Published in final edited form as:
Am J Med Genet B Neuropsychiatr Genet. 2008 June 5; 147B(4): 505–506.

BDNF Val66Met variant and age of onset in schizophrenia†

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Abstract

Brain-derived neurotrophic factor (BDNF) has been advanced as a candidate gene for schizophrenia by virtue of its effects on neurotransmitter systems that are dysregulated in psychiatric disorder and its involvement in the response to antipsychotic drugs. The extensively examined BDNF gene Val66Met (or rs6265) variant has been associated with schizophrenia, and studies have linked this polymorphism to brain morphology, cognitive function, and psychiatric symptoms in schizophrenia. Moreover the BDNF Val66Met variant has been reported to be associated with age of onset in schizophrenia. Genotyping of African-American subjects with schizophrenia for five BDNF coding region single nucleotide polymorphisms revealed variance only at the Val66Met allele. The results of statistical analyses indicate a relationship between the BDNF Val66Met genotype and the ages of first psychiatric hospitalization and first schizophrenia symptoms.

Keywords

African-American; polymorphism; psychiatric hospitalization

The expression and actions of brain-derived neurotrophic factor (BDNF) in brain regions regulating mood and behavior, its effects on neurotransmitter systems that are dysregulated in psychiatric disorder, and its involvement in the response to antipsychotic drugs, have supported widespread investigation of BDNF as a candidate gene for schizophrenia [Angelucci et al., [2005]; Shoval and Weizman, [2005]]. In particular, the Val66Met or rs6265 variant in the BDNF gene has been extensively examined in relation to psychiatric phenotype. The Val66Met variant is a single nucleotide polymorphism of G to A at nucleotide 196 in the 5′ pro-BDNF sequence resulting in a valine to methionine change. While BDNF Val66Met does not appear to affect mature BDNF protein function, it has been shown to alter intracellular trafficking of pro-BDNF and secretion of the mature peptide [Egan et al., [2003]; Chen et al., [2004]]. The findings from independent studies and from meta-analyses on the association of the BDNF Val66Met variant with schizophrenia have been equivocal [Gratacos et al., [2007]; Kanazawa et al., [2007]]. Nonetheless, the Val66Met genotype may be important for modulating the expression of psychiatric phenotype because it has been linked to brain morphology [Szeszko et al., [2005]], cognitive function [Egan et al., [2003]], and psychiatric symptoms [Numata et al., [2006]] in schizophrenia. In addition, the BDNF Val66Met variant was found to be associated with age of onset (defined as the age of first psychotic episode) in patients with schizophrenia. The mean age of onset was highest for the BDNF Val/Val group, lowest for BDNF Met/Met, and intermediate for BDNF Val/Met [Numata et al., [2006]].

†Please cite this article as follows: Chao HM, Kao H-T, Porton B. 2007. BDNF Val66Met Variant and Age of Onset in Schizophrenia. Am J Med Genet Part B.

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In this study, genomic DNA samples from 42 genetically unrelated African-Americans with the psychiatric evaluation of DSM-III-R schizophrenia from the NIMH Schizophrenia Genetics Initiative [Cloninger et al., [1998]] were genotyped for the BDNF gene single nucleotide polymorphisms rs6265, rs1048218, rs1048220, rs1048221, and rs8192466 (as listed in the NCBI dbSNP) using standard methods.

All 42 genomic DNA samples assayed were found to have the wild-type sequence at the BDNF gene rs1048218, rs1048220, rs1048221, and rs8192466 alleles. For the rs6265 or Val66Met variant, five subjects were heterozygous (GA or Val/Met), none were homozygous (AA or Met/Met), and the remaining subjects had the wild-type sequence (GG or Val/Val). These BDNF Val66Met frequencies are consistent with a previous report that found 4 Val/Met heterozygotes but failed to find Met/Met homozygotes in 20 African-American adults with a history of childhood onset mood disorder [Strauss et al., [2004]]. Moreover, in previous studies of predominantly Caucasian or Asian patients with schizophrenia and other psychotic disorders, the frequency of Met/Met homozygotes has been consistently lower than the frequencies for Val/Met and for Val/Val [Gratacos et al., [2007]].

The NIMH Genetics Initiative provides data related to age of onset of schizophrenia in three variables from the Diagnostic Interview for Genetic Studies (DIGS): (1) age when help was first sought; (2) age at time of first psychiatric hospitalization; and (3) age of first psychiatric symptoms. For two of the subjects genotyped for BDNF Val66Met, there was no information available for these three age of onset variables. For the remaining 40 subjects, statistical analysis of the age of onset variables in relation to BDNF Val66Met genotype revealed significant differences by genotype for the age variables of first psychiatric hospitalization and first schizophrenia symptoms (Table I). No statistically significant association was found between Val66Met genotype and gender (data not shown).

In summary, the results suggest a relationship between the BDNF Val66Met genotype and age of onset in African-Americans with schizophrenia. In a previous study performed in a Japanese cohort, the BDNF Val66Met variant was significantly associated with age of onset in patients with schizophrenia [Numata et al., [2006]]. However, this finding was not confirmed by an independent study [Naoe et al., [2007]], and was not observed in a Caucasian cohort [Gourion et al., [2005]]. The association between the BDNF Val66Met genotype and age of onset of schizophrenia may be ethnic group specific, but needs to be validated by further investigation in larger study populations.

Acknowledgements

Funding for this research was provided by grant R01 MH070898 (Dr. B. Porton). Data and biomaterials from the NIMH Schizophrenia Genetics Initiative used in this study were obtained through grant R03 MH062352 (Dr. H.M. Chao), and were collected by Dr. M.T. Tsuang, Dr. S. Faraone, and Dr. J. Pepple (Harvard University), Dr. C.R. Cloninger, Dr. T. Reich, and Dr. D. Svrakic (Washington University) and Dr. C. Kaufmann, Dr. D. Malaspina, and Dr. J.H. Friedman (Columbia University). Genotyping was performed by Cogenics, Inc.

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Table I

Age of Onset by BDNF Val66Met Genotype (n = 40)*

Age of onset variable	Mean ± SEM				*P*
	n	Val/Val	n	Val/Met	
Psychiatric help	34	26.18 ± 1.63	5	22.80 ± 5.94	0.484[a]
Psychiatric hospitalization	29	25.62 ± 1.63	3	14.67 ± 1.86	0.023[b]
Psychiatric symptoms	33	25.24 ± 1.79	5	11.20 ± 2.65	0.006[a]

*Some age of onset values are not available in the NIMH Genetics Initiative database.

[a]*t*-Test.

[b]Wilcoxon two-sample test.