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Genetic variation of the mitochondrial Complex I subunit *NDUFV2* and Parkinson disease

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Abstract

NADH dehydrogenase ubiquinone flavoprotein 2 (*NDUFV2*), encoding a subunit of mitochondrial complex I, is a candidate gene for several neuronal diseases; schizophrenia, bipolar disorder and Parkinson disease (PD). We screened the entire coding region of *NDUFV2* in 33 familial PD patients of North African Arab-Berber ethnicity in which all known genetic forms of PD had been excluded. We detected one novel substitution p.K209R (c.626A>G) in one PD. Segregation analysis within the family is inconclusive due to small sample size, but consistent with autosomal dominant mode of inheritance. Subsequent screening of this mutation in ethnically-matched sporadic PD patients (n=238) and controls (n=371) identified p.K209R in one additional patient. The clinical features of the mutation carriers revealed a mild form of parkinsonism with a prognosis similar to idiopathic PD. Our findings suggest further studies addressing the role of *NDUFV2* variation in PD may be warranted.

Keywords

Parkinson disease; *NDUFV2*; mutation; genetics

Introduction

Parkinson disease (PD) is the second most common neurodegenerative disorder in elderly populations. Studies to date have identified several genetic causes of PD and early-onset parkinsonism including; alpha-synuclein (*SNCA*), leucine-rich repeat kinase 2 (*LRRK2*), parkin *(PRKN)*, PTEN-induced kinase 1 (*PINK1*), and oncogene *DJ1* [1]. We have previously reported a high frequency of *LRRK2* c.6055G>A (p.G2019S) (30%) and *PINK1*

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homozygote mutation carriers (15%) within PD patients of Arab-Berber ethnicity in North Africa [2, 3]. In addition a small percentage (4%) of families with PD were explained by homozygote and compound heterozygote mutations in *PRKN* [4]. However, 33 familial PD probands (51%) did not present mutations in known PD genes. The NADH dehydrogenase ubiquinone flavoprotein 2 (*NDUFV2*; NIM 600532) located on chromosome 18p11.31-p11.2 has been nominated as a causative gene in PD, as well as other neurological diseases including schizophrenia, and bipolar disorder [5–7]. In addition, association studies with common variants in *NDUFV2* have shown positive results in Asian populations, although they did not replicate in a Caucasian series [5, 8, 9]. *NDUFV2* is also a good biological candidate as it encodes a 24-kDa subunit of mitochondrial complex I and mitochondrial dysfunction has been associated with several neurodegenerative disorders, including PD [10].

Herein, we describe the identification of a novel mutation Lysine 209 Arginine (p.K209R) c. 626A>G in *NDUFV2* in one familial PD proband and one sporadic PD patient. Segregation analysis supports pathogenicity, although further confirmation is needed.

Material and methods

Subjects

This study genetically characterized *NDUFV2* in a total of 33 familial probands with PD from the Institut National de Neurologie, Tunis. This group presented a mean age at disease onset of 53.0 ± 15.2 years (mean ± S.D) and a 12:21 male to female ratio. A previously described ethnically matched case-control series consisting of 238 sporadic PD cases and 371 controls was genotyped for the novel variant herein described [2]. The Institut National de Neurologie, Tunis provides a specialized neurological service to the entire country of Tunisia [11]. The site obtained local ethics committee approval before beginning recruitment (06-004383). Informed written or proxy consent for the study was given by all subjects. Individuals were diagnosed as “affected” if they satisfied the United Kingdom PD Society Brain Bank (UKPDS) criteria [12].

Sequencing and genotyping

Genomic DNA was extracted from peripheral blood lymphocytes using standard protocols. Primer pairs for *NDUFV2* were used to sequence all 8 exons and exon-intron boundaries. PCR products were purified using Agencourt bead technology (Beverly, MA) with Biomek FX automation (Beckman Coulter, Fullerton, CA). Genotyping of the p.K209R was performed on a Sequenom MassArray iPLEX platform (San Diego, CA, US). All primer sequences are available on request.

Results

Sequencing analysis of the *NDUFV2* in familial probands identified one novel missense mutation leading to a lysine to arginine substitution at aminoacid position 209 (p.K209R, c. 626A>G). Genotyping of additional family members from this pedigree revealed a total of three mutation carriers, two diagnosed with PD and one with essential tremor (ET). One additional family member not carrying the mutation had also been diagnosed with ET

(Figure 1). The clinical features of patient II-2 consisted of an age-at-onset of 57 years, with a disease duration of 13 years, Hoehn and Yahr stage I and MMSE 20/30. Patient II-4 presented disease with and age-at-onset of 66 years, and 17 years of disease duration, Hoehn and Yahr stage I and MMSE 22/30. Both presented with a mild form of parkinsonism and a typical clinical course. The last patient harboring this mutation (II-3) was diagnosed with ET and did not present any signs of parkinsonism at 75 years of age. Subsequent screening of 238 sporadic PD cases and 371 controls from the same ethnicity and geographical location identified one additional male patient diagnosed with PD at 60 years of age, harboring the p.K209R mutation; none of the controls were positive for this mutation.

Discussion

Association studies of *NDUFV2* gene have suggested it may be a genetic factor in a number of disorders including PD, bipolar disorder or schizophrenia. Hattori et al. first reported an association with the polymorphism p.A29V and PD in the Japanese population [5], however they did not identify any pathogenic mutations. In this study we evaluated the presence of novel mutations in 33 PD probands of Arab-Berber ethnicity. Sequencing the entire coding region of *NDUFV2* identified one novel lysine to arginine substitution (p.K209R), later identified in one additional sporadic patient with PD. Segregation analysis of p.K209R is consistent with pathogenicity, but inconclusive due to the small size of the pedigree. The existence of a mutation carrier (II-3) diagnosed with ET rather than PD, suggests that if pathogenic, the p.K209R could result in different disease phenotypes. Although this amino acid position appears to be highly conserved in many species, the mutant amino acid is the wild-type residue in rat (Figure 2). Although bioinformatics analysis using PolyPhen, and the presence of arginine in the wild-type protein sequence of rat may be taken as indicative of non-pathogenicity; equivalent data exists for the confirmed pathogenic α-synuclein p.A53T mutation [13].

NDUFV2 is one of the many components of the mitochondrial oxidative phosphorylation pathway, variation in the gene leading to altered energy production and mitochondrial function has been postulated as a factor to alter the risk of developing PD [5]. In this study we genetically characterized *NDUFV2* in an ethnically distinct population which led to the identification of a novel mutation in one kindred and one sporadic PD patient. Further studies characterizing *NDUFV2* in larger series and ethnically distinct populations are necessary to evaluate the role of this gene in PD, and discern whether p.K209R is a rare polymorphism in the Tunisian population or a global risk factor for PD.

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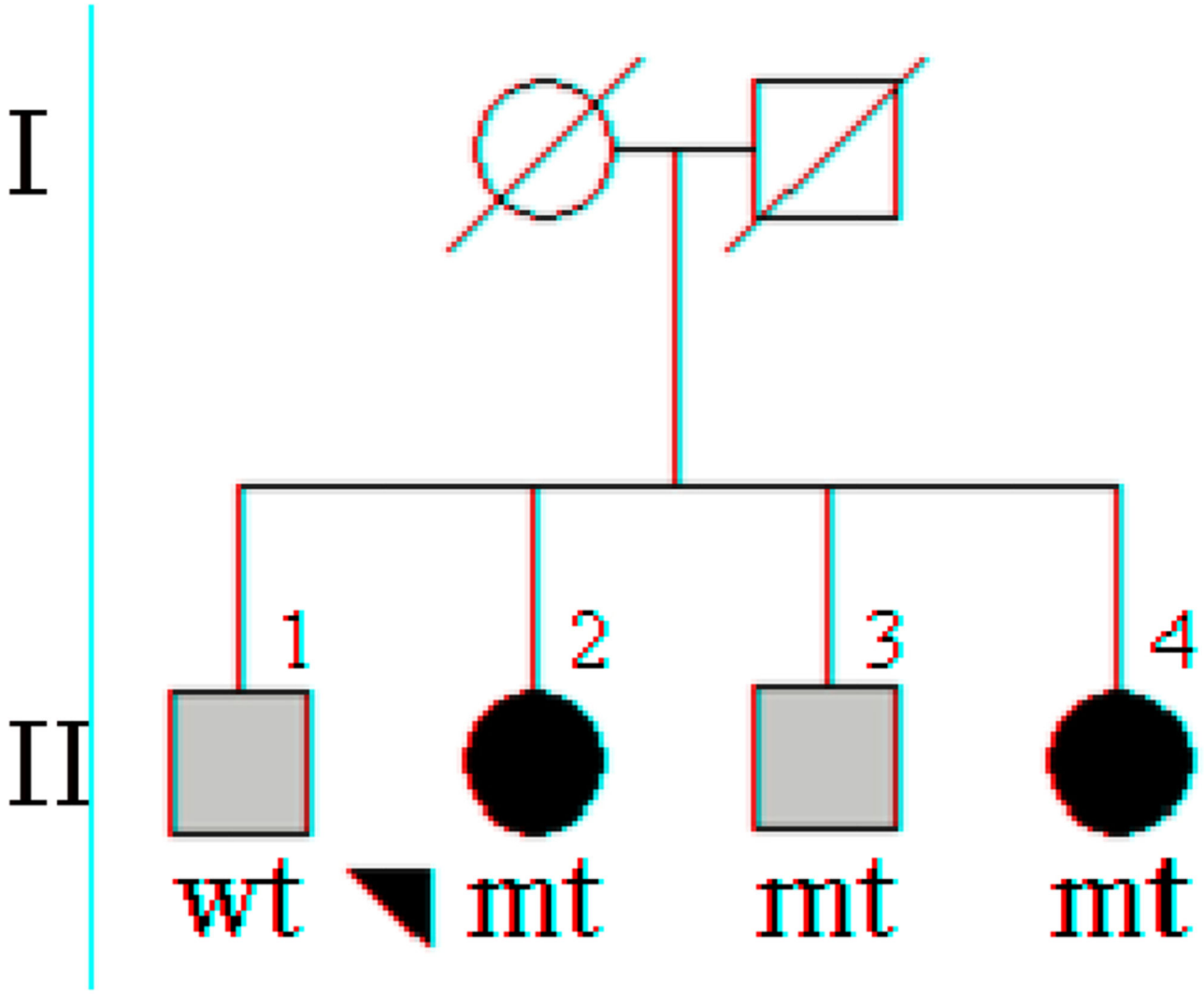

Figure 1. Segregation analysis of NDUFV2 p.K209R

A) Males are represented by squares, female by circles, and the probands is arrowed. Individuals diagnosed with Parkinson disease are indicated with black filled symbols, grey filled symbols indicate patients diagnosed with essential tremor. NDUFV2 p.K209R mutation carriers are indicated with mt, non carriers with wt.

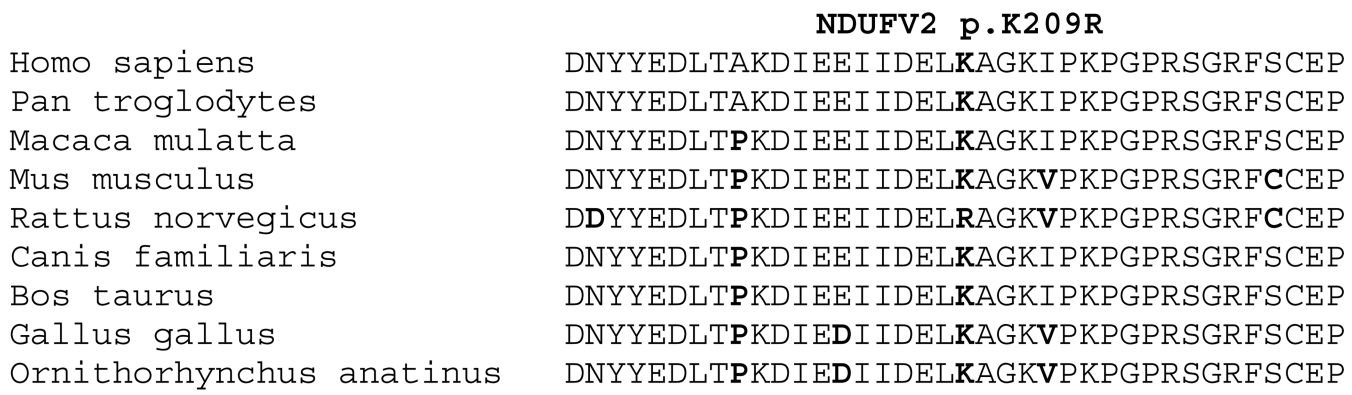

Figure 2. Conservation of NDUFV2 p.K209R

Protein homologues were aligned using ClustalW; p.K209R position is highlighted in black, non-conserved amino acid positions are highlighted in grey. GeneBank accession numbers: Homo sapiens, NP_066552; Pan troglodytes, NP_001065254; Macaca mulatta, XP_001099724; Mus musculus, NP_082664; Rattus norvegicus, NP_112326; Canis familiaris, XP_537328; Bos Taurus, NP_776990; Gallus gallus, XP_001232141; Ornithorhynchus anatinus, XP_001507932.