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LETTER TO THE EDITOR

Network analysis of positional candidate genes of schizophrenia highlights…more than… myelin-related pathways

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Using a selection of positional susceptibility genes with high 'genetic potential' (i.e., heritability) and information obtained from peripheral gene expression, Rietkerk *et al.*,[1] reported in the April issue of *Molecular Psychiatry* different biological pathways 'in which the actions of several of these genes converge,' that highlighted a putative (and consistent) role for myelin-related pathways in the etiology of schizophrenia. The authors' approach to 'define the

Table 1 Top five biological networks, canonical pathways and diseases and disorders obtained by Ingenuity analysis of the genes' list reported in the study by Rietkerk *et al.*

	Top networks	*Score*	*No. of candidate genes*
1	Genetic disorder, immunological disease, **lipid metabolism**	47	32
2	Cell death, cellular development, dermatological diseases	44	31
3	Gene expression, RNA post-transcriptional modification, cardiovascular system development and function	36	27
4	Cell death, hematological disease, immunological disease	34	28
5	**Lipid metabolism**, molecular transport, small molecule biochemistry	32	25

Canonical pathways	*P-value*
Top canonical pathways	
Antigen presentation pathway	9.2E−17
Dendritic cell maturation	1.8E−07
Protein ubiquitination pathway	6.7E−06
Glucocorticoid receptor signaling	5.5E−05
Role of NFAT in regulation of immune response	1.7E−04
Others pathways	
P38 MAPK signaling	0.025
PI3/AKT signaling	0.038

Disease and disorders	*P-value*
Top diseases	
Immunological disease	
Immunological disorder	1.7E−13–1.1E−02
Rheumatoid arthritis	1.9E−13
Autoimmune disease	3.9E−09–3.5E−03
Connective tissue disorders	
Rheumatoid arthritis	1.9E−13–9.3E−03
Genetic disorder	1.9E−13–1.2E−02
Rheumatoid arthritis	1.2E−13–3.6E−04
Autoimmune disease	1.5E−06–1.2E−05
Schizophrenia	1.5E−06–1.2E−05
Inflammatory disease	1.9E−13–1.2E−02
Skeletal and muscular disorders	1.9E−13–9.3E−03

MAPK, mitogen-activated protein kinase; NFAT, nuclear factor of activated T-cells.
In bold are pathways observed in the study by Rietkerk *et al.* and in our analysis. Network scores represent negative log values of right-tailed Fisher's exact tests for network consistence. Pathways and disease *P*-values represent significance of overrepresentation of candidate genes within respective gene groups. *P*-value ranges indicate values for various disease subclassifications (not shown).

biological coherence of schizophrenia positional candidate genes' was based on overrepresentation of gene ontology annotations among putative coexpression modules derived from lymphocyte gene microarray data. However, blood and brain (site of disease) transcriptomes show only $\sim$0.6 correlation.[2] Moreover, coregulation is a single window into functional relationships, which are overall likely to have been described in the literature, hence resulting in related gene ontology annotations.[3] Therefore, we speculated that a direct functional and clustering analysis of evidence-based literature may be more encompassing, and thus more sensitive to identifying biological clusters of candidate genes within putative etiological pathways of the illness.

To test this hypothesis, we overlaid the set of 766 genes selected by Rietkerk *et al*. from a combination of linkage studies, brain expression and substantial heritability onto the Ingenuity knowledge database (http://www.ingenuity.com/). This database includes over 2 million hand-curated literature-based links between genes and other bioactive molecules. In a process that was analogous to that of Rietkerk *et al*, we functionally characterized the top five sub-networks formed by candidate genes, on the basis of their connectivity within the global Ingenuity network (Table 1) and also assessed functions, canonical pathways and diseases/disorders that were otherwise associated with the gene set. Using this different analytical approach and pathway classification methodology, we confirmed the overrepresentation of genes implicated in the metabolism of lipids and sphingolipids (ASAH1, GLB1, NEU1) in two of the top networks, and of other canonical pathways (phospho-Inositol signaling and mitogen-activated protein kinase signaling pathways) identified in the study by Rietkerk *et al*. (Table 1). Schizophrenia was among the five disorders to be more likely associated with this set of genes, thus providing an internal validation of the approach.

The most striking difference provided by our more direct approach was the identification (through overrepresentation and redundancy) of gene groups implicated in immunological and inflammatory diseases, auto-immune disease (e.g., rheumatoid arthritis) or canonical pathways related to antigen presentation. These results are consistent with previous evidence that indicated that autoimmune pathologies may be associated with some forms of schizophrenia.[4] Furthermore, in rats, prenatal lipopolysaccharide-induced immune activation leads to altered prepulse inhibition and immune function in adulthood, which are both reversed by antipsychotics.[5] Focusing on this critical neurodevelopmental period, it has also been suggested that recruitment of the glucocorticoid receptor signaling pathway—represented herein as another highly significant canonical pathway in our analysis—in combination with prenatal stress increases the risk of developing schizophrenia (for a review, see Koenig *et al*.[6]).

Taken together, these results confirm the high biological information content and disease relevance of candidate genes identified by linkage studies through the putative convergence of candidate genes along known etiological pathways (immune system, myelin-related functions). These studies also confirm that literature-based evidence encompass information not otherwise captured by adopting coexpression approaches. Alternatively, differences in blood (as used in the study by Rietkerk *et al*.) and brain coexpression profiles may underlie the absence of immune-related findings in Rietkerk *et al*. With regard to putative disease mechanisms, in addition to confirming the role of myelin-related pathways, the present findings provide additional evidence suggesting an infective immune predisposition to schizophrenia,[7] and this predisposition is likely to interact with genetic susceptibility for developing the disease.

Conflict of interest

The authors declare no conflict of interest.

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