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Epidermal growth factor a61g polymorphism is associated with the age of onset of schizophrenia in male patients

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Abstract

There is evidence to suggest that dysfunction of dopaminergic neurotransmission in the central nervous system (CNS) plays a role in the etiopathology of schizophrenia. Epidermal growth factor (EGF) gene polymorphism has an impact on EGF production in mononuclear cells, and EGF seems to affect the development of midbrain dopaminergic neurons. The few studies concerning EGF gene polymorphism and schizophrenia have yielded contradictory results. Our aim was to investigate whether EGF gene A61G polymorphism predisposes to schizophrenia, and this polymorphism was therefore studied in 149 schizophrenic patients and in 94 healthy controls using 5′ nucleotidase assay (TaqMan). As far as EGF A61G polymorphism was concerned, we detected no significant differences in the allele and genotype frequencies between the patients and the controls. However, the G/G genotype was significantly associated with an earlier age of onset of schizophrenic psychosis in male subjects ($P = 0.005$) as well as in the entire population, but not in female patients ($P = 0.008$ and 0.46, respectively). The average age (±SD) of onset of schizophrenia was 20.1 ± 3.9 years in male EGF A61G G/G homozygotes and 23.7 ± 6.6 ($P = 0.02$) years in other genotypes. In conclusion, EGF gene polymorphism was not associated with the risk of schizophrenia. However, the EGF G/G genotype, which has been suggested to involve abundant production of EGF, was associated with early onset of schizophrenia in male patients.

Keywords: Schizophrenia; EGF; Association study; Genetic polymorphism; Gender; Finnish

1. Introduction

The developmental model of schizophrenia suggests that the changes in the central nervous system (CNS) that sensitize a person to schizophrenia date back to the fetal period or occur later during the development of the CNS. Dopaminergic dysfunction is thought to play a role in the etiopathology of schizophrenia (Goldstein and Deutch, 1992; Kerwin, 1993; Seeman, 1993; Weinberger, 1997). Epidermal growth factor (EGF) is a polypeptide that stimulates the proliferation of ectodermal and mesodermal cells (Carpenter and Cohen, 1979). It is a member of the EGF family with structurally related factors, such as transforming growth factor (TGF) α and heparin-binding EGF-like growth factor (HB-EGF). Peptides of the EGF family exert neurotrophic and neuromodulatory effects on developing dopaminergic neurons both in vitro and in vivo (Alexi and Hefti, 1993; Casper et al., 1991, 1994; Ferrari

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et al., 1991; Plata-Salamán, 1991). Lazar and Blum (1992) demonstrated EGF production as early as at embryonic day 14 in mouse brain, and widely distributed EGF production in the brain continued to be visible up to the postnatal period in the brain, including the brainstem, cerebral cortex, hippocampus, basal hypothalamus, striatum and thalamus. These are also the brain regions where changes have been demonstrated in schizophrenia (Bogerts, 1993; Conrad and Scheibel, 1987; Shelton et al., 1988). Futamura and colleagues (2002) studied the postmortem levels of EGF family protein levels in brains of schizophrenics compared to controls and found lower EGF levels in the prefrontal cortex and striatum of schizophrenic patients. No significant differences were detected in the levels of HB-EGF and TGF α between schizophrenics and controls in any regions examined. They also found elevated EGF receptor (EGFR) expression in the prefrontal cortex in schizophrenic patients. Moreover, serum EGF levels were decreased in the peripheral blood of young drug-free patients (Futamura et al., 2002).

The EGF gene has a functional single-nucleotide polymorphism (SNP) (G–A) at position 61 (Shahbazi et al., 2002), i.e., in vitro cells from 61A homozygous individuals produce significantly less EGF than cells from G/G or A/G individuals (Shahbazi et al., 2002). The studies concerning the possible association between the polymorphism of the EGF gene and schizophrenia have thus far yielded inconsistent results (Anttila et al., 2004; Lim et al., 2005; Watanabe et al., 2005). A recent study shows that the EGF A61G and tumour necrosis factor α polymorphisms interact in early-onset schizophrenia (Kampman et al., 2004).

Because of the contradictory results of the previous studies, we conducted a case-control association study of the EGF A61G polymorphism and schizophrenia in a fully independent patient sample of 149 Caucasian Finnish schizophrenics and 94 healthy controls. Furthermore, the possible effect of the EGF gene A61G polymorphism on the age of onset of schizophrenia was studied.

2. Material and methods

2.1. Subjects

The patient sample consisted of 149 patients (age range 18–76 years; mean age (±SD) 38.9 ± 12.2 years) meeting the DSM-IV criteria for schizophrenia. There were 94 men and 55 women. Sixty-one patients met the criteria for paranoid, 46 for undifferentiated, 36 for disorganized, three for residual and three for catatonic acute or chronic schizophrenia. The diagnoses had been assigned based on a Structured Clinical Interview for DSM-IV Axis I Disorders – clinician version (SCID-I/CV) (First et al., 1997) by three experienced psychiatrists (KH, HK and JM). Exclusion criteria were: another axis I diagnosis (substance abuse, organic mental disorders, affective disorders), neurological illness and diabetes mellitus. The mean age (±SD) of onset of schizophrenic psychosis was 23.6 ± 6.3 years. We defined the age of onset of schizophrenia as the first occurrence of positive psychotic symptoms (Meltzer et al., 1997). This information was acquired from the patients' medical records and from interviews with both the patients and their relatives. The mean duration (±SD) of schizophrenia was 15.4 ± 11.3 years. We divided the patient sample into four groups according to the family background of schizophrenia with the help of the patient documents and interviews. There were 34 patients who had first-degree relatives with confirmed schizophrenia, 17 patients with schizophrenia in the extended family history (no first-degree schizophrenic relatives), 77 patients with no schizophrenic relatives and 21 patients with an undefined family background. The patients were recruited from the Departments of Psychiatry at Helsinki University Central Hospital and South Karelia Central Hospital. All the patients had been hospitalized because of acute or chronic schizophrenia. They were assessed to be capable of understanding the study procedure after its nature had been fully explained in the interview and in a written description of the study given to them. After that, all patients gave written informed consent for the study. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The ethics committees of both hospitals had approved the study. All patients were of Caucasian Finnish origin and resident in southern Finland.

The control group consisted of 94 (49 males, 45 females) healthy blood donors (age range 26–64 years; mean age (±SD) 44.9 ± 10.3 years) from the Finnish Red Cross Blood Transfusion Service, Tampere, Finland. The controls were somatically healthy Caucasian Finnish citizens.

2.2. EGF genotyping

Genomic DNA was extracted from peripheral blood leukocytes of the controls using a commercially available kit (Qiagen Inc., Hilden, Germany) and from patients using the salting-out method (Miller et al., 1988). Genotypes were determined with fluorogenic allele-specific oligonucleotide probes with a conjugated minor groove binder (MGB) group (Livak, 1999). The nucleotide sequences of the primers and probes used in the PCR were deduced from published sequences deposited in the GenBank database and chosen and synthesized in conjugation with Applied Biosystems (Foster City, CA, USA). DNA samples were genotyped by employing the 5′-nucleotidase assay for allelic discrimination using the ABI Prism 7000 Sequence