Role of LRRK2 and SNCA in autosomal dominant Parkinson's disease in Turkey

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Abstract

Introduction: Mutations in the LRRK2 and alpha-synuclein (SNCA) genes are well-established causes of autosomal dominant Parkinson’s disease (PD). However, their frequency differs widely between ethnic groups. Only three studies have screened all coding regions of LRRK2 and SNCA in European samples so far. In Turkey, the role of LRRK2 in Parkinson’s disease has been studied fragmentarily, and the incidence of SNCA copy number variations is unknown. The purpose of this study is to determine the frequency of LRRK2 and SNCA mutations in autosomal dominant PD in Turkey.

Methods: We performed Sanger sequencing of all coding LRRK2 and SNCA exons in a sample of 91 patients with Parkinsonism. Copy number variations in SNCA, PRKN, PINK1, DJ1 and ATP13A2 were assessed using the MLPA method. All patients had a positive family history compatible with autosomal dominant inheritance.

Results: Known mutations in LRRK2 and SNCA were found in 3.3% of cases: one patient harbored the LRRK2 G2019S mutation, and two patients carried a SNCA gene duplication. Furthermore, we found a heterozygous deletion of PRKN exon 2 in one patient, and four rare coding variants of unknown significance (LRRK2: A211V, R1067Q, T2494I; SNCA: T72T). Genetic testing in one affected family identified the LRRK2 R1067Q variant as a possibly pathogenic substitution.

Conclusion: Point mutations in LRRK2 and SNCA are a rare cause of autosomal dominant PD in Turkey. However, copy number variations should be considered. The unclassified variants, especially LRRK2 R1067Q, demand further investigation.

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1. Introduction

While most cases of Parkinson’s disease (PD) are sporadic, changes in various genes are known to cause monogenic forms of PD. Autosomal dominant PD (ADPD) results from mutations in LRRK2 (leucine-rich repeat kinase 2), SNCA (alpha-synuclein) and VPS35 (vacuolar protein-sorting associated protein 35), with point mutations in LRRK2 and SNCA gene duplication being most common.

Known disease-causing mutations in LRRK2 include N1437H, R1441C/G/H, Y1699C, G2019S and I2020T [1–3]. G2019S plays a predominant role, occurring in 1–2% of sporadic and 5–6% of familial cases [4]. The LRRK2 gene is composed of 51 exons, and it encodes a large protein containing several domains [5]. All established mutations are located between exons 30 and 41 and fall within the ROC-COR or kinase domains [3]. The penetrance of known mutations is incomplete and age dependent [6]. Affected carriers display mostly a phenotype resembling sporadic PD with mean onset at 58 years, slow progression and effective dopamine-replacement therapy [6].

While known point mutations in SNCA (A30P, E46K, H50Q, G51D, A53E and A53T) and triplication of the gene are rare, SNCA gene duplication accounts for 1–2% of ADPD cases [7,8]. Duplication
 carriers usually present with a phenotype similar to sporadic PD, whereas triplication and point mutations often result in a more severe course of disease [2].

The frequency of LRRK2 and SNCA mutations in PD varies widely depending on the ethnicity of patients. Among LRRK2 mutations, G2019S has been studied most comprehensively. Its frequency in PD cases ranges from <0.1% in Asians [9] to 41% in North African Arabs [10]. Being less common, data on other LRRK2 and SNCA mutations are incomplete.

Most sequencing studies have focused on a few exons or even only screened for LRRK2 G2019S, thereby possibly underestimating the role of other mutations. A systematic PubMed search revealed that only three studies worldwide have examined all coding exons of LRRK2 and SNCA as well as SNCA copy number variations (CNVs) in patients with PD [11–13]. In a Belgian sample of 310 sporadic and familial PD cases, 1.9% carried the known LRRK2 R1441C mutation and 0.3% a duplication of the SNCA gene [11]. A Greek study screening 55 ADPD cases failed to identify any mutation carriers [12]. The third study included 352 sporadic and 126 familial PD patients who all self-identified as European Americans [13]. Of the sporadic cases, 0.6% carried the LRRK2 G2019S mutation. This mutation also accounted for 4.8% of familial cases. SNCA duplication was found in 0.8% of those with a positive family history.

As all comprehensive studies of LRRK2 and SNCA were restricted to samples of European descent, it seems worthwhile to employ their methods in a different population such as the Turkish. Turkey is situated at the crossroads of Europe, Asia and the Arabian Peninsula. Data on PD-related mutations are available from two neighboring countries: In Greece, the frequency of LRRK2 and SNCA mutations in PD cases is reported to be up to 0.4% and 4.5%, respectively [12,14]. In Iran, it is 0.5% and 5.9% [15,16].

So far, the genetic causes of PD in Turkey have been studied incompletely. A study examining LRRK2 exons 31, 35 and 41 did not identify any mutations in a sample of 255 sporadic and familial cases [17]. Another study screening for LRRK2 exon 41 mutations in 78 sporadic and familial cases found one G2019S carrier [18]. A third study reported no Turkish G2019S mutation carriers [19].

The only study assessing the frequency of SNCA mutations in Turkey analyzed all coding exons of SNCA, PRKN, PINK1 and DJ1 in 50 early-onset PD patients without finding any pathogenic variants [20]. Testing for CNVs was not performed. Another study investigating autosomal recessive PD (ARPD) in 86 Turkish patients examined nucleotide sequence variations as well as CNVs in PRKN, PINK1 and DJ1 [21]. PRKN mutations (mostly CNVs) were found in 16.9% and PINK1 mutations in 2.6% of the cases.

In comparison, the previous studies concerning LRRK2 were of limited scope, and SNCA multiplications has yet not been assessed in Turkish patients with PD. In this study, we aim to determine the frequency of all LRRK2 and SNCA mutations in a cohort of Turkish ADPD cases. All patients had a family history of PD compatible with autosomal dominant inheritance. The criteria for inclusion were as follows. First, there had to be a total of two or more affected family members. Second, these members must not be more than two generations apart. Sixty-nine patients had an affected first-degree relative, and 22 patients had an affected second-degree relative. The sample was not restricted to patients with affected first-degree relatives due to the incomplete penetrance of known mutations (see 1).

The consanguinity rate was 16.5%. Eighty patients were of Turkish origin. One each was of mixed Turkish-Bulgarian/-Greek/- Russian/-Syrian descent. Three were from Bulgaria, two from former Yugoslavia, one from Greece and another one from Croatia. Those of non-Turkish origin were Pomois, a Muslim minority inhabiting the Balkans.

Informed written consent was obtained from all patients or their surrogates. The study received approval by the research ethics committees at Istanbul University, Turkey and University of Tübingen, Germany. The patients were not part of previous publications.

2.2. Genetic analysis

Genomic DNA was isolated from peripheral blood samples by standard protocols. We performed Sanger sequencing of all coding regions and exon-intron boundaries of LRRK2 (exons 1-51) and SNCA (exons 2-6) using BigDye™ chemistry, 3130xl and 3500xl genetic analyzers (Applied Biosystems, Foster City, CA, USA) and the Sequence Pilot software (version 4.1.2, JSI medical systems, Tübingen, Germany).

Copy number variations in SNCA exons 1-6, PRKN exons 1-12, PINK1 exons 1-8, DJ1 exons 1-7 and ATP13A2 exons 2 and 9 were tested by MLPA™ with the SALSA MLPA P051-D1 Parkinson pro-bmix (MRC-Holland, Amsterdam, the Netherlands). Data were analyzed using the GeneMapper software (version 5.0, Applied Biosystems). Primer sequences and PCR protocols are available upon request.

2.3. Investigation of rare coding variants

Minor allele frequencies (MAF) were obtained from the ExAC browser (https://gool.gl/um2T8) and our intramural database. This dataset encompasses 1.450 PD cases of the IPDGC study (https://gool.gl/s2fgmm) and a total of 2.220 controls of IPDGC and the EROG study (https://gool.gl/9j1b4R). The exact number of genotyped individuals is given in Table 1. The mean age of onset in IPDGC cases was 42.2 years (median 42, range 6–98 years), and the mean age at examination was 51.5 years (median 51, range 16–101 years); 97.5% were of Caucasian descent.

Single nucleotide variants with a MAF <0.001 in the ExAC dataset were defined as rare. We used BLAST (https://gool.gl/cGEvL7) for amino acid and nucleotide conservation analysis across the following species: Homo sapiens, Pan troglodytes, Macaca mulatta, Felis catus, Mus musculus, Gallus gallus, Xenopus tropicalis, Takifugu rubripes and Danio rerio. In silico prediction of pathogenicity was performed using the Polyphen-2 (https://gool.gl/EZk28), PROVEAN and SIFT (https://gool.gl/3BhX7C) algorithms.
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