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DNAJC13 p.Asn855Ser mutation screening in Parkinson's disease and pathologically confirmed Lewy body disease patients

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Abstract

Recently, a novel mutation in exon 24 of *DNAJC13* gene (p.Asn855Ser, rs387907571) has been reported to cause autosomal dominant Parkinson's disease (PD) in a multi-incident Mennonite family. In the present study we have sequenced the mutation containing exon of the *DNAJC13* gene in a Caucasian series consisting of 1938 patients with clinical PD and 838 pathologically

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The authors declare no conflicts of interest.

diagnosed Lewy Body Disease (LBD). Our sequence analysis did not identify any coding variants in exon 24 of *DNAJC13*. Two previously described variants in intron 23 (rs200204728 and rs2369796) were observed. Our results indicate that the region surrounding the DNAJC13 p.Asn855Ser substitution is highly conserved and mutations in this exon are not a common cause of PD or LBD among Caucasian populations.

Keywords

DNAJC13; Parkinson's disease; Lewy body disease; genetics

Introduction

Parkinson's disease (PD) is the second most frequent movement disorder and one of the most common neurodegenerative diseases with a prevalence of 1–2% among individuals over the age of 60 years [1].

A number of different mutations/genes have been described which affect the susceptibility of individuals to the development of PD [2, 3]. Recently, a novel mutation located in exon 24 of the DnaJ (Hsp40) Homolog, Subfamily C, Member 13 (*DNAJC13*) gene (p.Asn855Ser, rs387907571) has been described to cause autosomal dominant PD and Lewy body pathology in a multi-incident Mennonite family [4]. *DNAJC13* is an excellent PD candidate gene given its relationship with two pathways that are involved in disease pathogenesis: recycling (the retromer complex) and the lysosomal system [4]. DNAJC13 is related to the retromer function via its interaction with the retromer component sorting nexin 1 [5] and it also binds (via its DNAJ-domain) to the molecular chaperone heat shock cognate 70 (Hsc70), which is involved in the endosomal system [6].

The DNAJC13 p.Asn855Ser substitution was first observed in a Dutch-German-Russian Mennonite family and additional carriers identified were of a similar ancestry and shared a common haplotype [4, 7, 8]. To assess the clinical relevance and assess mutation frequency, we have sequenced *DNAJC13* exon 24 in a series of Caucasian patients with clinical PD and pathologically confirmed LBD.

Material and Methods

A series of 1938 patients with PD from the US and Europe were assayed (Table 1). PD diagnosis was established according to standard clinical criteria [9] by an experienced neurologist (JAvG, RJU, JS, GO, AK-W, MB, KC, AM, TL, AP, IR, YS, BFB, RCP, NG-R and ZKW). An independent series of 838 Lewy body disease (LBD) patients from the US were also included in the study. This is a pathologically confirmed LBD series collected and examined according to standard criteria [10] by an experienced pathologist (DWD) from the Mayo Clinic, Jacksonville.

All subjects included in the study are unrelated, non-Hispanic Caucasians recruited at the following medical centers: Mayo Clinic, Jacksonville, US; Medical University of Silesia, Katowice, Poland; Jagiellonian University, Krakow, Poland; Medical Research Centre,

Polish Academy of Sciences, Warsaw, Poland; Central Hospital of the Ministry of Interior and Administration, Warsaw, Poland; Dublin Neurological Institute at the Mater Misericordiae University Hospital, University College Dublin, Ireland; Department of Neurology, Skåne University Hospital, Sweden; First Department of Neurology, Masaryk University, Brno, Czech Republic and Lviv Regional Clinical Hospital, Lviv, Ukraine. Written informed consent was obtained from all participants and the study was approved by all Institutional Review Boards from the participating centers.

DNAJC13 exon 24 was sequenced using the following primers: FOR: GGAGGAAGATGAGAATGAAG and REV: GACATGGACAAATTCTAACC with a genotype call rate over 95%. Variants were numbered according to standard nomenclature based on *DNAJC13* RefSeq NM_015268.3 mRNA and NP_056083.3 peptide accession numbers. The virtual effect of intronic variants on splicing was assessed *in silico* using the Human Splicing Finder (HSF) algorithm (<http://www.umd.be/SSF/>) [11].

Results and Discussion

The recent nomination of *DNAJC13* p.Asn855Ser as a cause of autosomal dominant PD adds to the list of candidate genes for this complex neurodegenerative disorder. Our sequencing analysis of 1938 patients with PD did not identify any further carriers of p.Asn855Ser or any other pathogenic variants in exon 24 of the *DNAJC13* gene, highlighting the conserved nature of this region of the gene/protein. We identified two previously described intronic mutations in intron 23 (rs200204728 and rs2369796), which had similar minor allele frequencies among cases and controls and those frequencies were comparable to the 1000 Genomes and Exome Sequencing Project databases. The HSF algorithm tool did not predict the generation of any novel splicing sites for either of the two intronic variants identified. Interestingly, the *DNAJC13* p.Asn855Ser has recently been observed in patients with essential tremor suggesting a level of heterogeneity in the manifestation of clinical signs associated with this gene mutation [8].

The results of our study show that *DNAJC13* p.Asn855Ser mutation is not a common cause of either PD or LBD among Caucasian populations. It should be noted that our study is focused on a single exon and does not rule out the possibility that variation in other regions of the *DNAJC13* gene could influence the risk of PD. A recent paper described the sequencing of the entire coding region of the *DNAJC13* gene in cases and controls and the identification of 18 novel rare missense mutations, however none of these were definitively shown to be pathogenic [12]. As next generation sequencing studies become more affordable, there will be an increasing number of rare variants nominated for pathogenicity and determining the true nature of these will be a major challenge. It will be critical though that pathogenicity is correctly designated to direct targeted therapeutic intervention strategies, drive biological understanding and define future clinical trial participants. There are few large multi-incident families remaining which would allow for significant segregation studies. Therefore, large collaborative population-based consortia studies will likely be necessary, which assess the frequencies of potential pathogenic variants not only in cases, but also in controls of the same genetic background. Finally, for unique or very rare

variants it will be crucial to develop gene-specific functional assays to provide a reliable read-out of pathogenicity.

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Table 1

Patient demographic data

	US PD (n = 695)	Polish PD (n = 705)	Irish PD (n = 372)	Swedish PD (n = 123)	Czech PD (n = 33)	Ukrainian PD (n = 10)	All PD (n = 1938)	US LBD (n = 838)
Age ¹ (±SD)	78.39 (11.28)	73.52 (11.37)	72.02 (10.30)	75.95 (9.67)	71.88 (11.02)	60.9 (13.90)	75.03 (11.40)	79.68 (8.72)
Age ¹ range	36–105	39–102	42–99	44–93	46–89	38–78	36–105	48–103
AAO ² (±SD)	63.94 (11.57)	58.57 (11.44)	55.7 (12.07)	62.68 (10.22)	58.85 (11.47)	54.2 (14.27)	60.19 (11.99)	NA
AAO ² range	28–94	25–89	18–87	37–84	32–80	29–74	18–94	NA
Female, %	36.69	37.59	44.35	37.40	51.52	40.0	38.80	43.32
Family history of PD, % ³	39.56	9.23	4.30	17.88	NA	80	19.91	NA

PD = Parkinson's disease; SD = standard deviation; AAO = age at onset; NA = data not available.

¹ Age refers to last visit for PD patients and age at death for LBD subjects. This value was not available for 10 PD samples.

² AAO was not available for 6 PD samples.

³ Family history of disease was not available for 33, 413, 205, 96, 33 and 2 subjects from the US, Polish, Irish, Swedish, Czech and Ukrainian series, respectively.