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Short communication

Trinucleotide repeat expansion of TATA-binding protein gene associated with Parkinson's disease: A Thai multicenter study

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ABSTRACT

Introduction: Spinocerebellar ataxia type 17 (SCA17) is an inherited cerebellar degeneration associated with trinucleotide repeat expansions in the TATA-binding protein gene (*TBP*). Low-range expansions of *TBP* have recently been described in association with Parkinson's disease (PD). However, these low-range expansion alleles were also observed in healthy individuals. Prior distinct findings may result from reduced penetrance or age-dependent susceptibility, which may influence phenotypic expression.
Methods: A case-control study of 456 PD patients and 374 control subjects was conducted. Data and blood samples were collected during 2008–2013. Control subjects were individuals over 65 years old without parkinsonism. Sizes of *TBP* trinucleotide repeats were analyzed. All available carriers of the *TBP* repeat of ≥40 repeats were re-examined.
Results: A high prevalence of carriers of *TBP* repeat expansion ≥41 developed PD, mainly at an advanced age. Half of these carriers had onset after 70 years of age (range 34–84). Seven participants carried expansion alleles of ≥42, and all had PD. Fourteen participants (six patients and eight controls) carried a heterozygous 41-repeat allele. At the current mean age of 79 years and mean follow-up period of 4 years, three out of the eight control carriers of the 41-repeat allele developed PD, while none of the thirteen asymptomatic carriers of the 40-repeat allele did.
Conclusions: A high prevalence of PD was observed in carriers of low-range expansions of *TBP* (41–45 repeats), especially in elderly. This finding suggests that cut-off value for pathological *TBP* repeat expansion appear to be 41.

1. Introduction

Spinocerebellar ataxia type 17 (SCA17) is an inherited cerebellar degeneration caused by CAG/CAA repeat expansions in the TATA box-binding protein gene (*TBP*) [1]. Patients commonly exhibit cerebellar dysfunction accompanied with cognitive impairment, parkinsonism, chorea, dystonia, pyramidal signs and psychiatric symptoms. Phenotypes are widely diverse; for example, the disease can manifest as Huntington's disease-like (HDL) or Parkinson's disease (PD) [2,3]. Phenotypic expressions of SCA17 often correlate with the length of the CAG/CAA expansion. HDL and PD phenotypes are almost invariably associated with repeat expansions in a smaller range, generally less than 50 repeats, compared with complex cerebellar phenotypes [2,3]. Additionally, studies of PD cohorts revealed that 0.5–1% of the patients carried small *TBP* expansion alleles ranging from 43 to 46 repeats [4,5].

The pathological cut-off value of the *TBP* expansion is still inconclusive. It is generally accepted that ≥43 repeat expansions are pathological alleles [4]. However, recent data suggested that the

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threshold might be lower. The 42 repeat allele was identified in association with autosomal dominant and sporadic ataxias, generally with mild phenotype [6,7]. In cell culture model, lymphoblastoid cell lines derived from patients carrying the low-range repeat expansions had a reduction of various heat shock proteins expression, and increased vulnerability to an oxidative reagent, leading to cell death [5]. Dopamine transporter (DAT) imaging revealed a decrease in striatal DAT uptake of asymptomatic carriers having expansion of 42–44 repeats, supporting a pathogenic role of the small *TBP* repeat expansions [4]. Further case reports of ataxia and parkinsonism were described in association with the 41-repeat allele [7–9]. In contrast, frequencies of the small expansion alleles were similarly observed in healthy individuals and patients with parkinsonism and ataxia in a recent large Korean study [10].

There has been increasing evidence supporting the important role of *TBP* repeat expansions in the risk of developing PD, especially in East Asian populations [4,5]. The authors previously identified that SCA17 was an important cause of spinocerebellar ataxia in Thailand. Additionally, ataxia, parkinsonism and cognitive impairment were often observed in carriers of the 41 and 42 repeat alleles in the study [7]. The present study was therefore carried out in a relatively large group of PD patients and elderly control subjects in order to clarify the significance of *TBP* repeat expansions in Thai PD patients.

2. Materials and methods

2.1. Ethics and consent

All participants were provided appropriate counseling and gave informed consent. This study was approved by the Ethical Committee, Ramathibodi Hospital, Mahidol University (ID 03-53-18).

2.2. Participants and clinical evaluations

Patients were enrolled using the UK Parkinson's Disease Society Brain Bank Criteria, except patients were allowed to have a family history of PD [11]. Cognitive impairment was defined as a Montreal Cognitive Assessment (MoCA) score of $\leq$24. Dementia was defined in patients with cognitive impairment leading to functional dependence. Control subjects were individuals aged $\geq$65 years old recruited from the Medicine Clinic, Ramathibodi Hospital. They were all examined by the author (T.P.) confirming that no signs of parkinsonism were evident. The first clinical evaluation and blood sample collection were undertaken during May 2008–December 2013. The second clinical evaluation, during October 2014–June 2015, was performed by two authors (T.P. and P.W.) only in accessible carriers having *TBP* repeats $\geq$40. Clinical findings and the sizes of the *TBP* repeats of the control group were previously published [7].

2.3. Genetic analysis

DNA samples were extracted from peripheral leukocytes by standard techniques. Genetic analysis, including SCA2 and SCA3 repeat expansions, direct sequencing of glucocerebrosidase (*GBA*) and *parkin*, and exon rearrangements of parkin by semi-quantitative PCR were previously performed. Forty-one patients (1 SCA2; 24 *GBA*; 16 *parkin*) who carried mutations in those genes were excluded from the study. Fluorescent PCR of the trinucleotide repeat alleles in the *TBP* gene was subsequently carried out in the remaining samples from 456 PD patients and 374 control subjects, using previously described methods [7]. Tandem repeat sizes were determined by running capillary electrophoresis on a 3730XL DNA Analyzer (Applied Biosystems, CA, USA). PCR fragments were analyzed using Peak Scanner v1.0 (Applied Biosystems). Sizes of tandem repeats were calculated by comparing the results with the sizes of a normal control sample as defined by direct sequencing.

3. Results

3.1. Carriers of the TBP $\geq$42-repeat

The study identified seven participants, three in the patient group and four in the control group, carrying heterozygous CAG/CAA repeat expansions of 42–45 repeats (Table 1). The four control subjects (participant numbers commencing with 2 in Table 2) were enrolled and initially examined from 3 to 8 years ago. Recent examinations revealed that they all had clinical signs of asymmetrical parkinsonism (Table 2). Two of these controls had already been diagnosed with levodopa-responsive PD by their primary physicians for 2 and 5 years. The two others had mild motor symptoms together with definite signs of parkinsonism. They subsequently responded well to levodopa. Overall, mean age at onset of the carriers of $\geq$42-repeat alleles was 65.9 $\pm$ 17.9, ranging from 34 to 84 years old. Cognitive impairment or dementia was observed in almost all patients, in whom it could develop within the first few years after the onset of motor symptoms. No cerebellar signs were observed in any of these patients. It was noted that none of these patients had a family history of PD or ataxia.

3.2. Carriers of the TBP 41-repeat

Fourteen participants carried a heterozygous 41-repeat allele: six in the patient group and eight in the control group (Table 1). Mean age at onset in this patient group was 68.3 $\pm$ 7.0, ranging from 59 to 80 years old. Regarding the control group, one (No. 20260) had left spastic hemiplegia, dementia, and epilepsy caused by multiple cardioembolic strokes. She subsequently died at the age of 80. So seven controls were re-examined. None of them complained of motor symptoms of PD. However, three of the carriers had asymmetrical parkinsonism, accompanied by unilateral pill-rolling rest tremor in one case (Table 2) [7]. All these affected carriers responded well to acute levodopa challenge test. MoCA was performed in five subjects, showing that cognitive impairment was also evident in three carriers (MoCA = 13, 18 and 23).

3.3. Carriers of the TBP 40-repeat

There were 23 participants who carried a heterozygous 40-repeat allele: 9 in the patient group and 14 in the control group (Table 1). Mean age at onset in these patients was 59.7 $\pm$ 13.9, ranging from 44 to 85 years. One of the control carriers was lost to follow-up. None of the 13 remaining control carriers had signs of parkinsonism at a recent re-evaluation. Only a 68-year-old female had bilateral postural and kinetic tremor without bradykinesia, or rigidity compatible with essential tremor.

4. Discussion

By comparing large groups of ethnic Thai PD patients and elderly subjects, the study identified that all carriers of *TBP* repeat expansions $\geq$42 developed PD. Onset of motor symptoms typically commenced after the eighth decade. Regarding carriers of the *TBP* 41-repeat allele, all but one PD patient had onset of motor symptoms in the seventh decade or later. Nearly half of the carriers in the control group also developed parkinsonism after the enrollment; their clinical signs were first noticed in the eighth or ninth decade. In contrast, none of the control carriers of the *TBP* 40-repeat allele developed parkinsonism, although they were evaluated at a similar

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