**Reference**

1. Wakefield JC, Schmitz MF, First MB, Horwitz AV: Extending the bereavement exclusion for major depression to other losses: evidence from the National Comorbidity Survey. Arch Gen Psychiatry 2007; 64:433–440

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## The Role of Epigenetics in Altered Gene Expression Involved in GABAergic Transmission in the Cerebellum of Schizophrenia Patients

TO THE EDITOR: In their article, published in the December 2008 issue of the *Journal*, W. Michael Bullock et al. (1) reported reduced expression of genes involved in gamma-aminobutyric acid (GABA)-ergic transmission in the postmortem cerebellum of individuals with schizophrenia relative to postmortem comparison subjects without a history of psychiatric illness. Bullock et al. found reduced expression of genes encoding the two isoforms of glutamic acid decarboxylase (GAD), which is the enzyme that catalyzes the conversion of L-glutamic acid to GABA, $GAD_{65}$, and $GAD_{67}$. These changes were found to be associated with compensatory changes in the expression of other genes. The authors did not determine the cause of the reduced expression of genes encoding $GAD_{65}$ and $GAD_{67}$. However, the introduction section of their article implied that genetic factors, such as genetic polymorphisms, could be the cause of this reduced expression.

Another possibility regarding the cause of reduced expression of genes involved in GABAergic transmission in the cerebellum of schizophrenia subjects examined in their study might involve epigenetics (i.e., heritable changes in gene expression not involving changes in DNA sequence). Epigenetics engages at least the following three interacting molecular mechanisms: DNA methylation, histone modification, and RNA-mediated regulation of gene expression (2). This suggestion is based on the fact that, to date, no genetic mutation or polymorphism predisposing to the pathogenesis of schizophrenia has been found (2, 3). In addition, there is increasing evidence that epigenetics plays a major role in the pathogenesis of schizophrenia and other idiopathic mental disorders (2, 3). Moreover, the promoter of the gene encoding GAD has been shown to be epigenetically modified in the cerebral cortex in schizophrenia patients, resulting in reduced expression of GAD (2, 4). Last, there is evidence suggesting that the gene encoding GAD is epigenetically modified in the cerebellum in individuals with autism, causing reduced expression of GAD (5).

**References**

1. Bullock WM, Cardon K, Bustillo J, Roberts RC, Perrone-Bizzozero NI: Altered expression of genes involved in GABAergic transmission and neuromodulation of granule cell activity in the cerebellum of schizophrenia patients. Am J Psychiatry 2008; 165:1594–1603
2. Peedicayil J: The role of epigenetics in mental disorders. Indian J Med Res 2007; 126:105–111
3. Abdolmaleky HM, Zhou JR, Thiagalingam S, Smith CL: Epigenetic and pharmacoepigenomic studies of major psychoses and potentials for therapeutics. Pharmacogenomics 2008; 9: 1809–1823
4. Costa E, Dong E, Grayson DR, Guidotti A, Ruzicka W, Veldic M: Reviewing the role of DNA (cytosine-5) methyltransferase overexpression in the cortical GABAergic dysfunction associated with psychosis vulnerability. Epigenetics 2007; 2:29–36
5. Peedicayil J, Thangavelu P: Purkinje cell loss in autism may involve epigenetic changes in the gene encoding GAD. Med Hypotheses 2008; 71:978

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## Dr. Perrone-Bizzozero and W. Michael Bullock Reply

TO THE EDITOR: We fully agree with Dr. Peedicayil that epigenetic mechanisms play an important role in the control of gene expression and that defects in these processes are associated with an increasing number of mental disorders. Moreover, recent reports suggest that reduced expression of $GAD_{67}$ (the GABA synthesizing enzyme encoded by the GAD1 gene) in schizophrenia patients is associated with both specific polymorphisms in the promoter region (1) and altered epigenetic regulation (2, 3), and we apologize for the oversight of not citing the latter in our article. However, we wish to clarify that it was not our intention to propose a mechanism for the decreases in $GAD_{67}$ in schizophrenia but to put these changes in the context of neuronal circuitry (4). Specifically, our goal was to investigate gene expression alterations as they relate to a dysfunction in GABAergic and glutamatergic transmission in the cerebellum of individuals with schizophrenia. Our results strongly suggest that Golgi cells, which are the GABAergic interneurons that inhibit granule cell activity, are affected in schizophrenia. These results not only explain our previous observation of increased activity-dependent granule cell gene expression in schizophrenia (5) but also give further support to the hypothesis that some subtypes of GABAergic interneurons may be compromised in this illness. Along these lines, we recently found that Golgi cells are primarily affected by chronic intermittent exposure to relatively low doses of phencyclidine (data available upon request from W.M. Bullock et al.), suggesting that *N*-methyl-D-aspartic acid hypofunction could lead to decreases in GABA synthesis and neurotransmission in schizophrenia. Moreover, we feel that it is very important to determine the causes of the decrease in $GAD_{67}$ mRNA in postmortem cerebellar tissue, and we plan to address whether these deficits are associated with genetic factors and/or epigenetic dysregulation in future studies.

**References**

1. Straub RE, Lipska BK, Egan MF, Goldberg TE, Callicott JH, Mayhew MB, Vakkalanka RK, Kolachana BS, Kleinman JE, Weinberger DR: Allelic variation in GAD1 (GAD67) is associated with schizophrenia and influences cortical function and gene expression. Mol Psychiatry 2007; 12:854–869

2. Costa E, Dong E, Grayson DR, Guidotti A, Ruzicka W, Veldic M: Reviewing the role of DNA (cytosine-5) methyltransferase overexpression in the cortical GABAergic dysfunction associated with psychosis vulnerability. Epigenetics 2007; 2:29–36
3. Huang HS, Matevossian A, Whittle C, Kim SY, Schumacher A, Baker SP, Akbarian S: Prefrontal dysfunction in schizophrenia involves mixed-lineage leukemia 1-regulated histone methylation at GABAergic gene promoters. J Neurosci 2007; 27:11254–11262
4. Bullock WM, Cardon K, Bustillo J, Roberts RC, Perrone-Bizzozero NI: Altered expression of genes involved in GABAergic transmission and neuromodulation of granule cell activity in the cerebellum of schizophrenia patients. Am J Psychiatry 2008; 165:1594–1603
5. Paz RD, Andreasen NC, Daoud SZ, Conley R, Roberts R, Bustillo J, Perrone-Bizzozero NI: Increased expression of activity-dependent genes in cerebellar glutamatergic neurons of patients with schizophrenia. Am J Psychiatry 2006; 163:1829–1831

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## Mitochondrial Neurogastrointestinal Encephalomyopathy Mimicking Anorexia Nervosa

TO THE EDITOR: Mitochondrial neurogastrointestinal encephalomyopathy is a rare autosomal recessive mitochondrial disorder caused by mutations in the thymidine phosphorylase gene (1). It is characterized by severe cachexia, gastrointestinal dysmotility, progressive external ophthalmoplegia, peripheral neuropathy, and diffuse leukoencephalopathy on magnetic resonance imaging (MRI). The accumulation of thymidine and deoxyuridines causes imbalances of mitochondrial nucleotide pools that may lead to depletions of mitochondrial DNA and multiple deletions (2). We present the case of a patient with prominent cachexia in mitochondrial neurogastrointestinal encephalomyopathy mimicking anorexia nervosa.

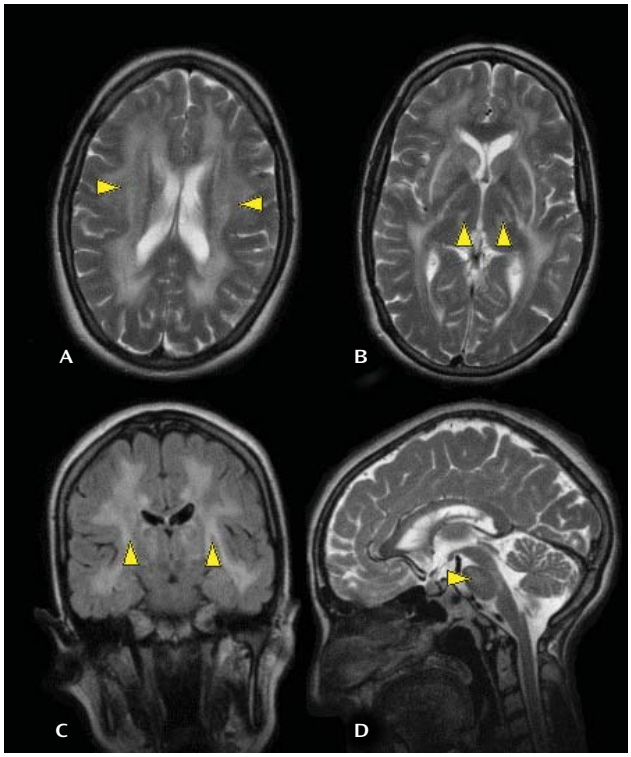
**"Miss A" was a 21-year-old Indian woman diagnosed as having treatment-resistant anorexia nervosa. She was referred to our department of psychiatry after her weight decreased by 25 kg (body mass index: 11.6), despite receiving specific treatment in a psychosomatic hospital.**

**Miss A was thin and appeared to be growth-retarded. She had a flat mood and showed infantile behavior. In addition to diffuse abdominal complaints, she had demonstrated anorectic symptoms since puberty and had peculiar, restrictive eating habits. Since a distorted body image could not be clearly elicited, our working hypothesis regarding a diagnosis was atypical anorexia nervosa (ICD-10: F50.1; DSM IV: 307.1).**

**The patient was unable to gain weight, despite her effort, solely by normal clinical support, such as structured meals, psychotherapy, and additional medical treatment. After placement of a gastric tube to provide high-caloric nutrition, her clinical state rapidly worsened. She began to vomit and experienced loud borborygmi, abdominal pain, fever, and physical exhaustion.**

**A neurological examination revealed that the patient had bilateral ptosis, infranuclear ophthalmoparesis, and generalized areflexia. Her diagnostic work-up indicated that lactate was increased two-fold above the upper limit of normal in the serum and CSF. Her urine analysis for purines and pyrimidines yielded increased concentrations of thymidine and deoxyuridine. Electromyography showed marked demyelinating sensorimotor polyneuropathy, and diffuse leukoencephalopathy was found by MRI (Figure 1). A genetic analysis revealed a hitherto nondescribed homozygous mutation (c.605G>A,p.Arg202Lys) in the ECGF1 gene, which encodes for thymidine phosphorylase. This mutation could not be detected in 68 healthy, ethnically matched comparison subjects from India. Miss A was then diagnosed as having mitochondrial neurogastrointestinal encephalomyopathy.**

**FIGURE 1. Diffuse Leukoencephalopathy in Patient Mimicking Anorexia Nervosa[a]**




[a] The magnetic resonance images illustrate increased signal intensity (arrowheads). The images demonstrate diffuse leukoencephalopathy with involvement of the A) centrum semiovale (axial T2-weighted images), B) parts of the thalamus (axial T2-weighted images), C) internal capsule (coronal fluid-attenuated inversion recovery images), and D) pons (sagittal T2-weighted images).

With regard to the present case of prominent cachexia in mitochondrial neurogastrointestinal encephalomyopathy mimicking anorexia nervosa, we would like to emphasize that syndromes of eating disturbances and cachexia could be the most prominent features of a number of somatic and psychiatric disorders. In addition to prominent eating disturbance in common psychiatric diseases such as anorexia nervosa, depression, and schizophrenia, such behavior and symptoms can also be prominent in mainly somatic disorders such as ju-