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Editorial: Clustering of Schizophrenia With Other Comorbidities—What Can We Learn?

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Despite great efforts to the contrary, the molecular basis underlying schizophrenia and many other psychiatric disorders remains elusive. Examination of the nonpsychiatric manifestations that sometimes accompany schizophrenia provides opportunities to more fully explore the scope of biochemical and metabolic abnormalities characterizing the disease spectrum. This issue of the Journal features a series of articles that focus on the systemic manifestations of schizophrenia.

A more complete understanding of disease spectrum can provide important insights into disease etiology. For example, pathologic analyses of atherosclerotic vascular tissue revealed the presence of immune infiltrates, thereby helping to revamp our view of coronary artery disease as an inflammatory disease.[1] In the psychiatric field, nonpsychiatric dimensions to schizophrenia have been well described, including a long-recognized association between diabetes and schizophrenia.[2] While intriguing, the mechanisms that underlie this association are unclear. While there is little evidence that glucose intolerance itself may increase schizophrenia risk, one possibility is that the co-occurrence of diabetes and schizophrenia could be due to shared environmental/lifestyle factors that predispose subjects to both disorders. This possibility is supported by observations that newly diagnosed and/or drug-naive schizophrenia patients have higher than expected rates of glucose intolerance and/or diabetes.[3,4] Alternatively, schizophrenia could increase risk of diabetes through reduced physical activity and concomitant obesity or via insulin desensitizing or weight gain promoting effects of antipsychotic medications.

There is also a possibility that a shared genetic susceptibility characterizes both diabetes and schizophrenia, as has been suggested by a small number of family studies, with limited sample sizes, showing that first-degree relatives of schizophrenia patients have higher than expected prevalence of type 2 diabetes (eg, Fernandez-Egea et al,[5] Ryan and Collins,[6] and Spelman et al[7]). If there are genes that jointly influence schizophrenia and diabetes susceptibility, what are they and what might they do? Some recent data suggest a common pathway might involve regulation of mitochondrial oxidative energy metabolism.[8] However, identifying the specific genes involved is likely to be difficult. Of the 20 or so bona fide diabetes susceptibility genes identified to date,[9] none have been implicated in psychiatric disease etiology. Genetic linkage studies, however, have identified some chromosomal regions in common to both disorders, including chromosome 1q21–25.[10,11] This region contains a large number of genes, some with potential joint effects on both metabolic and psychiatric outcomes, such as *NOS1AP* (carboxy-terminal PDZ ligand of neuronal nitric oxide synthase, also known as *CAPON*), for which polymorphisms have been associated with schizophrenia[12] and cardiac repolarization,[13,14] although not yet firmly with type 2 diabetes. Whether polymorphisms in *NOS1AP* or in any other gene will ultimately show joint and robust association to both diabetes and schizophrenia remains to be seen, but when found, such observations could provide valuable clues to unraveling the overlap between these disorders.

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