Autosomal-dominant Parkinson’s disease linked to 2p13 is not caused by mutations in transforming growth factor alpha (TGF alpha)

Short Communication

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Received March 12, 2001; accepted April 27, 2001

Summary. A susceptibility gene for Parkinson’s disease (PD) with late onset and typical Lewy-body pathology maps to chromosome 2p13 (PARK3). In the present study we examined the gene for transforming growth factor alpha (TGF alpha), which is located in the PARK3-region, as a potential candidate gene. This polypeptide mitogen exerts trophic actions on dopaminergic neurons and TGF alpha-deficient mice have fewer dopaminergic neurons.

We did not find mutations in the exonic or exon-flanking intronic sequences of index patients of two families linked to 2p13. This result excludes mutations in the coding region of TGF alpha as a cause for hereditary PD, but does not rule out a possible role of sequence variants in regulatory regions or splice sites.

Key words: Transforming growth factor alpha, Parkinson’s disease, autosomal dominant, neurogenetics, exon-intron boundaries.

Introduction

In the vast majority of cases, Parkinson’s disease (PD) is a sporadic disorder. Nevertheless mutations in several genes have recently been identified as the causes of the disease in small subgroups of patients. Five genes have been mapped: missense mutations in the gene for alpha-synuclein (PARK1, 4q21–q23) segregate with the illness in an autosomal-dominant fashion (Heintz et
A second locus (PARK2) has been mapped on 6q25.2–27 and mutations in the gene for parkin have been identified in families suffering from autosomal-recessive juvenile parkinsonism (Kitada et al., 1998; Matsumine et al., 1998). Two additional genes map to 2p13 (PARK3) (Gasser et al., 1998) and 4p14 (Farrer et al., 1995). Finally, a mutation in the gene for ubiquitin C-terminal hydrolase has been found in a small family of German ancestry (Leroy et al., 1998).

One of the genes located in the PARK3-region, which is defined by a common haplotype in 2 families comprising approximately 3cM between CA-repeat markers D2S2113 and D2S2109, is the gene for transforming growth factor alpha (TGF alpha).

The polypeptide mitogen TGF alpha (Lee et al., 1995) acts at the epidermal growth factor receptor and has defined neurobiological functions: TGF alpha is developmentally regulated and expressed in neurons and glia of the central nervous system (Ferrer et al., 1995). It exerts trophic actions on mesencephalic neurons in vitro (Santa-Olalla et al., 1995) especially dopaminergic neurons of the midbrain (Alexi et al., 1993; Engele et al., 1996). Expression levels of TGF alpha change after CNS-lesioning in rats (Kornblum et al., 1994) and are higher in brains of parkinsonian patients than in controls post mortem (Mogi et al., 1994) or in ventricular cerebrospinal fluid in vivo (Mogi et al., 1996). This has been interpreted as a compensatory upregulation during the process of neurodegeneration (for review see Connor et al., 1998). TGF alpha-deficient mice have fewer dopaminergic neurons in the substantia nigra (Blum, 1998), indicating a necessary trophic function on the neuronal subgroup degenerating in PD.

Because of these neurobiological data and due to the fact, that TGF alpha maps to the PARK3-region, TGF alpha can be considered as a candidate gene for autosomal-dominant Parkinson’s disease. The aim of this study was to show or to exclude mutations in the translated exonic or exon-flanking intronic sequence of the TGF alpha-gene.

The exon-intron-structure of the human TGF alpha-gene has been published (Collin et al., 1999). We simultaneously obtained exon-flanking intronic sequences by an inverse PCR-approach (Groden et al., 1991).

**Material and methods**

*PAC library screening and inverse PCR*

A human PAC library (plasmid artificial chromosome) constructed by P. de Jong was screened and circular fragments of one clone (LLNPL704106312, resource centre of the German Human Genome Project) were used as template for inverse PCR with primer pairs derived from the exons but directed towards the introns. The sequence obtained was with some exceptions identical to the one published by Collin et al. (1999).

*PCR and sequence analysis*

PCR-amplification followed standard conditions (Perkin Elmer) and fluorescence sequencing was performed on a ABI-373A automated sequencer (Applied Biosystems Inc.) using dye-labelled terminating nucleotides. In order to sequence a PCR-product of n