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Gender differences in the IL6 −174G>C and ESR2 1730G>A polymorphisms and the risk of Parkinson's disease

M. San Luciano[a,*], L. Ozelius[b], R.B. Lipton[c], D. Raymond[a], S.B. Bressman[a], R. Saunders-Pullman[a,c]

[a] Department of Neurology, Beth Israel Medical Center, 10 Union Square East Suite 5K, New York, NY 10003, United States
[b] Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, One Gustave L Levy Place, Box 1498, New York, NY 10019, United States
[c] Department of Neurology, Albert Einstein College of Medicine, Yeshiva University, Louis and Dora Rousso Building, 1165 Morris Park Ave, Bronx, NY 10461, United States

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ABSTRACT

The −174G>C (rs1800795) single nucleotide polymorphism (SNP) in the promoter of the interleukin-6 (IL6) gene and the 1730G>A (rs4986938) SNP in the estrogen receptor beta (ESR2) may influence the risk of Parkinson's disease (PD). We investigated these SNPs in 380 unrelated US Caucasian PD cases and 522 controls, including 452 individuals of Ashkenazi Jewish (AJ) origin (260 PD, 192 controls). The G allele of the −174G>C SNP was more common in AJ PD cases ($p = 0.033$) as well as in Non-Jewish (NJ) men with PD ($p = 0.022$). The GG genotype increased the risk of PD by over two fold in NJ men (OR = 2.11, 95%CI: 1.14–3.89, $p = 0.017$), and approached significance in the total AJ group with PD (OR = 1.42, 95%CI: 0.97–2.06, $p = 0.067$). The A allele of the ESR2 1730G>A SNP was associated with a decreased risk for PD in AJ women, and in this group, having the AA genotype decreased the risk of PD by half (OR = 0.45, 95%CI: 0.22–0.92, $p = 0.029$). Our data supports a role for the IL6 −174G>C G allele in AJ individuals overall. In NJ Caucasians, this role appears to be gender mediated. In both groups, the effect is independent from ESR2 1730G>A. A separate association for the ESR2 1730G>A SNP was found exclusively in women of AJ descent. Other polymorphisms in tight linkage disequilibrium with the SNP differentially influencing expression, ethnic differences in allele distribution, and gender differences in genetic load related to PD, may underlie our findings. Larger studies in diverse populations, including analysis of surrounding regions are recommended.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by bradykinesia, rest tremor, rigidity and postural instability [18], and is of unknown etiology in most cases. Previously assumed that the genetic contribution was important primarily in early onset cases [39], monogenic causes and common variants have been identified, and are being increasingly recognized as important causative factors in late-onset cases as well [15,21,23,31]. Both inflammation and gender may also affect PD risk. Polymorphisms in the genes coding for interleukin-6 (IL6) and estrogen receptor beta (ESR2) are genetic factors that may be associated with PD [16].

Inflammation has been recognized to have a role in the pathogenesis of PD [3,19]. Non-steroidal anti-inflammatory agents have been suggested to protect against PD [9,10]. Activated microglia have been reported in the substantia nigra of PD patients [26] as well as proinflammatory cytokines [1,42]. Further, levels of the cytokine IL6 are increased in striatal tissue, cerebrospinal fluid and serum of PD patients [6,27,38]. A G/C single nucleotide polymorphism (SNP) at −174 (rs1800795) in the promoter region of the IL6 gene is known to influence IL6 expression, although it is debated which genotype is related to highest expression [7,13,22,33]. The G allele and GG genotype have been previously associated with an elevated risk of PD, particularly in early-onset cases [16].

Elevated endogenous estrogen levels may be associated with a decreased risk of PD [34], and the neuroprotective effect of estrogen may be partly mediated by inhibition of IL6 production [29,32,40]. Genetic variations of the estrogen receptor-β ESR2 gene have been associated with increased risk for earlier age of onset, particularly the GG genotype of the SNP at position 1730 (rs4986938). This effect was observed in both men and women [16,41].

However, the association of IL6 −174G>C and PD is debated [20,35]. In order to test two hypotheses: (1) that the IL6 1730G>A SNP G allele represents a gain-of-function variant resulting in a

* Corresponding author. Present address: Department of Neurology, SUNY Downstate Medical Center, 450 Clarkson Ave, Box 1213, Brooklyn, NY 11203, United States. Tel.: +1 718 270 3210; fax: +1 718 270 1946.
E-mail addresses: Marta.SanLuciano@downstate.edu, martasanluciano@hotmail.com (M. San Luciano), laurie.ozelius@mssm.edu (L. Ozelius), Richard.lipton@einstein.yu.edu (R.B. Lipton), draymond@chpnet.org (D. Raymond), sbressma@chpnet.org (S.B. Bressman), rsaunder@chpnet.org (R. Saunders-Pullman).

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proinflammatory state associated with PD, and (2) that the ESR2 1730G>A G allele confers a higher risk of PD, we evaluated the distribution of these SNPs in a Caucasian sample.

2. Methods

Subjects were recruited from parent studies of Genetics and Parkinson's disease at Beth Israel Medical Center (BIMC) and the Einstein Aging Study (EAS) at Albert Einstein College of Medicine. Additionally, 95 controls from the Centre d'Etude du Polimorphisme Humain (CEPH) were included.

PD subjects were systematically examined by movement disorders specialists at BIMC. At the EAS, formal neurologic evaluation was performed by a physician, and a subset of elderly subjects without PD was included. Eligible participants were those who self-identified as Caucasian. This group was stratified as Jewish or non-Jewish based on self-report of ethnicity/religion. The study was approved by the respective Institutional Review Boards.

DNA was available from blood or buccal swab drawn at the parent study. The samples were centrifuged and stored in freezers at −80° C, and DNA was extracted from white blood cells following standard procedures. The IL6 −174G>C and ESR2 1730G>A polymorphisms were amplified by polymerase chain reaction using primers and conditions as previously determined [16,41]. Genotyping was performed using a Pyrosequencing PSQ HS 96A system 1.2 (Biotage, Uppsala, Sweden). All subjects were blinded to their genotype status.

Demographic characteristics are summarized in Table 1. Statistical evaluation of differences in frequencies of alleles and genotypes was performed by Chi-square test or Fisher's exact test, and continuous variables were compared using Student's *t*-test. Logistic regression was used for testing gene-gene interaction and for estimation of odds ratios with 95% confidence intervals.

3. Results

902 subjects (456 women) were genotyped for both SNPs. We included 380 individuals with PD, of which 91 had disease onset before or at age 50. The sample included 452 individuals of Jewish origin (260 with PD), of which 447 were of Ashkenazi descent (AJ) and 5 of Sephardic origin. Separate analysis without the individuals of Sephardic origin yielded the same results, and they were included in the final analysis with the AJ group. Even though the combined control population did not deviate from Hardy–Weinberg equilibrium, a separate analysis for AJ and NJ individuals is presented, as genotype and allele distributions differed between the two sub-populations. Allele and genotype frequencies are summarized in Tables 2–5. The IL6 −174G>C G allele was found to be significantly more common in the AJ PD cases and in NJ men with PD when compared to controls ($p = 0.033$, $p = 0.022$, respectively), but not in the group of NJ women with PD or in the overall NJ group. An elevated frequency of the GG genotype in the AJ group and in NJ men with PD subjects was observed (45.45% vs. 34.35% in AJs, 49.15% vs. 31.41% in NJ men). Among NJ men, the GG genotype increased the risk of PD by over two fold ($OR_{GG} = 2.11$, 95%CI: 1.14–3.89, $p = 0.017$), and in AJs, it was associated with an OR_{GG} of 1.42, although this association was no longer significant (95%CI: 0.97–2.06, $p = 0.067$). Among those subjects with early disease onset, the excess of GG genotype persisted in both groups (55.17% vs. 49.22% for AJs, 56.76% vs. 31.41% for NJ men), but the differences were no longer significant ($p = 0.087$, $p = 0.233$, respectively).

The ESR2 1730G>A G allele was found to be more common in the group of AJ women with PD (61.36% vs. 50.90%, $p = 0.027$), including the group of early disease onset (52.38% vs. 26.13%, $p = 0.044$). For AJ women, the AA genotype decreased the risk of PD by more than half when compared to the GG and GC genotypes ($OR_{AA} = 0.45$, 95%CI: 0.22–0.92, $p = 0.029$). However, no significant differences in allele or genotype frequencies were observed in AJ men or between NJ PD subjects and controls for the ESR2 1730G>A SNP in the overall group or either gender, or between young-onset PD cases and controls. No interaction between the two genes was observed in a logistic regression model in either group, and no association was found for the combined high-risk genotypes (GG/GG).

4. Discussion

Our data support the hypothesis that the IL6 −174G>C SNP G allele represents a probable gain-of-function variant resulting in a proinflammatory state associated with PD in some populations. The neuroinflammatory reaction in PD pathogenesis may represent a secondary process of more upstream cascade events. However, chronic inflammation may lead to harmful consequences and it may mediate in perpetuating neurodegeneration [19]. A main feature of the inflammatory hypothesis proposed in PD is the marked increase in certain pro-inflammatory cytokines in striatum and cerebrospinal fluid, including IL6 [6,27,38]. While the precise role of IL6 in PD is unknown, this particular cytokine has been implicated in PD. Transgenic mice overexpressing IL6 develop progressive tremor and ataxia and extensive neuropathological changes including neuronal damage, reactive astrocytosis and proliferative angiopathy [8]. On the other hand, IL6 increased survival in cultured dopaminergic neurons [17] and increased levels of IL6 in cerebrospinal fluid correlated inversely with PD severity [27], although this is not consistently reported [38]. Analyses of IL6 gene polymorphisms have also yielded controversial results. The G allele and GG genotype of the IL6 SNP −174G>C have been associated with an elevated risk of PD, particularly in early onset cases [16]. However, these findings were not replicated in Spanish [20] and Irish samples [35]. A German cohort also failed to demonstrate an association of a different IL6 promoter SNP with PD [25]. Our findings concur with one previous association of the G allele with increased risk for PD, supporting a role for this cytokine in PD [16]. In contrast to the Hakansson study, we demonstrated a difference in gender effect in our Non-Jewish subgroup. We did not demonstrate an association with early onset PD, although our study was not powered to detect such differences in this subgroup. The lack of association in other populations and our AJ/NJ discrepancies may be explained by ethnic differences in the polymorphisms distribution, as cytokine gene polymorphisms have been reported to vary between different geographical regions. The frequency of the GG genotype in NJ controls observed in our study (34.35%) was higher than those reported previously in other European and US Caucasian populations (range: 12–25.6%) [5,12,13,16,20,33], and it was even higher in our AJ control group (69.05%).

Other explanations may account for the findings, including the existence of other polymorphisms in tight linkage disequilibrium with the C/G SNP differentially influencing IL6 expression, which may vary by populations, as well as methodological differences and sample size considerations. Finally, as cytokines and chemokines form a complex network with multiple interactions between components, single gene association studies may not capture this complexity and be in part responsible for the lack of reproducibility.

To our knowledge, this is the first report of a differential gender effect of the risk SNP in a Non-Jewish Caucasian population. A differential gender effect of IL6 polymorphisms has been demonstrated in other conditions [11] and an interaction between IL6 polymorphism and gender is conceivable, as estrogen may influence IL6 −174G>C activity [24]. An association between the CC and CG genotypes with higher serum IL6 levels was reported in healthy elderly Italian men, but not in women [28] and a trend for reduced frequency of the GG genotype among elderly men has been suggested [33]. While increased IL6 has been associated with inflammation in PD, the relative roles of the specific alleles in IL6 expression are debated [7,13,22,33], and therefore the causal pathway is uncertain.

Animal models suggest a neuroprotective role for estrogen in PD [14]. There is a higher prevalence of PD in men [2], women with PD are more likely to have undergone hysterectomy, and exposure to estrogen replacement therapy is associated with a milder severity of disease [4,36]. Estrogen is known to influence the activity of the

Table 1
Demographic characteristics.

Non Jewish Caucasians	All subjects ($N=450$)	Women ($N=235$)	Men ($N=215$)	p-Value
Age at exam (mean ± SD)	71.2 ± 13.5	71.1 ± 14.3	71.4 ± 12.6	0.822
PD (n, % affected)	121 (26.89)	62 (26.38)	59 (27.44)	
Controls (n, %)	329 (73.11)	173 (73.62)	156 (72.56)	0.800
PD onset ≤age 50 (n, % affected)	33 (27.27)	22 (35.48)	11 (18.64)	0.115
Ashkenazi Jewish Caucasians	**All subjects ($N=452$)**	**Women ($N=221$)**	**Men ($N=231$)**	**p-Value**
Age at exam (mean ± SD)	73.4 ± 11.2	74.4 ± 10.1	72.3 ± 12.1	0.057
PD (n, % affected)	260 (57.52)	110 (49.77)	149 (64.50)	
Controls (n, %)	192 (42.48)	111 (50.23)	82 (64.50)	0.002
PD onset ≤age 50 (n, % affected)	58 (22.39)	21 (19.09)	37 (24.83)	0.273

Table 2
Allele frequencies of IL6 −174G>C.

	All Subjects			Women			Men		
	G	C	p-Value	G	C	p-Value	G	C	p-Value
Non-Jewish Caucasians									
Controls (n, %)	391 (59.42)	267 (40.58)		212 (61.27)	134 (38.73)		179 (57.37)	133 (42.63)	
PD (n, %)	159 (65.70)	83 (34.30)	0.087	77 (62.10)	47 (37.90)	0.871	82 (69.49)	36 (30.51)	0.022
Ashkenazi Jewish Caucasians									
Controls (n, %)	270 (69.05)	116 (30.05)		153 (68.92)	69 (31.08)		117 (71.34)	47 (28.66)	
PD (n, %)	395 (76.25)	123 (23.75)	0.033	164 (74.54)	56 (25.45)	0.189	231 (77.52)	67 (22.48)	0.141

Table 3
Genotype frequencies of IL6 −174G>C.

	All Subjects				Women				Men			
	GG	GC	CC	p-Value	GG	GC	GG	p-Value	GG	CG	CC	p-Value
Non-Jewish Caucasians												
Controls (n, %)	113 (34.35)	165 (50.15)	51 (15.50)		64 (36.99)	84 (48.55)	25 (14.45)		49 (31.41)	81 (51.92)	26 (16.67)	
PD (n, %)	55 (45.45)	49 (40.50)	17 (14.05)	0.092	26 (41.94)	25 (40.32)	11 (17.74)	0.527	29 (49.15)	24 (40.68)	6 (10.17)	0.049
Ashkenazi Jewish Caucasians												
Controls (n, %)	95 (49.22)	80 (41.45)	18 (9.33)		54 (48.65)	45 (40.54)	12 (10.81)		41 (50.00)	35 (42.68)	6 (7.32)	
PD (n, %)	150 (57.92)	95 (36.68)	14 (5.41)	0.101	59 (53.64)	46 (41.82)	5 (4.55)	0.211	91 (61.07)	49 (32.89)	9 (6.04)	0.264

IL6 −174G>C [24] and its neuroprotective effect may be in part explained by inhibition of IL6 production [29,32]. The GG genotype of the ESR2 1730G>A polymorphism has been previously associated with PD [16,41]. We determined an association of the G allele and GG genotype with PD in AJ women, both in late and in young-onset disease. We were however unable to replicate these findings in AJ men or in our NJ population.

There are many reasons which could explain inconsistency between different studies in showing association, or lack of association, with SNPs, including that the effect observed may be due to

Table 4
Allele frequencies of ESR2 1730G>A.

	All Subjects			Women			Men		
	G	A	p-Value	G	A	p-Value	G	A	p-Value
Non Jewish Caucasians									
Controls (n, %)	411 (62.46)	247 (37.54)		227 (65.61)	119 (34.19)		184 (58.97)	128 (41.03)	
PD (n, %)	145 (59.92)	97 (40.08)	0.486	77 (62.10)	47 (37.90)	0.483	68 (57.63)	50 (42.37)	0.800
Ashkenazi Jewish Caucasians									
Controls (n, %)	200 (58.30)	143 (41.70)		113 (50.90)	109 (49.10)		87 (53.05)	77 (46.95)	
PD (n, %)	288 (55.60)	230 (44.40)	0.432	135 (61.36)	85 (38.64)	0.027	153 (51.34)	145 (48.66)	0.725

Table 5
Genotype frequencies of ESR2 1730G>A.

	All Subjects				Women				Men			
	GG	GA	AA	p-Value	GG	GA	AA	p-Value	GG	GA	AA	p-Value
Non-Jewish Caucasians												
Controls (n, %)	130 (39.51)	151 (45.90)	48 (14.59)		71 (41.04)	85 (49.13)	17 (9.83)		59 (37.82)	66 (42.31)	31 (19.87)	
PD (n, %)	43 (35.54)	59 (48.76)	19 (15.70)	0.743	24 (38.71)	29 (26.47)	9 (14.52)	0.600	19 (32.20)	30 (50.85)	10 (16.95)	0.532
Ashkenazi Jewish Caucasians												
Controls (n, %)	50 (25.91)	100 (51.81)	43 (22.28)		29 (26.13)	55 (49.55)	27 (24.32)		21 (25.61)	45 (54.88)	16 (19.51)	
PD (n, %)	80 (30.89)	128 (49.42)	51 (19.69)	0.488	39 (35.45)	57 (51.82)	14 (12.73)	0.060	41 (27.52)	71 (47.65)	37 (24.83)	0.543

linkage disequilibrium with another variant affecting mRNA levels, as it has previously been suggested for the ESR2 1730G>A SNP [30], and ethnic allele distribution differences. While our NJ control population had similar frequencies for the G allele comparable to other Caucasian populations studied [30], our AJ control population had lower frequencies (58.30% vs. 62.46%). In addition, a relative greater genetic load in women with PD of AJ descent is suggested [37].

In conclusion, our study supports a previously suggested role for IL6 and ESR2 in PD. The IL6 effect may be gender mediated in Non-Jewish Caucasians and independent from ESR2. An ESR2 effect was found exclusively in Jewish women. Larger studies in various populations and analysis of SNPs in surrounding regions are warranted to further assess a role for this inflammatory cytokine and the estrogen receptor beta in PD.

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