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POLG1 polyglutamine tract variants associated with Parkinson's disease

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Abstract

A possible role of allelic variation of the mitochondrial DNA polymerase gamma (*POLG1*) gene in Parkinson's disease (PD) has been suggested. First, *POLG1* missense mutations have been found in patients with familial parkinsonism and mitochondrial myopathy. Second, increased frequency of rare alleles of the *POLG1* CAG-repeat (poly-Q) has been found in Finnish idiopathic apparently sporadic PD patients, but conflicting reports exist. The *POLG1* poly-Q exhibits one major allele with 10 repeats (10Q, frequency $\geq 80\%$) and several less common alleles such as 11Q (frequency 6–9%), 6Q–9Q and 12Q–14Q (frequencies $< 4\%$). It is not known, whether the poly-Q variation modulates *POLG1* function. Here we sequenced the poly-Q in 641 North American Caucasian PD patients and 292 controls. Caucasian literature controls were also used. Normal allele was defined either as 10/11Q or as 10Q according to previous literature. The frequency of the non-10/11Q alleles in cases was not significantly different from the controls. Variant alleles defined as non-10Q were significantly increased in the PD patients compared to the North American controls (17.6% vs. 12.3%, $p=0.004$) as well as compared to the larger set of 897 controls (17.6% vs. 13.2%, $p=0.0007$). These results suggest that *POLG1* poly-Q alleles other than the conserved 10Q allele may increase susceptibility to PD. This finding may be attributable to a beneficial function of the 10Q repeat protein or linkage disequilibrium between the 10Q allele and another variation within or close to *POLG1*. Other large case-control studies and analyses on functional differences of *POLG1* poly-Q variants are warranted.

Keywords

Polymerase gamma; Trinucleotide repeat; Polyglutamine; Parkinson's disease; Genetic susceptibility; *POLG1*

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INTRODUCTION

The most well-known symptoms of Parkinson's disease (PD), slowness, stiffness, tremor, and postural instability, are caused by the degeneration of the dopaminergic neurons in substantia nigra, although the neurodegeneration as well as symptom spectrum are broader. Mutations in seven genes have been identified in familial forms of Parkinson's disease (alpha-synuclein, LRRK2, GBA) and in more complex early-onset phenotypes presenting with parkinsonism (Parkin, PINK1, DJ-1, ATP13A2) (reviewed in [15]).

Most cases of PD are sporadic. The role of a genetic component in sporadic PD has been shown in pedigree and twin studies [24,31,33]. Moreover, pathogenic mutations in LRRK2 and GBA have been found in sporadic cases [16,19,22,23] and hitherto undetermined variations of alpha-synuclein and microtubule associated protein tau have been shown to predispose to sporadic PD in several studies [4,21,35].

Mitochondrial dysfunction has been shown to play a role in the pathogenesis of PD [29]. It was learned already in 1980s that exposure to mitochondrial respiratory chain complex I inhibitor MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) results in dopaminergic neuron loss and parkinsonism [13,14]. Mitochondrial complex I deficiency in substantia nigra and platelets of PD patients has been reported [6,30] and several gene products of familial parkinsonism (*PINK1*, *DJ-1*, *Parkin*) have a connection to mitochondrial function [29].

We, and others have found missense mutations of the mitochondrial DNA polymerase gamma (*POLG1*) to co-segregate with a phenotype that includes progressive external ophthalmoplegia and parkinsonism [9,17]. *POLG1* mutations have also been described in case studies, in which parkinsonism was part of the clinical spectrum [3,25]. These findings indicate that parkinsonism is part of the phenotypic consequences of *POLG1* point mutations. *POLG1* plays an important role in mitochondrial DNA maintenance. *POLG1* mutations have been shown to lead to gradual accumulation of secondary deletions in mitochondrial DNA, resulting in dysfunction of the respiratory chain [8]. It is of interest that during aging mitochondrial DNA deletions have been shown to accumulate especially in substantia nigra, and this process was accelerated in subjects with PD in a study of elderly brains [1,12].

POLG1 contains a CAG-repeat, encoding a polyglutamine (poly-Q) tract [28]. It is presently not known, whether length variation of the poly-Q modulates its function. CAG-repeat instability, usually leading to its expansion, is a mutational mechanism that underlies various neurodegenerative disorders [26,36]. The expansions often exhibit a pathogenic threshold (number of repeats), but androgen receptor is an example demonstrating that even short and long CAG-repeats within the "normal range" may have phenotypic consequences [5]. Earlier, we have found an increased frequency of variant length alleles of the *POLG1* poly-Q tract in 140 Finnish PD patients vs. controls [18]. To study whether these findings can be replicated in another population and larger sample, we sequenced the *POLG1* poly-Q tract in a North American series of 641 PD patients and 292 controls.

MATERIAL AND METHODS

Our study material consisted of previously published publicly available DNA samples from North American PD patients (plates NDPT001, NDPT005, NDPT007, NDPT014, NDPT015, NDPT016, NDPT017, NDPT018) and from neurologically normal Caucasian control samples (plates NDPT002, NDPT022, NDPT023, and NDPT024) from NINDS repository (<http://ccr.coriell.org/Sections/Collections/NINDS/DNAPanel.aspx?PgId=19#>).

Of the 736 patients 24 were excluded, because they carried likely pathogenic mutations in either *parkin*, *LRRK2*, or *PINK1*. Ten patients with an age-of-onset <20 years were excluded.

One PSP patient, erroneously included in this sample collection, was excluded from our study. *POLG1* CAG-repeat sequencing was successful in 641 patients. Of these 280 (44 %) were females and 361 (56 %) males. The mean age of the PD patients was 65.3 (range 29-88) years. The mean age-of-onset of the PD patients was 56.9 (range 23-87) years. All patients were Caucasians, 13 of them Hispanics. *POLG1* CAG-repeat sequencing was successful in 292 control samples (51% females). The mean age of the controls was 68.2 (range 55-95) years. Caucasian controls with sequencing-based *POLG1* CAG repeat analysis were also retrieved from literature. One such control group was found: the Mixed Caucasian control group (n=605) from Rovio (2006) <http://acta.uta.fi/english/teos.phtml?10863> (p.60), which is composed of unselected control samples from several European countries and Australia. There were also 21 Chinese controls from Taiwan; hence this material is 97% Caucasian. For the sake of simplicity we call it mixed Caucasian controls.

We used previously reported primers for *POLG1* exon 2 PCR and performed sequencing using Big Dye chemistry (Applied Biosystems, Foster City) on an ABI 3100 Genetic Analyzer automatic sequencer. We used Sequencher program (Gene Codes) in the sequence analysis. We used χ^2 test with two-tailed p-values to compare the frequencies of alleles and genotypes in PD patients and controls. Odds ratios (OR) with confidence intervals were calculated using an OR-calculator in <http://www.hutchon.net/ConfidOR.htm>. Hardy-Weinberg equilibrium (HWE) for the three most common alleles 10Q, 11Q and 12Q was analysed with the HWSIM program (<http://krunch.med.yale.edu/hwsim>).

RESULTS

The allele frequencies in the North American PD, North American controls and sequencing-based “Mixed Caucasian Controls” are shown in Table 1. The genotype distributions for the three most common alleles (10Q, 11Q, 12Q) did not deviate from HWE in patients or in controls ($p>0.05$). There were no significant differences in allele frequencies between the two control groups (Table 1 footnote, $p=0.58$).

Poly-Q allele lengths 10Q and 11Q constitute $\geq 95\%$ of alleles in all studied populations. These were considered “neutral alleles” in our previous report on PD, whereas non-10/11Q alleles were considered as putative predisposing “variant” alleles [18]. We compared these alleles in the 641 North American PD patients and 292 controls. In accordance with our previous results the non-10/11Q alleles showed tendency to be more common in PD patients (5.8 %) than in controls (3.8 %) but this difference did not reach statistical significance ($\chi^2=3.31$, 1 df, $p=0.07$; OR 1.56, 95%CI 0.96-2.55). In the more powerful analysis with the larger group of literature controls we neither found a statistically significant difference in the frequency of the non-10/11Q in the PD patients vs. controls (PD vs. mixed Caucasian controls 5.8% vs. 5.5%, $\chi^2=0.12$ $p=0.73$, and 5.8% vs. 4.9% when all controls were pooled, $\chi^2=1.13$, 1 df, $p=0.29$).

In previous studies on male infertility and testicular cancer the 10Q allele has been considered as the only “normal” allele and non-10Q as “variant” alleles [2,28]. The frequency of the non-10Q alleles was 17.6% in the North American PD group vs. 12.3% in North American controls (Table 2, $\chi^2=8.40$, 1 df, $p=0.004$; non-10Q OR 1.52, 95% CI 1.14-2.02). The association of the non-10Q alleles with PD was significant also when compared to the literature controls (PD vs. mixed Caucasian controls $p=0.007$, PD vs. pooled controls $p=0.0007$, Table 2). Genotypes other than 10Q/10Q were significantly more frequent in PD patients (32.4%) than in controls (22.9%) in this analysis ($\chi^2=8.72$ 1 df, $p=0.003$).

In the PD population poly-Q allele and genotype frequencies in patients with early age-at-onset (≤ 45 years, $n=89$ non-10Q allele frequency 18.8%) did not show significant deviation from patients with late age-at-onset (> 45 years, $n=552$, non-10Q allele frequency 17.0%). The poly-

Q alleles in patients with positive family history for PD (n=168, non-10Q allele frequency 18.3%) did not differ significantly from those without family history (non-10Q allele frequency 17.3%). We performed an additional analysis in males separately, because PD is slightly more common in males than in females in most populations [7] and there are previously suggested male-specific phenotypic effects of *POLG1* poly-Q [2,28]. In this analysis the frequencies of the non-10Q alleles in PD vs. controls were 16.8% vs. 13.0% in males (361 PD, 142 controls) and 18.8% vs. 11.7 % in females (280 PD, 150 controls). These results indicate that the observed association is not restricted to males but it is contributed by both sexes.

Previous reports in smaller datasets have not found association between non-10Q alleles and PD. We made a pooled analysis of all available studies on *POLG1* poly-Q and idiopathic PD [10,18,32,34]. *POLG1* poly-Q allele frequencies of 1163 patients and 1214 controls were available. In this analysis the frequency of non-10Q alleles was 16.3% in PD and 13.4 % in controls ($\chi^2= 7.74$ 1 df, 2-sided $p=0.005$, Table 3).

DISCUSSION

Earlier evidence has shown that parkinsonism belongs to the clinical spectrum of *POLG1* mutations in patients with myopathy or ataxia. The role of *POLG1* variation in idiopathic sporadic PD, however, is lacking definite conclusion.

In our previous analysis we sequenced the whole *POLG1* gene in Finnish sporadic PD patients. We found several missense amino acid substitutions, but none of them was associated with PD. Instead we found that the rare variants of the poly-Q tract (non-10/11Q alleles) were increased in Finnish PD patients vs. controls [18]. In the present analysis in US PD patients and controls a trend of non-10/11Q as risk alleles was found, but our original hypothesis was not confirmed at a statistically significant level. Comparisons to literature controls consolidated the lack of significant difference in this setting.

When we applied the other criteria of previous studies, e.g. [2,11,28], considering the major 10Q allele as the only 'neutral' variant, we found a significant difference in the frequency of the non-10Q alleles in North American PD patients vs. North American controls or mixed Caucasian controls (Table 2). We did not detect any effect of age-of-onset, family history or sex in this association. Four statistical tests were made with the non-10Q paradigm and one test with non-10/11Q (altogether 5 tests). The observed association remains significant after Bonferroni correction with a factor of 5.

Three earlier studies on *POLG1* poly-Q variation in PD did not detect any association [10, 32,34]. These previous studies were, however, smaller than the present study (numbers of patients/control were 22/31, 140/90 and 220/157), and were not completely sequencing-based, which influences the resolution of alleles, e.g. 4R+9Q is not detected without sequencing. Different ethnic backgrounds could also partly explain the discrepancy in the results. By pooling all studies a significant association between PD and non-10Q alleles and genotypes other than 10Q/10Q was found (Table 3). This association was contributed by the US and Finnish datasets (Table 3).

The allele distribution of the poly-Q repeat of *POLG1* is relatively uniform in humans, as over 80% of people in all studied populations carry the 10Q allele [2,20,27,28]. Natural selection is a factor that could explain this, but it is not clear at present whether purifying selection or low mutation rate is responsible for the unusually uniform allele distribution. In primates, the repeat length is also highly conserved within species, the two most common alleles accounting for >90% of all alleles [27]. In primates the length of the poly-Q region tends to be more conserved than its' exact amino acid composition [27]. The poly-Q is not evolutionary conserved, but has appeared to the *POLG1* sequence relatively recently during evolution. In

dog the poly-Q is found in combination with polyproline, but it is not present at all in cattle (horse, cow), rodents (rat, mouse), or lower eukaryotes (with the exception of *Candida albicans*).

In conclusion, our present results in the North American PD patient sample suggest that *POLG1* poly-Q alleles other than the conserved 10Q allele may increase susceptibility to PD. This finding may be attributable to a beneficial function of the 10Q repeat protein. Alternatively, the 10Q allele may mark, by linkage disequilibrium, another variation within or close to *POLG1* that confers protection against PD. Since mutations of *POLG1* have already been implicated in several complex phenotypes with parkinsonism, it is an interesting candidate gene in sporadic PD as well. More large-scale sequencing-based studies, as well as studies on the functional consequences of *POLG1* poly-Q variants are warranted.

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Table 1

POLG exon 2 polyQ (CAG-repeat) allele frequencies in the present study

	NORTH AMERICAN PD PATIENTS n=641		NORTH AMERICAN CONTROLS n=292		MIXED CAUCASIAN CONTROLS ^a n=605		POOLED CONTROLS n=897	
PolyQ	2n	%	2n	%	2n	%	2n	%
6Q	1	0,1	0	0	0	0	0	0
7Q	10	0,8	1	0,2	2	0,2	3	0,2
8Q	5	0,4	2	0,3	5	0,4	7	0,4
9Q	12	0,9	7	1,2	22	1,8	29	1,6
4R+9Q	5	0,4	0	0	4	0,3	4	0,2
10Q	1056	82,4	512	87,7	1045	86,4	1557	86,8
11Q	152	11,9	50	8,6	99	8,2	149	8,3
12Q	40	3,1	12	2,1	28	2,3	40	2,2
13Q	0	0	0	0	4	0,3	4	0,2
14Q	1	0,1	0	0	1	0,1	1	0,06
Σ	1282		584		1210		1794	

^aFrom Rovio A. (2006) <http://acta.uta.fi/english/teos.phtml?10863> (p. 60). The control groups did not show significant differences in their allele frequencies; North American vs. mixed Caucasian controls p=0,58. The rarest long alleles 13Q and 14Q and rarest short alleles 6Q, 7Q and 4R+9Q were pooled in this comparison. The allele 4R+9Q results from a Q->R substitution of the first amino acid of the polyQ tract.

Table 2

Association of POLG1 polyQ (CAG-repeat) alleles with PD

	NORTH AMERICAN PD		NORTH AMERICAN CONTROLS		MIXED CAUCASIAN CONTROLS ^a		POOLED CONTROLS ^b	
	n=641		n=292		n=605		n=897	
Alleles	2n (%)		2n (%)		2n (%)		2n (%)	
10Q	1056 (82.4)		512 (87.7)		1045 (86.4%)		1557 (86.8)	
Non-10Q	226 (17.6)		72 (12.3)		165 (13.6)		237 (13.2)	
<i>p-value vs. PD^c</i>			<i>p=0.004</i>		<i>p=0.006</i>		<i>p=0.0007</i>	

^aFrom Anja Rovio (2006) in <http://acta.uta.fi/english/teos.phtml?10863> (p. 60).

^bIncludes North American and mixed Caucasian controls.

^cTwo-sided p-values were determined by chi-square test with 1 df, North American PD vs. each control group.

Table 3

Pooled analysis of POLG polyQ allele frequencies in PD vs. controls

US PD PATIENTS N=641		FINNISH PD [18] N=140		TAANMAN PD [32] N=22		TIANGYOU PD [34] N=140		HUDSON PD [10] N=220		ALL PD N=1163		US Controls N=292		FINNISH Controls N=644		TAANMAN Controls N=31		TIANGYOU Controls N=90		HUDSON Controls N=157		ALL Controls N=1214		
PolyQ	2n	%	2n	%	2n	%	2n	%	2n	%	2n	%	2n	%	2n	%	2n	%	2n	%	2n	%		
6Q	1	0,08	1	0,4	0	0	0	0	0	2	0,09	0	0	4	0,3	0	0	0	0	0	0	4	0,16	
7Q	10	0,8	0	0	1	2	1	0,36	8	1,8	20	0,86	1	0,2	0	0	0	0	1	0,56	4	1,3	6	0,25
8Q	5	0,4	3	1,1	0	0	0	0	0	8	0,34	2	0,3	4	0,3	0	0	1	0,56	1	0,3	8	0,33	
9Q	12	0,9	13	4,6	0	0	7	2,5	6	1,4	38	1,6	7	1,2	22	1,7	3	5	3	1,67	5	1,6	40	1,6
4R+9Q	5	0,4	2	0,7	n.a.	n.a.	n.a.	n.a.	n.a.	7	0,30	0	0	2	0,15	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	2	0,08	
10Q	1056	82,4	237	84,6	37	84	241	86,1	377	85,7	1948	83,7	512	87,7	1132	87,9	51	82	147	81,7	261	83,1	2103	86,6
11Q	152	11,9	15	5,4	6	14	26	9,3	44	10,0	243	10,4	50	8,6	103	8,0	6	10	23	12,8	37	11,8	219	9,0
12Q	40	3,1	7	2,5	0	0	5	1,8	5	1,1	57	2,45	12	2,1	19	1,5	2	3	5	2,8	6	1,9	44	1,8
13Q	0	0	2	0,7	0	0	0	0	0	0	2	0,09	0	0	0	0	0	0	0	0	0	0	0	0
14Q	1	0,08	0	0	0	0	0	0	0	1	0,043	0	0	2	0,15	0	0	0	0	0	0	2	0,08	
Σ	1282		280		44		280		440		2326		584		1288		62		180		314		2428	
PolyQ alleles		ALL PD										ALL CONTROLS												
10Q		1948 (83,7%)										2103 (86,6%)												
Non-10Q		378 (16,3%)										325 (13,4%)												
		χ ² = 7.74, 1 df, 2-sided p=0.0054																						