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Research article

The different faces of the p. A53T alpha-synuclein mutation: A screening of Greek patients with parkinsonism and/or dementia

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ABSTRACT

Background: The p. A53T mutation in the alpha-synuclein (*SNCA*) gene is a rare cause of autosomal dominant Parkinson's disease (PD). Although generally rare, it is particularly common in the Greek population due to a founder effect. A53T-positive PD patients often develop dementia during disease course and may very rarely present with dementia.

Methods: We screened for the p. A53T *SNCA* mutation a total of 347 cases of Greek origin with parkinsonism and/or dementia, collected over 15 years at the Neurogenetics Unit, Eginition Hospital, University of Athens. Cases were classified into: "pure parkinsonism", "pure dementia" and "parkinsonism plus dementia".

Results: In total, 4 p. A53T *SNCA* mutation carriers were identified. All had autosomal dominant family history and early onset. Screening of the "pure parkinsonism" category revealed 2 cases with typical PD. The other two mutation carriers were identified in the "parkinsonism plus dementia" category. One had a diagnosis of PD dementia and the other of behavioral variant frontotemporal dementia. Screening of patients with "pure dementia" failed to identify any further A53T-positive cases.

Conclusions: Our results confirm that the p. A53T *SNCA* mutation is relatively common in Greek patients with PD or PD plus dementia, particularly in cases with early onset and/or autosomal dominant family history.

1. Introduction

The p.A53T mutation in the alpha-synuclein (*SNCA*) gene is a rare cause of autosomal dominant Parkinson's disease (PD), originally described in an Italian kindred (Contursi family) and in Greek families from the Peloponnese [1]. Although generally rare, it appears to be particularly common in the Greek population due to a founder effect [2,3]. Most of the p.A53T cases described to date originated from the Peloponnese, though mutation carriers in Central Greece (Thessaly) and other Greek regions have also been reported [4].

A53T-positive patients, as well as cases carrying other *SNCA* mutations, usually present with early onset pure parkinsonism but they often develop dementia during disease course and may very rarely present with dementia [5–8]. Interfamilial as well as intrafamilial phenotypic variability has been noted in carriers of the p. A53T mutation [5]. Recently, cases presenting with a behavioral variant frontotemporal dementia (FTD)-like phenotype preceding parkinsonism have been reported, representing one extreme of the broad phenotypic spectrum of A53T-associated PD [8].

The aim of this study was to estimate the frequency of the p. A53T mutation in a Greek cohort of parkinsonism and/or dementia. To the best of our knowledge, no previous systematic screening of dementia cohorts for the p.A53T mutation has been reported, excepting 66 patients with FTD from the present cohort that were included in the recent report on FTD-like presentation of A53T-positive cases [8].

2. Materials and methods

A total of 347 cases were included in the present study. Patients from all regions of Greece, with parkinsonism and/or dementia, collected over 15 years at the Neurogenetics Unit, Eginition Hospital, University of Athens were screened for the p. A53T *SNCA* mutation. The study was approved by the Ethics Committee of Eginition Hospital and written consent was obtained from all patients for the performance of

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molecular genetic testing. All patients were examined neurologically. Patients with dementia underwent baseline cognitive testing that included, as a minimum, mini-mental state examination (MMSE), frontal assessment battery (FAB), clock drawing test (CDT), instrumental activities of daily living (IADL), neuropsychiatric inventor (NPI) and frontal behavioral inventory (FBI). A large majority, but not all patients, also underwent more detailed neuropsychological assessment. The diagnosis of parkinsonism with or without dementia was made at the specialist movement disorder outpatient clinic of Eginition Hospital based on established diagnostic criteria [9]. Early onset parkinsonism was defined as parkinsonism starting before the age of 50 years [3]. Diagnosis of Parkinson's disease was established according to Queen Square Brain Bank criteria [10]. The diagnosis and classification of dementia with or without parkinsonism was made at the inpatient Dementia Unit of Eginition Hospital, according to established diagnostic criteria [9,11–13].

Following initial diagnostic clarification, cases were further classified into the following categories: 1. “pure parkinsonism” (consisting of typical PD and atypical parkinsonism without dementia); 2. “pure dementia” (consisting of FTD without parkinsonism and typical Alzheimer disease, as well as a few single cases with other dementia diagnosis); and 3. “parkinsonism plus dementia” (consisting of FTD with parkinsonism, PD dementia, dementia with Lewy bodies (DLB) and atypical parkinsonism with dementia). The p. A53T mutation in *SNCA* was detected in blood leukocyte DNA using RFLPs, as previously described [3]. Statistical analysis was performed on SPSS version 24.0.

3. Results

The patient cohort included 347 cases (males 59.0%, mean age 63.2 ± 13.8 years), consisting of a “pure parkinsonism” subgroup (n_1 = 137, males 62.1%, mean age 62.6 ± 13.6); a “pure dementia” subgroup (n_2 = 121, males 60.4%, mean age 63.6 ± 10.4); and a “parkinsonism plus dementia” subgroup (n_3 = 89, males 52.8%, mean age 66.5 ± 11.6). Table 1 displays in detail, demographic, clinical and genetic data of the patient cohort. Specifically regarding the “parkinsonism plus dementia” subgroup, 39 patients presented with dementia followed by parkinsonism with a latency of 2.2 ± 4.3 years, and 50 patients presented with parkinsonism followed by dementia with a latency of 5.4 ± 7.1 years.

In total, 4 p. A53T SNCA mutation carriers were identified in the 347-patient cohort. All patients positive for the p. A53T mutation were index patients of Peloponnesian origin (unrelated, from distant towns/villages) and had autosomal dominant family history and early onset.

Screening of the “pure parkinsonism” category revealed 2 cases with typical PD (Cases 1, 2). Case 1 and 2 had onset of PD at the age of 30 years and 44 years respectively, autosomal dominant family history, typical PD phenotype and Peloponnesian origin (Fig. 1). The other two mutation carriers were identified in the “parkinsonism plus dementia” category. One had a diagnosis of PD dementia and the other of behavioral variant FTD (Case 3, 4). Case 3 had an onset of parkinsonism at age 43 and fulfilled the criteria for PDD diagnosis, with a latency between the onset of parkinsonism and dementia of 10 years. At the age of 53, he had visual hallucinations, paranoid ideation, apathy, executive dysfunction, impaired memory, fluctuating attentional deficits and impaired visuospatial skills, with a MMSE = 20, a FAB = 8 and a CDT = 2. He died aged 60. Baseline brain MRI at the time of PD diagnosis and 10-year follow-up at the time of PDD diagnosis are displayed in Fig. 2. The presence of predominantly posterior parietal cortical atrophy is noted in the follow-up scan. It is noteworthy that Case 3 had an asymptomatic 67-year old sister, who is a carrier of the A53T mutation, supporting previous observations of incomplete penetrance [2,14]. Case 4 developed at age 30 cognitive impairment followed after months by parkinsonism and behavioral disturbances, fulfilling the criteria for possible behavioral variant FTD. Case 4 was also included in the recent publication on FTD-like presentation of A53T mutation-carriers [8]. Screening of patients with “pure dementia” failed to identify any further A53T-positive cases.

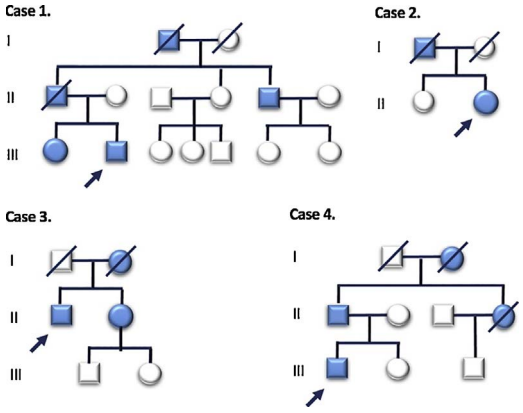

Fig. 1. Family Pedigrees of A53T positive patients.
Case 1 had an affected father who died at age 63 and an affected sister with onset at 35 years. Case 2 had an affected father who died at age 71. Case 3 had an affected mother who died at age 40 and a 67-year-old asymptomatic sister carrier of the A53T mutation. Case 4 had an affected father diagnosed with PD at age 47, followed by dementia 10 years later, and an affected paternal aunt and grandmother.

Table 1
Demographic, clinical and genetic features of Greek patients with parkinsonism and/or dementia.

Variable	Total Cohort	Pure Parkinsonism Cohort	Pure Dementia Cohort	Parkinsonism plus Dementia Cohort
n	n = 347	n_1 = 137	n_2 = 121	n_3 = 89
Gender (%)	M:205 (59.0)	M:85 (62.1)	M:73 (60.4)	M:47 (52.8)
	F:142 (40.9)	F:52 (37.9)	F:48 (39.6)	F:42 (47.2)
Age (years)	63.2 ± 13.8 (25–85)	62.6 ± 13.6, (25–85)	63.6 ± 10.4 (40–85)	66.5 ± 11.6 (32–85)
Age at onset (years)	56.8 ± 13.9 (23–80)	55.7 ± 13.7 (23–80)	59.7 ± 10.5 (36–80)	61.0 ± 11.4 (25–79)
Familial (%)	63 (18.1)	31 (21)	19 (15.7)	13 (14.1)
Early onset (%)	77 (22.1)	39 (28.4)	23 (19.0)	15 (16.8)
A53T (+) patients (%)	4 (1.1)	2 (1.5)	0	2 (2.2)
Geographical distribution of patient origin, %				
Attica	*14.7*			
Peloponnese	*13.0*			
Thessaly	*10.4*			
Northern Greece	*14.1*			
Central Greece	*15.3*			
Epirus	*13.5*			
Aegean Islands/Crete	*11.2*			
Ionian Islands	*7.8*			