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Genetic bases and phenotypes of autosomal recessive Parkinson disease in a Turkish population

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Background and purpose: To evaluate the phenotype and the frequencies of mutations in PRKN, DJ1 and PINK1 genes in patients with Parkinson disease (PD) in Turkey.

Methods: Eighty-six patients from 77 PD families participated in the study. Seventy-four families were originating from Turkey, two families from Greece and one family from Bulgaria. All patients underwent detailed neurological examination. PRKN, PINK1 and DJ1 genes were sequenced, and dosage analysis was performed by multiplex ligation-dependent probe amplification.

Results: Sixteen patients with PD were found to carry homozygous (n = 14) or compound heterozygous (n = 2) PRKN mutations. We identified exon rearrangements, three point mutations and one new point mutation in exon 2 (p.K27del). In two families, two new PINK1 point mutations (L31X and P416L) were identified. No pathogenic mutations were found in DJ1 gene. Clinical phenotypes of PRKN patients were comparable to previously described features, but only in four of 13 families, the pedigree structure was clearly consistent with an autosomal recessive (AR) mode of inheritance in comparison with nine families where also different pattern of transmission could have been possible.

Conclusions: Our data suggest that the PRKN gene mutation is the most frequent form of ARPD in Turkey. The proportion of mutations with regard to the age of onset in our population is in the range of those previously described, but our pedigrees are characterized by high rate of consanguinity, which might explain the high proportion of families with homozygous mutations and of patients in more than one generation. Pathogenic DJ1 mutations do not seem to play a major role in Turkey.

Introduction

Parkinson disease (PD) has been traditionally considered a non-genetic disorder. Our knowledge about genetic contribution, however, increased considerably over the past decade. Several genes are associated with monogenic forms of PD: SCNA and LRRK2 with autosomal dominant and PRKN, PINK1, DJ-1 and ATP13A2 with autosomal recessive PD [1]. At least four additional genes (UCHL1, GIGYF2, Omi/HTRA2) are suspected to be involved in susceptibility to PD [1]. To date, very little is known on the prevalence and the nature of the mutations implicated in PD in Turkey, and no larger study has been conducted. There have been several individual cases of PRKN carriers [2,3], and one family with DJ-1 gene mutation carriers reported [4]. A study including five Turkish patients with PD amongst others could not identify any causative mutation in DJ-1 [5]. Two studies including also Turkish patients with PD in an analysis of the LRRK2 gene detected only one of 78 Turkish patients who carried the heterozygous LRRK2 G2019S mutation [6,7]. Lack of LRKK2 mutations was confirmed in a study including more than 200 Turkish families with PD performed by our group [8]. No large-scale studies for PINK1 mutations have been

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conducted in Turkish patients with PD, and Kumazawa *et al*. [9] reported one of five Turkish patients with PD carrying homozygous missense PINK1 mutation.

Turkey is a country with a relatively young population, consanguinity rate is high (up to 42%, especially in the eastern regions) [10]. Therefore, autosomal recessive forms of PD are expected to be highly prevalent. The objective of our study was to evaluate the frequency and phenotypes of mutations in genes implicated in autosomal recessive Parkinson disease (ARPD) in Turkish patients with PD.

Methods

Patients

Eighty-six patients from 77 families (33 with parental consanguinity) were included for molecular analysis of PRKN, DJ-1 and PINK1 gene mutations. All patients were recruited over two years in the Movement Disorders Unit, Department of Neurology, Istanbul Faculty of Medicine. The study population comprised 31 women and 55 men with mean age at examination (SD) 51.8 (15.1) years (age range 4–85), age at onset 43.9 (16.3) years (range 3–83) and duration of disease 7.9 (5.0) years (range 1–30). Most of the families were originating from Turkey (n = 74), two were from Greece and one from Bulgaria, with Turkish ethnic origin. Diagnosis of PD was based on the presence of Parkinsonism (akinesia, rigidity, rest tremor), good response to anti-PD treatment and if necessary, by auxiliary examinations to exclude alternative diagnosis. The clinical evaluation was performed using the Unified Parkinson's Disease Rating Scale (UPDRS). The response to treatment was ascertained by examining patients both on and off levodopa. For purposes of clinical comparisons between PRKN carriers with and without parental consanguinity, we also used clinical data from French patients who carried PRKN mutations, which have been already published [11]. Novel PRKN and PINK1 sequence variants were tested in 100 Turkish healthy controls, which were individuals free from neurodegenerative disorders and with no family history of PD, with a mean age of 69.48 (10.97) years (49–90). Peripheral blood samples were collected, and genomic DNA was extracted by Qiagen DNA isolation maxi kit (Qiagen, Hilden, Germany). All blood samples and clinical information were obtained by a neurologist after obtaining informed consent from the patients and their participating family members. The study was approved by the Ethics Committee of Istanbul Faculty of Medicine, Istanbul University.

Mutation analyses

All 12 exons of PRKN (reference sequence: NM_004562.1) and their intron–exon boundaries were screened for point mutations and exonic rearrangements by direct sequencing and MLPA (multiplex ligation-dependent probe amplification), respectively, in all cases. PRKN exons were amplified by PCR using intronic primers. Primer sequences and PCR protocols are reported in Table 1. Direct sequencing of both strands was performed using the BigDye Terminators 3.1 Cycle sequencing Kit (Applied Biosystems, Foster city, CA, USA) on an ABI 3730 Genetic Analyzer. Seqscape 2.5 (Applied Biosystems) software was used for the analysis of the sequencing electropherograms. Eight exons of PINK1 (reference sequence: _NM_0032409.2) and seven exons of DJ1 (reference sequence: _NM_001123377) were screened by direct sequencing and MLPA in those patients without or only one PRKN gene mutation. MLPA analysis was carried out according to the manufacturer's recommendations (MRC Holland, Amsterdam, the Netherlands). The amplification products were separated by electrophoresis on an ABI 3730 capillary DNA sequencer. The heights and areas of the peaks were checked visually using the GeneMapper software version 3.7 (Applied Biosystems), and the data were exported to an Excel file for further calculations. Consequences of the mutation at the protein level in the PRKN gene were predicted according to following mRNA sequence (accession number: _NM_004562 for PRKN).

Statistical analyses

We used the chi-square test or the Fisher exact test where appropriate for the comparison of percentages, the Mann–Whitney U-test for the comparison of ranks and independent samples t-test for comparison of means. A Wilcoxon signed-rank test was used for Hoehn and Yahr scores of the matched groups in terms of disease duration. As there was more than one carrier in some families, we repeated the analyses this time including only one carrier per family so as to exclude any possible familial influence in the comparison between PRKN gene mutation carriers and gene mutation non-carriers.

Results

A total of 86 patients from 77 families originating from Turkey (n = 74), Greece (n = 2) and Bulgaria (n = 1), including 54 patients with sporadic PD, were

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Table 1 PCR primers and conditions

Gene	Exons	Forward primer 5′ → 3′	Reverse primer 3′ → 5′	Annealimg TM °C
PRKN	Promotor	GCATTTGTTAAGCTCAGGGTCTCT	GTTAGAACTACGACTCCCAGCAGG	TD 50–60[a]
	1	AGGCCTGGAGGATTTAAC	TCCCCAGCTCAGCGAGGCG	TD 50–60[a]
	2	ATGTTGCTATCACCATTTAAGGG	CATGCCGCCTGCGCTGCCAATCT	55
	3	ACATGTCACTTTTGCTTCCCT	GCAGTCTGCATGGAGCATGGCCT	59
	4	ACAAGCTTTTAAAGAGTTTCTTGT	TGTGTACTAACATTGCCT	55
	5	ACATGTCTTAAGGAGTACATTT	TGCAAGAAAATGACATCTTC	59
	6	AGAGATTGTTACTGTGGAAACA	AGGATCTAAAAATAGCATCACTC	59
	7	TGCCTTTCCACACTGACAGGTACT	TCTCTAATGCTAATGAAGAACAGA	57
	8	CGTCTGTGTCCTCCCAAAAG	GCTAATGAGACAGTTTGGGC	55
	9	GGGTGAAATTTGCAGTCAGT	TGCACATGGGCTGGGATTATATT	55
	10	GACCCATCATCTGTAGCCCTG	AGGGACAAGGCATGTGAGCATT	58
	11	ACAGGGAACATAAACTCTGATCC	TCTGAAGGTGCCTGGTGTGTTG	57
	12	GTTTGGGAATGCGTGT	AGAATTAGAAAATGAAGGTAGA	TD 50–60[a]
PINK1	1	TCACTGCTAGAGGCGC	CGGCCCTCGATCTGC	55.8
	2	ATTGATCTGGTCGACGT	CCTTTCCTGTGCATAATC	51.2
	3	CTCGAAGGTCAGAGCCA	CTGTCATATCAGACACTG	TD 54–64[a]
	4	GAATGTCAGTGCCAGTG	AGATATGTTCCCTTTGCA	TD 54–64[a]
	5	CGTATTGGGAGTCGTCG	GACCTGAAGAGTCAGTCC	55.9
	6	GTCAGCTATGTCTTGCT	ATCACAAGGCATCGAGT	50.7
	7	TGGATCAGGTGATGTGC	AGGATCTGTCACTGTGG	53.1
	8	GAGAAGGGAAGACCCTC	CAGACTGAACTCTCACTC	54.7
DJ-1 1	1	GAGGTAGACTCGGCCGG	TTCTGGACGCTTCAGCGT	TD 54–64[a]
	2	TAGGAAGTACTTACTCTGCT	TATTTATTCTTATGTCATCTC	TD 54–64[a]
	3	CAGCTGTGTAAACGTTAC	ATTCTGTATCAAGCAATTG	TD 54–64[a]
	4	CTATCTCCTGTACTTCCC	ACAGAACATAAGCAGATGC	53.2
	5	TGAGAAATGCCTTGaCTTG	GCTATTTGGAATCAAACCAT	51.4
	6	TTTGCCAGATGTGCTCAGCAAAT	ACTGCACTCCAGCCTGGGCGAT	TD 54–64[a]
	7	CACATAGCCCATTAGGATG	AGCTGCAAATGAAGGTGAT	53.5

[a]We used standard touch down 50–60 and 54–64 thermo-cycling programmes.

recruited into the molecular part of the study. 32 patients from 23 families had a pattern compatible with an autosomal recessive inheritance, and in 33 families, there was first-degree parental consanguinity, several of them had multiple consanguineous marriages (Fig. 1). Age at onset ranged from 3 to 83 years (43.9 ± 16.3 years).

Various mutations in the PRKN gene were detected (Table 2): two patients were found to carry exon 3–4 compound heterozygous deletion and eight patients were carriers of homozygous deletion of exon 3, 4 and 5. We also identified three pathogenic point mutations: homozygous p.K27del, homozygous p.E311X and p.D243N mutation in three different families. One family carrying homozygous p.G361GfsX74 mutation was previously reported by Lohmann *et al*. [11]. The newly reported in-frame variant p.K27del was found in highly conserved lysine residue and was not found in 200 control chromosomes and was therefore defined as a pathogenic mutation.

For the index case of family PD-147, we found no PRKN mutation, but one of his brothers carried a homozygous p.D243N mutation (Fig. 1, Table 2). At clinical examination, he showed a very mild rigidity of the right arm and a mild bilateral hand tremor, which had started at the age of 15 years without any progression and without requiring antiparkinsonian treatment. Another brother was found to be heterozygous for the same mutation but without any clinical symptoms at the age of 39 years. The parents were second-degree consanguineous, and the mother suffered from PD and dementia with onset at age 69. No blood samples were obtained from the parents, but this new reported mutation was not found in 200 healthy control chromosomes. PD55 was a family including two cousins affected by PD and carrying both the same ex3het/ex4het deletion, but their age at onset differed by more than 30 years (33 and 65 years) (Fig. 1, Table 2).

In two families with multiple consanguinity, two new homozygous PINK1 mutations (PD-178: L31Xhom and PD-197: P416Lhom) were identified (Fig. 1, Table 2) and these new variants were not found in 100 healthy controls. Age at onset varied between 33 and 52 years, but all affected family members showed very mild symptoms with an excellent improvement after levodopa therapy. Interestingly, the phenotype did not differ significantly between two affected and married cousins (PD-197, Fig. 1), although one of them was a

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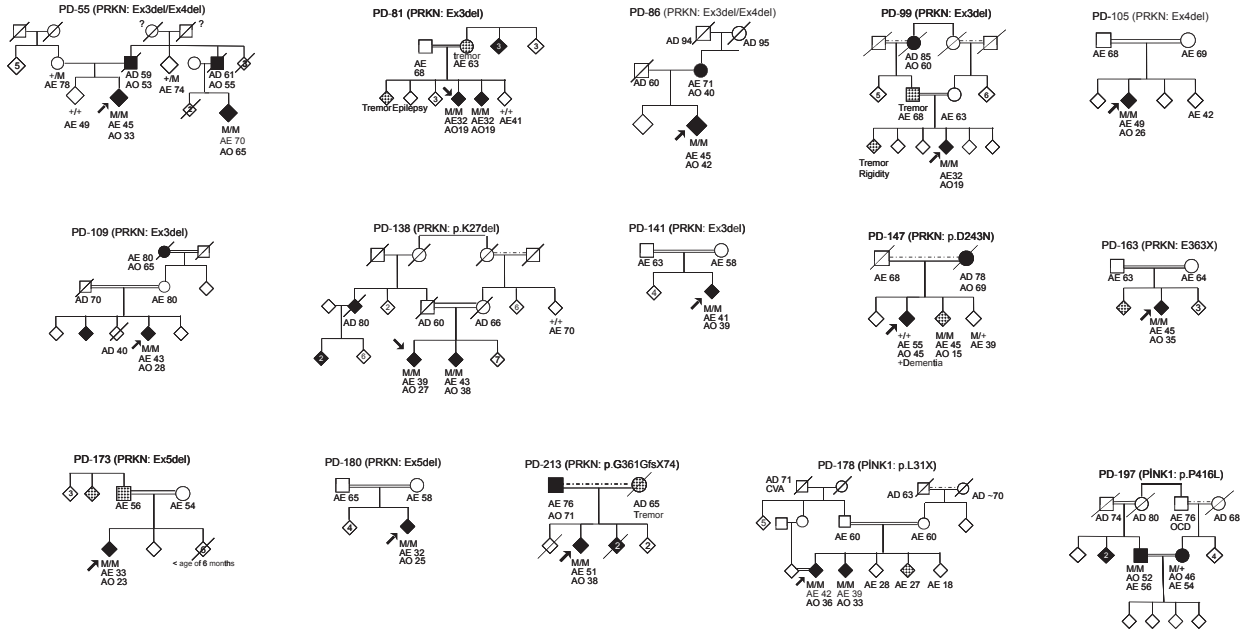

Figure 1 Families with ARPD gene mutations. AE, age at examination (years); AO: age at onset of PD (years); AD, age at death (years); CVA, cerebrovascular accident; OCD, obsessive compulsive disorder; M, gene mutation; +, no mutation; Checkered square, tremor, akinesia and/or rigidity at clinical examination without anti-PD treatment and diagnostic od PD.

Table 2 Characteristic clinical features of patients with PRKN and PINK1 mutations

Family	Gene	Mutation	Zygosity	Mutation type	Age at onset	Clinical features
PD-055 (n = 2)	PRKN	Ex3del/Ex4del	Compound heterozygous	Deletion	33, 65	
PD-081 (n = 2)	PRKN	Ex3del	Homozygous	Deletion	19, 19	ID-5: mild cerebellar syndrome upper limbs, epilepsy
PD-086	PRKN	Ex3del/Ex4del	Compound heterozygous	Deletion	42	Hypopallesthesia lower limbs
PD-099	PRKN	Ex3del	Homozygous	Deletion	24	
PD-105	PRKN	Ex4del	Homozygous	Deletion	26	Thalamotomy
PD-109	PRKN	Ex3del	Homozygous	Deletion	28	
PD-138 (n = 2)	PRKN	p.K27del	Homozygous	Small in-frame Deletion	27, 38	ID-6: dystonic posture on the right hand ID-3: hypopallesthesia lower limbs
PD-141	PRKN	Ex3del	Homozygous	Deletion	39	Migraine, breast cancer
PD-147	PRKN	p.D243N	Homozygous	Missense	15	Very mild PD, no progression
PD-163	PRKN	p.E311X	Homozygous	Stop	35	
PD-173	PRKN	Ex5del	Homozygous	Deletion	23	
PD-180	PRKN	Ex5del	Homozygous	Deletion	25	Polyneuropathy
PD-213[a]	PRKN	p.G361GfsX74	Homozygous	Frameshift	38	Heavy dystonia and fluctuation
PD-178 (n = 2)	PINK1	p.L31X	Homozygous	Stop	33, 36	
PD-197	PINK1	p.P416L	Homozygous	Missense	52	

[a]Previously reported [11].

heterozygous PINK1 mutation carrier. Their children were between 28 and 38 years old and did not report any symptoms.

Only one heterozygous IVS4-31 C>T variant located in the intron 4 of the DJ1 gene was detected (PD-116) in a 58-year-old woman, daughter of a consanguineous marriage, who started to have typical parkinsonian symptoms at the age of 54. This variant is probably not pathogenic as it is not involved in the splicing process.

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Table 3 Phenotype of 82 patients with and without PRKN mutations

	Parkin mutation carriers (n = 16)[a]	Non-Parkin mutation carriers (n = 66)[b]
Sex ratio (men:women)	10:6	42:24
Consanguinity (n)*	13	21
Age (years)*	42.4 ± 9.8 (29–70)	54.3 ± 15.6 (4–85)
Age at onset (years)*	31 ± 12.1 (15–65)	47.1 ± 16.1 (3–83)
PD duration (years)*	11.4 ± 7.1 (2–30)	7.2 ± 4.2 (1–21)
UPDRS 'on'*	11.7 ± 6.6 (3–27) n = 15	24.5 ± 12.6 (5–49) n = 55
UPDRS 'off'	25.8 ± 16.5 (10–58) n = 12	32.6 ± 12.3 (12–54) n = 19
MMS (30/30)*	29.2 ± 1.72 (24–30) n = 13	27.3 ± 3.1 (19–30) n = 47
H&Y 'on'*	0.93 ± 0.7 (0–2) n = 15	1.7 ± 0.7 (0–3) n = 57
H&Y 'off'	2.1 ± 1.22 (0–5) n = 14	2.5 ± 0.9 (1–4) n = 19
Daily dose of Levodopa (mg)	411 ± 246 (0–800) n = 9	493 ± 268 (0–1200) n = 57
Duration of treatment (years)	7.1 ± 5.35 (1–21) n = 15	5.6 ± 4.1 (0–20) n = 65
Self-estimated amelioration (%)*	75.7 ± 15.3 (50–95) n = 15	58.4 ± 21.1 (4–85)
Objective amelioration (%)*	62.3 ± 12.7 (40–79) n = 11	47.8 ± 15.5 (11–71) n = 17

[a]16 Parkin mutation carriers from 13 families; [b]66 non-Parkin mutation carriers from 62 families; *$P < 0.05$ between Parkin mutation carriers and non-carriers; UPDRS, Unified Parkinson Disease Rating Scale; H&Y, Hoehn and Yahr Scale; MMS, Mini Mental Scale.

The clinical comparison between PRKN carriers and non-carriers is shown in Table 3. After excluding the extra family members affected in the families with multiple carriers (n = 3 from the Parkin carriers and n = 5 from the non-carriers), no significant changes in values were to be observed, suggesting that the significant differences were not the result of correlation between family members. Those P-values are presented in cursive parentheses behind the P-value including all patients of the cohort.

Patients carrying variants of the PINK1 (n = 3) or DJ-1 gene (n = 1) were excluded in this comparison. The groups differed in five respects: (i) mean age at onset and at examination in patients with PRKN mutation was earlier [31 ± 12.1 vs. 47.1 ± 16.1 years, P = 0.0001 (28.8 ± 8.1 vs. 48.0 ± 14.3 years, P = 0.000) and 42.4 ± 9.8 vs. 54.3 ± 15.6 years, P = 0.005 (41.2 ± 6.4 vs. 55.4 ± 13.4 years, P = 0.000)]; (ii) PRKN mutation carriers had significantly higher frequency of parental consanguinity than non-carriers χ^2 (1, N = 82) = 12.96, $P < 0.01$ [χ^2(1, N = 74) = 11.83, $P < 0.01$)]; (iii) urgency at the time of examination was more frequent in non-PRKN mutation carriers χ^2(1, N = 82) = 6.41, $P < 0.05$ [χ^2(1, N = 47) = 5.45, $P < 0.05$)] despite longer mean disease duration (11.4 ± 7.1 vs. 7.2 ± 4.2 years, P = 0.001) (12.46 ± 7.46 vs. 7.41 ± 4.21 years, P = 0.001); (iv) the percentage of subjectively perceived and objectively measured improvement following levodopa was greater {75.7 ± 15.3 vs. 58.4 ± 21.1, P = 0.0001 [76.3 ± 17.1 (n = 12) vs. 58.5 ± 21.2, P = 0.008] and 62.3 ± 12.7 vs. 47.8 ± 15.5, P = 0.016 [63.5 ± 12.7 (n = 10) vs. 47.8 ± 15.5 (n = 17), P = 0.012]} in patients with PRKN mutations; (v) the mean rate of progression assessed by UPDRS (on treatment) adjusted for disease duration was significantly lower in the PRKN group (11.7 ± 6.6 vs. 24.5 ± 12.6; z = −3.69) (11.33 ± 6.51 vs. 24.27 ± 12.84; z = −3.36) independent of age at onset. The mean rate of progression assessed by the Hoehn and Yahr score (on treatment) was also lower in the PRKN group (0.93 ± 0.7 vs. 1.71 ± .71, t = 3.77), (0.87 ± 0.7 vs. 1.69 ± 0.70, t = 3.62), and this difference was evident even when the data were adjusted for disease duration (z = −2.66, P = 0.008) [z = −2.106, P = 0.035 (n = 8)] The performance on the Mini Mental State evaluation was significantly better in PRKN mutation carriers than in non-carriers ([29.2 ± 1.72 vs. 27.3 ± 3.1, P = 0.042)] [29.5 ± 0.85 (n = 10) vs. 27.2 ± 2.9 (n = 25), P = 0.02]). Gender had no influence on the phenotype.

Discussion

This is the first large-scale study to evaluate genetics and phenotypes of autosomal recessive PD in a Turkish population. The rate of parental first-degree consanguinity in our population was very high (44%) compared to the average in Turkey (20.92%) [10]. The clinical features in our population were comparable to those described by Yamamura *et al.* [12], in their first report of autosomal recessive juvenile-onset parkinsonism as a clinical entity. Out of 77 families, 13 with PD were found to have homozygous or compound heterozygous PRKN mutation carriers, corresponding to a PRKN mutation frequency of 16.9%. In accordance with a previous studies [13], PRKN mutations were found to be responsible for over 45% of patients with onset up to age 35, and for 40% with onset up to age 40 in our study.

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The most common mutations found in our study were deletions of exons 3 ($n = 5$), and 3 and 4 ($n = 3$), a finding comparable to that described by Nuytemans *et al.* [14]. We also found deletions of exon 5 ($n = 2$) and exon 4 ($n = 1$), which also have been shown to be present in various populations (http://www.molgen.ua.ac.be/PDmutDB). All our exon rearrangements were localized in common fragile site of the PRKN gene as described earlier by Mitsui *et al.* [15]. Interestingly, those recurrently observed breakpoints were only reported in this study in patients from Asia. However, the study population comprised 128 Asian versus only 64 European patients and further studies are required to confirm these findings. Although mutations in the PRKN gene are not limited to a particular region or ethnic group, their frequencies vary according to geographical origin. We found only five of 16 patients to carry point mutations, which are also reported to be infrequent in Japanese patients compared with Caucasians, exonic deletions being common ($n = 12$ in our study) in both populations [16]. In family PD-147, the homozygous p.D243N mutation carrier presented very mild and non-progressive PD symptoms since the age of 15, whereas his brother, suffering since the age of 45 of doparesponsive PD with dementia, did not. Additionally, the mother also suffered from late onset PD associated with cognitive decline (Fig. 1). It has not been clearly demonstrated whether the p.D243N mutation is pathogenic or not [17,18] and we cannot exclude an additional aetiology in this family. Anyhow, the very early onset (15 years) in the p.D243N carrier compared to his non-carrier sib (45 years) and the absence of the mutation in 200 healthy control chromosomes suggest a pathogenic effect of the p.D243N mutation. Additionally, other close RING1 mutations like T240R are known to inhibit interaction of Parkin with hSel-10 and consequently Cullin-1 [19], which in normal state form together a multi-protein complex that, along with the E2, UbcH7, ubiquitinates Cyclin E. As a Parkin substrate, Cyclin E accumulates in the absence of Parkin. Increased levels of Cyclin E result in neuronal cell apoptosis.

Only two of the patients in our study carried compound heterozygous PRKN mutation (PD86 and PD55, ex3delhet/ex4delhet) and both of them did not have parental consanguinity. Both patients, though, had a parent reported to suffer from PD (age at onset 53 and 40 years). It had been proposed that some heterozygous PRKN mutations may act in true dominance [20,21] or as risk factor for PD [18,22], but as no molecular testing could be performed in them, more detail analysis remains speculative. The cousins in family PD55 (Fig. 1) carried the same compound heterozygous deletions of exon 3 and exon 4 but had a 32 year age difference at the onset of PD symptoms. However, for different genotypes of PRKN mutations, a great variability in age at onset has been described despite the presence of the same mutations [11]. The difference in age at onset in these patients carrying the same heterozygous mutations of the PRKN gene might indicate that each of these mutations act differently.

Fourteen patients of 13 PRKN families carried homozygous mutations, and all of them had parental consanguinity (Fig. 1). In only four of these 13 families is the pedigree structure clearly consistent with an autosomal recessive mode of inheritance (PD105, PD141, PD163 and PD180) in comparison with nine families where different pattern of transmission could also have been possible. The very high prevalence of consanguinity might play an important role and additional factors other than PRKN mutations might be involved. Gene frequency and genetic structure are changed by consanguineous marriages. Nevertheless, it seems that there is no influence on the phenotype: clinical comparison in 34 previously reported French patients [11] between PRKN carriers with ($n = 23$) and without ($n = 27$) parental consanguinity did not show any significant differences (data not shown). Clinical comparison between PRKN mutation carriers and those without mutation confirmed previously described findings such as an earlier age at onset, better response to lower daily doses of levodopa, even after a longer duration of disease and tendency to perform better on global cognitive examination in PRKN mutation carriers (Table 3).

To date, most PINK1 gene mutations have been reported to be point mutations. In this study, we found three homozygous and one heterozygous PINK1 point mutations (L31X and P416L) in four affected patients from two families. The P416L substitution is located in an APE site within the kinase domain, a universally conserved activation segment motif and most likely to be essential for protein function. The very close P416R mutation was previously found in a homozygous state in a single family from Jordan with very young onset (23 and 25 years). However, the additional possible influence of even multiple consanguineous marriages in our family might also be important here, but as the heterozygous mutation carrier had an earlier age at onset than the homozygous mutation carrier, the pathogenicity of P416L should be considered (Fig. 1).

Our data suggest that the PRKN gene mutations are the most frequent form of ARPD in Turkey, corresponding to a mutation frequency of 16.9% followed by PINK1 gene mutations at 2.6%. Pathogenic DJ1 mutations not found in these families do not seem to play a major role in Turkey. The high number of PRKN or PINK1 families with homozygous mutations

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(13/15) or with PD patients in multiple generations (8/15) mimicking dominant inheritance might be partly explained by the very high prevalence of consanguinity in our population. Indeed, the rate of parental first-degree consanguinity in our population was very high (44%) compared to the average in Turkey (20.92%). However, there is a tendency for later onset in patients in the older generations who are not genotyped. It is therefore impossible to conclude whether their disease is caused by PRKN mutations with great age at onset variability, as seen in family PD55 (Fig. 1), or to other factors.

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