39\)\(^\text{43}\) see supplementary methods).

**Subjects**

We used individual GWAS data from the Psychiatric Genomics Consortium (PGC1) schizophrenia working group\(^3\) combined with an independent GWAS sample from Sweden.\(^6\) Details on sample collection for PGC1 and Swedish data sets have been described previously\(^5\)\(^\text{6}\) and can be found in supplementary methods. In total, 19 samples were available from 16 different sites. The combined sample totaled 13 833 cases and 18 310 controls and between 250 000 and 700 000 genotyped SNPs per data set (supplementary table 1).

**Quality Control**

Site-specific quality control (QC) has been explained previously in detail.\(^3\)\(^\text{5}\)\(^\text{6}\) Overall, technical QC was performed on genotypes generated by various GWAS platforms, which was conducted separately at each collection site using a common approach. Both the PGC1 and Swedish samples were quality controlled following the PGC1 QC pipeline. Common QC parameters were applied: (a) missing rate per SNP <0.05 (before sample removal below), (b) missing rate per individual <0.02, (c) missing rate per SNP <0.02 (after sample removal above), (d) missing rate per SNP difference in cases and controls <.02, (e) SNP frequency difference to HapMap <0.15, and (f) Hardy-Weinberg equilibrium (controls) \(P < 10^{-6}\). The number of SNPs per study after QC varied between 250 000 and 680 000. Samples were genotyped on 4 different platforms. After basic QC, 77 986 autosomal SNPs directly genotyped on all included GWAS platforms were extracted and pruned to remove SNPs in linkage disequilibrium (\(r^2 > .05\)) or with minor allele frequency <.05, leaving 39 239 SNPs suitable for robust relatedness testing and population structure analysis. All SNPs that survived quality control were mapped to genes on the basis of National Center for Biotechnology Information human assembly build 37.3 and dbSNP release 135\(^25\)\(^\text{6}\) (see supplementary methods for additional information).

Relatedness testing was done with PLINK\(^4\) (http://pngu.mgh.harvard.edu/purcell/plink/). Pairs with genome identity (\(\hat{D}\)) > 0.9 were reported as “identical samples” and with \(\hat{D}\) > .2 as being closely related. After random shuffling, one individual from each pair was excluded from downstream analysis. From groups with multiple related pairs (eg, a family), only 1 individual was kept. To control for spurious association by population stratification, principal component analysis was performed for each sample separately, and the first 10 principal components
were included as covariates in subsequent gene set analysis. An additional 144 cases and 84 controls were removed as population outliers, bringing the total sample size for the analysis to 31,915 (13,689 cases and 18,226 controls; supplementary table 1).

**Gene Set Analysis**

Gene set analysis was done using Joint Association of Genetic Variants (http://ctglab.nl/software). Self-contained tests were performed for each gene set using the sum over $-\log_{10}$ of SNP $P$ values in that gene set as test statistic. Empirical $P$ values ($P_{SC}$) were obtained by permutation of the phenotype. These were computed separately for each data set and then combined using Stouffer’s $Z$-score method. Bonferroni corrections were used to account for multiple testing (at $\alpha = .05$) within each of the 3 glial groups. For gene sets that were significant on the self-contained test, an additional competitive test was performed. For each of these gene sets, 750 random gene sets containing the same number of genes were generated and tested using the self-contained test. The competitive $P$ value ($P_{COMP}$) was then computed as the proportion of those 750 random gene sets with a self-contained $P$ value lower than that of the original gene set. If none of the random gene sets achieved a self-contained $P$ value lower than that of the original gene set, the competitive $P$ value was set to $0.5/750 = .00067$.

**Sensitivity Analysis**

For the gene sets that were statistically significant based on $P_{SC}$ and $P_{COMP}$, we examined the individual contribution of each gene in that gene set. This was computed...
Table 1. Overview of Glial Functional Gene Sets

<table>
<thead>
<tr>
<th>Level</th>
<th>Functional gene sets</th>
<th>Number of genes</th>
<th>Level</th>
<th>Functional gene sets</th>
<th>Number of genes</th>
<th>Level</th>
<th>Functional gene sets</th>
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</table>

Note: GPCR, G protein–coupled receptor; MAPKKK, Mitogen-activated protein kinase kinase kinase; P<sub>sc</sub>, empirical P values; GO, Gene Ontology; SNPS, single nucleotide polymorphisms.

Functional gene sets were based on GO “biological processes” classification. For each glial cell type, gene sets, level indications, and numbers of genes are listed. Level 1 sets are composed of the complete astrocyte, oligodendrocyte, and microglia sets (thus all genes in the glial cell type lists). Level 2 and 3 sets represent children nodes of level 2 and 3 sets, respectively, and were all tested. The sets in bold/italic were not tested but represent the labels for the overarching processes and depict the range of the analyses. The sets in bold are the “miscellaneous” sets, and these were also included in the analyses. Number of genes represent the genes for which genotyped SNPS were included in the analyses. Genes could be annotated into multiple gene sets, and not all genes were annotated into level 2 or 3 sets; hence, numbers of genes of lower level sets do not exactly add up to those of higher level sets. Significantly associated gene sets are italicized, with Bonferroni-corrected P<sub>sc</sub> values indicated in brackets. All results can be found in supplementary table 2.
as the change in $P_{SC}$ for that gene set when all SNPs in that gene were excluded, providing a measure of both the relative and absolute impact.

**Results**

**Glial Gene Lists Are Representative of Glial Cell Type Functioning**

In order to increase specific associations of genes in these lists with specific cell types, we applied 2 filtering steps where overlap between the different glial cell types as well as with a general neuronal gene list was removed. This resulted in enriched and nonoverlapping gene lists for astrocytes (1998), oligodendrocytes (1650), and microglia (289). The inclusion of multiple glial cell type–specific markers validated the glial gene groups, eg, GFAP, APOE, SLC1A2, SLC1A3 (astrocytes), MBP, PLP1, MAG, CNP (oligodendrocytes) and CD74, CX3CR1, and multiple HLAs and FC receptors (microglia). Furthermore, an enrichment analysis for GO biological processes was performed, which showed for each glial cell type, a unique overrepresentation of known biological functions for that cell type (figure 2). Overrepresentation analysis thus confirmed that the final, filtered lists are indeed good representatives of glial cell type–specific functioning.

**Risk of Schizophrenia Is Influenced by Astrocyte and Oligodendrocyte Genes**

We then conducted gene set analysis using the first level of astrocyte, oligodendrocyte, and microglia gene-sets and found highly significant associations for the total groups of astrocyte ($P_{SC} = 5.17 \times 10^{-19}$) and oligodendrocyte ($P_{SC} = 3.43 \times 10^{-12}$) genes to the risk of schizophrenia, but no significant association for the microglia genes ($P_{SC} = .09$). Next, we used competitive testing to determine whether the complete sets of astrocyte and oligodendrocyte genes were also more significantly associated with schizophrenia than randomly created gene-sets matched for the same number of genes. This was indeed the case for the complete list of astrocyte genes ($P_{COMP} = .00067$), whereas the complete set of oligodendrocyte genes showed a nominally suggestive stronger association than the matched controls ($P_{COMP} = .073$).

**Risk of Schizophrenia Is Influenced by Specific Subgroups of Glial Functioning**

To gain insight into the roles of specific glial functions, the genes in the glial lists were functionally annotated resulting in 31 astrocyte, 29 oligodendrocyte, and 19 microglia gene sets (figure 1 and table 1). We identified

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**Fig. 2.** Gene ontology–overrepresentation analysis for biological processes of the glial gene lists. This analysis shows that for each gene list, unique overrepresentation of biological processes known to be associated with the specific roles of these cells in brain functioning is present, with no overlap in enriched processes between the cell types. A) The astrocyte gene list shows overrepresentation of many metabolic functions in accordance with important roles of these cells in brain metabolic support and homeostasis. B) The oligodendrocyte gene list shows overrepresentation of functions associated with myelin membrane biogenesis and oligodendrocyte development. C) The microglia gene list shows mainly processes associated with immune system signaling. D) In the neuronal gene list, processes associated with synapse functioning and neurotransmitter signaling are present, indicating this list is a valid source for filtering of neuronal genes from the glial lists.
that 6 of the astrocyte gene sets (signal transduction, tyrosine kinase signaling, G protein–coupled receptor [GPCR] signaling, small GTPase-mediated signaling, cell adhesion, and gene transcription), and 3 of the oligodendrocyte gene sets (lipid metabolism, oxidation-reduction, and gene transcription) were significantly associated with schizophrenia ($P_{SC} < .05$), and more significantly so than randomly created gene sets matched for the same number of genes ($P_{COMP}$; table 1; supplementary table 2; supplementary figure 2). No significant associations were found for microglia gene sets (supplementary table 2). We confirmed that these results for the significantly associating glial gene sets were consistent across the different schizophrenia samples in our data set (supplementary table 3).

**Significant Associations of the Glial Gene Sets Are Due to the Effects of Multiple Genes**

To determine whether gene set associations were driven by a few genes or relied on the combined effect of multiple genes, we conducted a gene-based analysis. This showed that the associations of the gene sets did not rely on the effect of only a few genes but were due to the accumulated effect of multiple genes with small effect (supplementary table 4). These results indicate that the specific combinations of genes were mandate for the observed glial gene set associations.

**Post Hoc Analyses Indicate Cell type–bound Mechanisms**

Our glial sets were created to ensure nonoverlap between the 3 different glial cell types (astrocytes, oligodendrocytes, microglia) and a general list of neuronal genes. This assured that our gene sets were cell type specific. To determine whether our results would change if we would include gene sets cell adhesion and lipid metabolism lost significance (table 2). Moreover, while tyrosine kinase signaling, GPCR signaling and gene transcription did remain significant when cell type boundaries were not taken into account, they lost significance when astrocyte genes were removed (table 2). This indicates that the associations of these groups were mainly driven by the astrocytic component. One exception was formed by the signal transduction set, which also remained significantly associated without astrocyte genes. Together, these results show that the significant associations of glial gene sets with schizophrenia are strongly dependent on genes that are specific to one cell type, with the exception of the signal transduction gene set.

**Discussion**

Converging evidence indicates direct roles for each of the 3 known glial cell types in modulation of neuronal functioning and synaptic transmission. Astrocytes are actively involved in bidirectional signaling with neurons at the “tripartite synapse.”

Table 2. Association With Schizophrenia for Functional Gene Sets Generated From Genes Present in all 4 CNS Cell Types

<table>
<thead>
<tr>
<th>Functional Gene Set</th>
<th>$P_{SC}$</th>
<th>$P_{COMP}$</th>
<th>Overlap With Unfiltered Astrocyte Gene Set Removed</th>
<th>Relative Impact</th>
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<td>.00149</td>
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<td>.106</td>
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<tr>
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<td>Cell adhesion</td>
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<td>.000612</td>
<td>.0844</td>
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*Note: CNC, central nervous system; $P_{COMP}$, competitive $P$ value; GPCR, G protein–coupled receptor.

Results are shown for each cell type in order of strength of association. “Relative impact” indicates change in $log_{10} P_{SC}$ value when astrocyte genes are removed from the gene set. Functional gene sets significantly associated according to Bonferroni-corrected $P_{SC}$ values are shown *cursive*. For these sets, $P_{COMP}$ is also shown. Those more significantly associated with schizophrenia than matched controls according to $P_{COMP}$ are shown furthermore **bold**. Signal transduction remained significant after removal of astrocytic expressed genes.

*For gene transcription, oligodendrocyte genes were not included anymore.
be plastic by experience and electrical activity,12,13 and microglia might be involved in activity-induced pruning of newly formed synapses during development and learning.12,15 Thus, it might be hypothesized that part of the genetic defects in schizophrenia are mediated by glial cell dysfunction. Schizophrenia is known to be highly polygenic and likely influenced by thousands of alleles each of small effect. Each single allele is not sufficient to cause the disease, but it is the accumulation of multiple risk alleles in a biological system that is important for schizophrenia and that influences the risk to disease. Here, we investigated accumulation of risk alleles in specific cell types and cell functions. We applied a functional gene set analysis to investigate whether glial genes contribute to the occurrence of schizophrenia, and if so, which specific glial functions may be implicated. Using a sample of 13,689 cases and 18,226 controls, we showed that 6 astrocyte gene sets and 3 oligodendrocyte gene sets were strongly associated with schizophrenia. The significant associations were mainly driven by genes that were specific to 1 cell type thus supporting different roles for these cell types in schizophrenia pathology.

**Distinct Astrocyte Gene Sets as Risk Factor in Schizophrenia**

The astrocyte gene transcription gene set consists mainly of transcription factors and genes involved in epigenetic control mechanisms. Nearly half of these have previously been implicated in developmental processes, including PAX6, which is an important factor in glial differentiation,45 and influences prepulse inhibition, an endophenotype in animal models for schizophrenia.46 The large contribution of epigenetic control genes in the astrocyte gene transcription gene set, as SETDB1 and SMARCD2,30,32 is in line with the proposed role of epigenetic mechanisms in schizophrenia.47 In particular, modifications in histone and DNA methylation patterns have been described as “scars” of early experience.47

The signal transduction gene set seems particularly interesting because of the bidirectional signaling between neurons and astrocytes at the tripartite synapse.12,14 Notably, 3 specific subsets of signal transduction, ie, GPCR signaling, tyrosine kinase signaling, and small GTPase-mediated signaling were also significantly associated. Astrocytic GPCRs can sense neurotransmitter release during synaptic activity and stimulate release of gliotransmitters that can modulate neuronal signaling.48 The astrocyte GPCR signaling gene set contains GRM3 and GABBR1, which are metabotropic receptors for the respective neurotransmitters glutamate and gamma amino butyric acid. GRM3 has previously been linked to schizophrenia. Interestingly, subjects with a high-risk GRM3 haplotype also had lower prefrontal cortical expression of the astrocytic glutamate transporter EAAT2 and showed impaired cognitive performances.49 GRM3 and EAAT2, as well as GABBR1, are predominantly found at, or close to, synapses, suggesting an involvement of astrocytes at tripartite synapses in the occurrence of schizophrenia. Moreover, most of the other genes in this group, as EDNRB and NMB, have been implicated in various aspects of tripartite neuron-astrocyte signaling as well (supplementary figure 3). However, it should be noted that these astrocyte genes might also function at other locations than the tripartite synapse, where they may contribute to the observed changes in schizophrenia. The tyrosine kinase signaling subset of signal transduction consists mainly of receptor tyrosine kinases (RTKs) and their ligands. Recently, converging evidence shows involvement of many of these receptors in aspects of tripartite synapse processing and modulation. Finally, the signal transduction subset small GTPase-mediated signaling has generally been linked to trafficking of cargo, eg, receptors, from and to the membrane, modulation of exocytotic release, and morphology changes of perisynaptic astrocytes at the tripartite synapse. Thus, genetic alterations in the tyrosine kinase signaling and small GTPase-mediated signaling subsets could, like for GPCRs, have profound influences on astrocyte modulation of synapse function in schizophrenia (figure 3b).

Cell adhesion molecules (CAM) are transmembrane proteins that are involved in cell-cell or cell-matrix interactions. Interestingly, glial CAMs are well known players in promotion and/or inhibition of axon outgrowth and synapse formation.60,61 Interestingly, our cell adhesion gene set includes different cadherins (CDH4, NCad) and protocadherins (PCDH10, PCDH20), which enable astrocytes to guide synapse function and morphology,12 thus further indicative of an important astrocyte-neuron interaction element in our findings. Importantly, association of CAMs with schizophrenia was also found in our previous functional gene group analysis of manually curated synaptic gene sets,5 and a Kyoto Encyclopedia of Genes and Genomes pathway analysis in which genes were not restricted to specific CNS cell types.62 These findings support involvement of both neuronal and glial CAMs in schizophrenia and may involve altered contact of astrocytic perisynaptic processes with synaptic terminals.

Taken together, our astrocyte findings are thus in line with the novel implication of neuron-astrocyte tripartite communication in schizophrenia pathology (figure 3b) and identify astrocytes as important contributors to schizophrenia within the context of a neurodevelopmental disease (figure 3a).

**Oligodendrocyte Gene Sets as Risk Factor in Schizophrenia**

Our findings of oligodendrocyte lipid metabolism, oxidation-reduction, and gene transcription sets
Fig. 3. Proposed mechanism of action; how the functional glial gene sets with increased risk in schizophrenia might contribute to glial and neuronal function. Significantly associated functional gene sets are depicted in green, bold squares. Derived secondary processes are depicted in white squares. Functional gene sets that contain genes implicated at the tripartite synapse are depicted with a red border. A) Alterations in glial “gene transcription,” including SOX10 and PAX6 transcription factors (see main text), influence glial developmental processes and epigenetic mechanisms. In addition to inherent defects in central nervous system (CNS) development, these mechanisms may also influence vulnerability of glial cells to early environmental risk factors. B) Genetic alterations in astrocytic “receptor tyrosine kinase (RTK)” “G protein-coupled receptor (GPCR),” and “small GTPase-mediated signaling” processes at tripartite synapses might interfere with intracellular glial response to neuronal signals, causing aberrant astrocytic modulation of synapse strength via downstream processes as calcium signaling, gliotransmission, and neurotransmitter uptake (not in figure). Indeed, these gene sets included molecules well known to localize and function at the synapse, including GMR3 and GABBR1 (respectively glutamate and gamma amino butyric acid receptors) and the EphB3 RTK. Alterations in cell adhesion molecules, including the cadherins CDH4 and NCad, or protocadherins PCDH10 and PCDH20, might interfere with structural association of synapses and glia-induced plasticity. C) Genetic alterations in oligodendrocyte lipid metabolism may have downstream effects on myelin sheath composition and integrity. Changes in oxidation-reduction interfere with lipid metabolic processes and/or lead to generation of free radicals as reactive oxygen species (ROS) and subsequent myelin sheath damage via lipid peroxidation. See main text for further explanation.

associating with schizophrenia are in line with accumulating evidence implicating oligodendrocytes in the disease. Recent studies suggest that oligodendrocyte and myelin dysfunction leads to changes in synapse formation, function, and connectivity between related but anatomically different brain regions, which might lead to cognitive dysfunction in schizophrenia. Our data support these findings and indicate that alterations in specific oligodendrocyte functions might be causally involved in schizophrenia and associated white matter pathology.

Most of the genes in the lipid metabolism gene set were found to be involved in metabolism of structural membrane lipids of the myelin sheath. In addition, oligodendrocyte lipids play important roles in sorting, trafficking, and anchoring of myelin proteins to the myelin sheath. Interestingly, decreases in brain lipid levels and metabolism have been reported previously in schizophrenia patients. Moreover, several antipsychotics have been shown to upregulate the expression of genes involved in cellular fatty acid and cholesterol biosynthesis controlled by SREBP transcription factors. At least in the peripheral nervous system, SREBPs are regulators of myelin membrane synthesis, and were linked to schizophrenia. Oligodendrocyte lipid metabolism dysfunction may thus play a role in myelin integrity and the control of intracellular transport and deposition of myelin proteins and lipids in schizophrenia (figure 3c), an insight, which is an incentive to design and improve lipid-based interventions.

Most genes in the oxidation-reduction gene set are also involved in lipid metabolism, thereby further supporting the involvement of genes of the lipid metabolism group in schizophrenia. Genes in this group also function in oxidative stress, which has been implicated in development of schizophrenia, albeit here specifically linked to oligodendrocytes for the first time (figure 3c).

The gene transcription gene set for oligodendrocytes, consists, like the above discussed astrocyte gene transcription gene set, mainly of transcription factors and of molecules involved in epigenetic control. Because oligodendrocyte-specific transcription factors regulate the differentiation of oligodendrocytes and myelin membrane synthesis, genes encoding these transcription factors have been regarded as prime candidates for oligodendrocyte-mediated dysfunction in schizophrenia. In particular, the DNA methylation status of sox10 correlates with oligodendrocyte dysfunction in schizophrenia, suggesting that epigenetic mechanisms that affect oligodendrocyte development and myelogenesis may further increase vulnerability to the disease (figure 3a).

Surprisingly, the “myelin” gene set, which includes the structural myelin proteins MAG and CNP that have been suggested to play a role in schizophrenia pathology, did not reach criteria for statistical association. Our findings thus indicate that the myelin defects reported for schizophrenia might not be directly caused by genetic defects in structural myelin proteins themselves but are rather caused by genetic defects in other key oligodendrocyte gene sets, such as lipid metabolism or gene transcription.

No Risk Found for Microglia Gene Sets in Schizophrenia

Unexpectedly, we found no association of microglia gene sets with schizophrenia, whereas previous research
showed microglia activation in the CNS of schizophrenia patients.\textsuperscript{17,20} Thus, gene sets that are most specifically regulated during the activation of microglia do not seem to genetically contribute to schizophrenia, indicating that previously reported microglial changes and neuroinflammatory symptoms involving these genes might represent secondary effects in response to primary schizophrenia-induced pathology. However, it should be noted that because the microglia gene list mainly contains genes specifically enriched in the activated cellular state, the complete set of microglia genes might not have encompassed all microglia functions (ie, those associated with the quiescent phenotype), thereby not fully appreciating the role of microglia in schizophrenia.

**Concluding Remarks**

Previous studies on schizophrenia have primarily focused on neuronal dysfunction. To our knowledge, this is the first genomic study to implicate functional gene sets that are highly associated with specific glial cell types. We found significant, replicated associations of cell type-specific astrocyte and oligodendrocyte gene sets with schizophrenia, though not for microglia gene sets. Our results indicate that glial cells are key candidates contributing to the primary development of underlying pathological processes of schizophrenia, which may have important implications for its understanding and treatment.

**Supplementary Material**

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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