Association of the cerebral dopamine neurotrophic factor (CDNF) gene intron 1 polymorphism rs11259365 with Parkinson’s disease in the Greek population.

Kallirhoe Kalinderi¹, Liana Fidani¹, Zoe Katsarou², Sevasti Bostantjopoulou³

¹Department of General Biology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
²Department of Neurology, Hippocration Hospital, Thessaloniki, Greece
³Third University Department of Neurology, G. Papanikolaou Hospital, Thessaloniki, Greece

ABSTRACT: Cerebral dopamine neurotrophic factor (CDNF) is a newly identified neurotrophic factor. In this study, we examined the CDNF rs11259365 polymorphism in 53 Greek patients with sporadic Parkinson’s disease (PD) and 52 control subjects, using a PCR-RFLP method. No association was found between this polymorphism and PD, in the Greek population.

Key Words: Parkinson’s disease, Gene, CDNF, Polymorphism.

INTRODUCTION

Parkinson’s disease (PD) is a common neurodegenerative disorder affecting approximately 1% of the population over 60 years of age. The core neuropathological features of PD are the loss of dopaminergic neurons in the substantia nigra and the deposition of specific cytoplasmic protein aggregates, known as Lewy bodies. Approximately 90-95% of PD patients have sporadic disease attributed to interactions between environmental conditions and the genetic constitution of each individual, whereas 5-10% of PD cases have a positive familial background with five genes: a-synuclein, parkin, PTEN induced putative kinase 1, DJ-1 and Leucine-rich repeat kinase 2 being definitely associated with the Mendelian inheritance of the disease.

Neurotrophic factors are small secreted proteins which regulate neuronal survival, growth, differentiation and migration in the nervous system. Neurotrophic factors belong to three main protein families: neurotrophins, neurotrophic cytokines and glial cell line-derived neurotrophic factor family. Recently, a novel family of neurotrophic factors has been discovered, consisting of mesencephalic astrocyte-derived neurotrophic factor and cerebral dopamine neurotrophic factor (CDNF). Neurotrophic factors are considered as promising factors for the treatment of a variety of neurological diseases including Alzheimer’s disease, PD, Huntington’s disease, epilepsy and neuropathies. In the present study, in an attempt to investigate the role of genetic variations in the CDNF in PD pathogenesis, we examined for the first time the possible association of the CDNF rs11259365 polymorphism with PD, in the Greek population.

PATIENTS AND METHODS

In the present study, we examined 53 unrelated individuals diagnosed for PD without positive family history. The control group consisted of 52 healthy individuals. All participants gave informed consent for this study. Genomic DNA was extracted in all subjects from peripheral blood leukocytes according to standard procedures. The CDNF genotypes were determined using a polymerase chain reaction-restriction fragment length polymorphism method. The target region of CDNF was amplified with the following
set of primers: forward 5’-AAAGAAACCCCCAGTATTCC-3’; reverse 5’- ATATGGTAGGCGCTCAGTTT-3’. The PCR conditions used for the rs11259365 polymorphism were: initial denaturation at 94°C for 5 minutes followed by 25 cycles of 94°C for 30 seconds, 60 to 50°C touchdown annealing for 30 seconds at 0.5°C per cycle, and 72°C for 45 seconds, with a final extension at 72°C for 10 minutes. Digestion with Sau3AI restriction enzyme (New England Biolabs) at 37°C yields 146+89 bp bands for the G allele and 111+89+35 bp bands for the C allele, respectively. Digestion products were resolved on a 4% agarose gel, stained in ethidium bromide solution and visualized with an ultraviolet light.

RESULTS
In our cohort the distribution of genotype frequencies was GG = 90.6%, GC = 7.5%, CC = 1.9%; and GG = 92.3%, GC = 7.7%, CC = 0.0% for the PD and control group, respectively (p = 0.607). Allele frequencies were G= 93.34%, C = 5.66% and G = 96.15%, C = 3.85% for patients and controls, respectively (p = 0.538) (Table 1).

DISCUSSION
CDNF is a newly identified neurotrophic factor with neurotrophic, neuroprotective and neurorestorative activities. In vivo studies, have shown CDNF to exert a neurotrophic effect as well as to protect and repair dopaminergic neurons. Interestingly, injecting CDNF before 6-hydroxydopamine into the striatum in a rat model, significantly reduced amphetamine-induced ipsilateral turning behaviour and almost completely rescued dopaminergic tyrosine hydroxylase-positive cells in the substantia nigra. When CDNF was injected into the striatum four weeks after the lesion, significant recovery of motor function was noticed after eight weeks, supporting the neurorestorative role of CDNF.

CDNF is located on chromosome 10p13. CDNF contains 4 exons and spans 18,732bp. The rs11259365 polymorphism is located on intron 1 of CDNF. After the discovery of CDNF as a member of a new neurotrophic family, the genetic role of variations in CDNF was firstly examined in cocaine dependence, as cocaine induced neuroplasticity changes in the mesocorticolimbic dopamine systems are thought to be implicated in the pathophysiology of this behaviour. However, negative results were found for this association. We examined the possible association of the intronic rs11259365 polymorphism with PD in the Greek population. An intronic SNP may act as a susceptibility factor for a disease if it is in linkage disequilibrium with other functional SNPs in exonic regions or it can directly affect gene expression. In our study no association was found between the rs11259365 polymorphism and PD, in the Greek population. These preliminary results provide a strong indication that this polymorphism does not have a major role in PD pathogenesis. In the study of Choi et al, only the C allele of the rs7094179 CDNF intronic polymorphism was found to be a possible susceptibility allele for PD, in the Korean population. Additional studies with larger sample size and in different populations are needed to further investigate the possible role of genetic variations in CDNF in PD.

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDNF rs11259365 polymorphism</td>
<td>G/G</td>
</tr>
<tr>
<td>PD (N = 53)</td>
<td>48 (90.6)</td>
</tr>
<tr>
<td>CONTROLS (N = 52)</td>
<td>48 (92.3)</td>
</tr>
</tbody>
</table>

X² (OR = 0.8, 95% CI:0.20-3.15) (OR = 0.67, 95% CI:0.19-2.39)

Abbreviations
PD: Parkinson’s disease
CDNF: cerebral dopamine neurotrophic factor
ΠΕΡΙΛΗΨΗ: Ο εγκεφαλικός νευροτροφικός παράγοντας ντοπαμίνης (CDNF) είναι ένας νεοανακαλυφθείς νευροτροφικός παράγοντας. Στην παρούσα μελέτη εξετάστηκε ο πολυμορφισμός CDNF rs11259365 σε 53 Έλληνες ασθενείς με σποραδική νόσο Πάρκινσον (ΝΠ) και 52 υγιή άτομα, με τη μέθοδο PCR-RFLP. Δε βρέθηκε κάποια συσχέτιση μεταξύ του συγκεκριμένου πολυμορφισμού και της ΝΠ, στον Ελληνικό πληθυσμό.

Λέξεις Κλειδιά: Νόσος Πάρκινσον, Γονίδιο, CDNF, Πολυμορφισμός.

REFERENCES