ORIGINAL ARTICLE

Cytokine Gene Polymorphisms and Parkinson's Disease: A Meta-Analysis

Chu Ketan, Zhou Xiao, Luo Ben-yan

ABSTRACT: ***Background:*** Cytokines, which are involved in immunological responses, play important role in the development and progression of Parkinson's disease (PD). The functional polymorphisms identified in cytokine genes are thought to influence PD risk. However, the findings of studies investigating the association between cytokine gene polymorphisms and PD risk are still controversial. Therefore, we conducted a meta-analysis, in order to investigate the potential associations between cytokine gene polymorphisms and PD. ***Methods:*** Studies of PD and cytokine polymorphisms were identified by searches of PubMed and PDGene. Pooled analyses were performed to assess the association between cytokine gene polymorphisms and PD. ***Results:*** Our results indicated a positive association of TNFα -1031 CC genotype in overall analysis(CC vs. TT: OR=3.146; 95%CI: 1.631-6.070, p=0.008; CC vs. CT+TT: OR=3.187; 95%CI: 1.657-6.128, p=0.008), and an Asian subgroup, C variant(OR=1.328; 95%CI: 1.053-1.675, p=0.034) also conveyed an increased PD risk as well as CC genotype (CC vs. TT: OR=3.207; 95%CI: 1.614-6.373, p=0.004; CC vs. CT+TT: OR=3.238; 95%CI: 1.636-6.410, p=0.004). A decreased risk for PD was associated with IL-6-174C allele (OR=0.761; 95%CI: 0.641-0.903, p=0.008) and IL-1RA VNTR 2 allele(OR=0.641; 95%CI: 0.456-0.826 p=0.004). For the polymorphisms of IL-1β C[-511]T, IL-1α C[-889]T , TNFα G[-308]A, and IL-10 G[-1082]A no significant association was found between the gene polymorphisms and PD risk. ***Conclusions:*** Our meta-analysis suggested that gene polymorphisms of TNFα -1031, IL-6-174 and IL-1RA VNTR may be associated with PD risk. However, more large well-designed studies will be necessary to validate our findings.

RÉSUMÉ: Polymorphismes des gènes des cytokines et maladie de Parkinson : Méta-analyse. ***Contexte :*** Les cytokines sont impliquées dans la réponse immunitaire et elles jouent un rôle important dans l'apparition et la progression de la maladie de Parkinson (MP). On pense que les polymorphismes fonctionnels identifiés dans les gènes des cytokines influencent le risque d'être atteint de la MP. Cependant les résultats des études sur ce sujet demeurent controversés. Nous avons donc procédé à une méta-analyse afin d'étudier l'association potentielle entre des polymorphismes des gènes des cytokines et la maladie de Parkinson. ***Méthode :*** Nous avons identifié les études sur la MP et les polymorphismes des cytokines au moyen d'une recherche dans PubMed et PDGene. Des analyses des résultats combinés de ces études ont été effectuées pour évaluer l'association entre les polymorphismes des gènes des cytokines et la MP. ***Résultats :*** Nos résultats indiquent qu'il existe une association positive du génotype CC de TNFα-1031 à l'analyse globale (CC vs TT : RC = 3,146 ; IC à 95% 1,631 à 6,070, p = 0,008 ; CC vs CT + TT : RC = 3,187 ; IC à 95% 1,657 à 6,128, p = 0,008) et dans le sous-groupe asiatique, la variante C (RC = 1,328 ; IC à 95% 1,053 à 1,675, p = 0,034) comportait également un risque plus élevé de MP ainsi que le génotype CC (CC vs TT : RC = 3,207 ; IC à 95% 1,614 à 6,373 ; = 0,004 ; CC vs CT +TT : RC = 3,238 ; IC à 95% : 1,636 à 6,410, p = 0,004). Un risque plus bas de MP était associé à l'allèle C d'IL-6-174 (RC = 0,761 : IC à 95% : 0,641 à 0,903, p = 0,008) et au polymorphisme VNTR du 2e intron d'IL-1RA (RC = 0,641 ; IC à 95% : 0,456 à 0,826, p = 0,004). Aucune association significative n'a été constatée entre la MP et les polymorphismes C[-511]T d'IL-1β, C[-889]T d'IL-1α, G[-308]A de TNFα et G[-1982]A d'IL-10. ***Conclusions :*** Notre méta-analyse suggère que des polymorphismes de TNFα-1031, d'Il-6-174 et des VNTR d'IL-1RA pourraient être associés au risque de MP. Cependant nos constatations devront être validées par d'autres grandes études bien conçues.

Can. J. Neurol. Sci. 2012; 39: 58-64

Parkinson Disease (PD) is the second most common neurodegenerative disease and is characterized by a progressive loss of dopaminergic neurons in the substantina nigra region of the brain. The exact cause of the neuronal loss is still largely unknown[1]. For the past decade, accumulating evidence has proved that chronic inflammation of the brain may play a crucial role in neuronal death. Several studies suggested that infection can increase the risk of developing PD[2-4]. Activated microglia and increased levels of inflammatory mediators have been detected in the striatum of PD patients[5,6] and animal models[7,8]. Epidemiological studies also indicated that using nonsteroidal anti-inflammatory drugs (NSAIDs) could reduce the risk of developing PD[9,10].

Neuroinflammatory processes might be involved in the progression of neuronal degeneration by producing inflammatory molecules, such as cytokines. Previous studies have shown that the levels of tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β) and interleukin-6 (IL-6) were elevated in the serum, cerebrospinal fluid(CSF) and postmortem brain of PD patients[1,11-13]. Several kinds of cytokine receptors are expressed by midbrain dopaminergic neurons[14,15], and *in vitro* study of PD

From the Department of Neurology, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.

Received June 6, 2011. Final Revisions Submitted August 12, 2011.

Correspondence to: Ben-yan Luo, Department of Neurology, First Affiliated Hospital, Zhejiang University School of Medicine, 76# Qingchun Riad, Hangzhou, 310003, China.

showed that neuroprotection can be achieved by using neutralizing antibody for these receptors[15].

In recent years, interests in interactions between inflammatory cytokines and PD have spurred a great number of genetic studies on associations between polymorphisms of cytokine genes and PD. These genes mainly included interleukin-1α (IL-1α)[16-25], IL-1β[16,18,20,22,25-27], IL-1 receptor antagonist (IL-1RA)[16,20,25], TNFα[24,27-32], IL-6[24,30,33], interleukin-10 (IL-10)[24,32,34] etc. The results of these studies were quite controversial. A previous meta-analysis by Liu et al indicated that polymorphisms of IL-1α -889 and IL-1β -511 were not associated with increased PD risk. However, gene effects were evaluated only in a dominant model and recent emerging studies[25,35] showed a protective effect of IL-1β -511 TT genotype.[25] It is also difficult to evaluate the effects of the other cytokine gene polymorphisms based on separate studies. We therefore conducted a comprehensive meta-analysis to summarize the findings of separate studies exploring the associations between polymorphisms in cytokine genes and PD risk.

Materials and Methods

Selection of studies

A comprehensive PubMed search up to May 2011 was conducted, using the keywords: ''Parkinson'', ''Parkinson's disease'', ''interleukin'', ''IL'', ''tumor necrosis factor'', ''TNF'', "cytokine" and "polymorphism". We also searched the PDGene for studies investigating IL or TNF gene polymorphisms. The retrieved abstracts were read to identify eligible studies investigating the associations between cytokine polymorphisms and PD risk. Then the full texts were read to assess their appropriateness for inclusion. The references of all identified publications were reviewed for any additional studies not indexed by PubMed and PDGene. Criteria for the inclusion in the analysis were: case-control studies, sufficient data was provided to estimate the association in the form of odds ratio (OR). We contacted authors when there were questions regarding their studies.

Data extraction

Two reviewers independently extracted the data for analysis. The results were compared and disagreements were resolved by consensus. For overlapping and reused data, only the largest study was included.

Statistical analysis

For each gene variant, pooled OR along with the 95% confidence interval (CI) was calculated to measure the strength of the genetic associations with PD. The random effects model was applied if between-studies heterogeneity was present otherwise the fixed effects model was applied. The between-studies heterogeneity was assessed with chi-square-based Q test and I-square test[36]. We computed the genetic contrast of the rare allele versus the common type (allele comparison), the associations of the genotype and PD in homozygote comparison, dominant, and recessive model. For IL -1RA Variable Number of Tandem Repeats (VNTR), L signified the long alleles including allele 1, 3, 4, and 5, and was considered as the common allele compared to allele 2[37]. Stratified analysis based on the racial descent of subjects and Hardy–Weinberg equilibrium (HWE) status (Sensitivity analysis) in control group were also conducted if there were two or more studies included. Publication bias was assessed using the Egger's regression method[38] for the analysis including more than eight studies. For multiple testing, we used

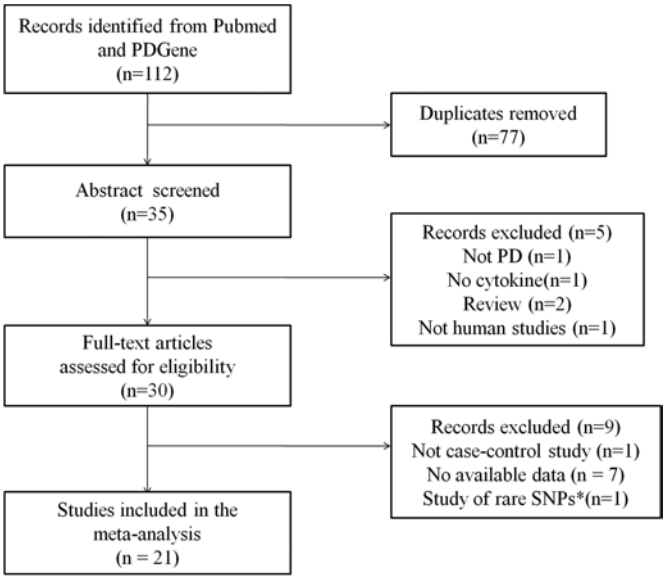

Figure: *Flow diagram of the selection of eligible studies. *Rare SNPs are the SNPs studied by less than three studies, and these SNPs were not selected for pooling.*

Table 1: The list and the characteristics of studies that were included in the meta-analysis

Authors	Year	Country	Racial descent	Case	Control	Gene, polymorphism
Nishimura et al.	2000	Japanese	Asian	122	112	IL-1α C[-889]T, IL-1β C[-511]T, IL-1RA VNTR
Krüger et al.	2000	Germany	Caucasian	237	177	TNFα G[-308]A
Nishimura et al.	2001	Japanese	Asian	172	157	TNFα T[-1031]C
Dodel et al.	2001	Germany	Caucasian	201	197	IL-1α C[-889]T
McGeer et al.	2002	Canada	Caucasian	100	100	IL-1α C[-889]T, IL-1β C[-511]T
Schulte et al.	2002	Germany	Caucasian	257	260	IL-1α C[-889]T, IL-1β C[-511]T
Mattila et al.	2002	Finland	Caucasian	52	73	IL-1α C[-889]T, IL-1β C[-511]T, IL-1RA VNTR
Möller et al.	2004	Germany	Caucasian	176	170	IL-1α C[-889]T
Ross et al.	2004	Ireland	Caucasian	90	93	IL-6 C[-174]G, TNFα G[-308]A
Håkansson et al.	2005	Sweden	Caucasian	265	308	IL-6 C[-174]G
Håkansson et al.	2005	Sweden	Caucasian	265	308	IL-10 G[-1082]A
Nishimura et al.	2005	Japanese	Asian	361	257	IL-1β C[-511]T
Wu et al.	2007	Taiwan	Asian	493	388	IL-1α C[-889]T, IL-1β C[-511]T
Wahner et al.	2007	USA	Mixed	289	269	IL-1β C[-511]T, TNFα G[-308]A
Bialecka et al.	2007	Poland	Caucasian	341	315	IL-10 G[-1082]A
Wu et al.	2007	Taiwan	Asian	369	326	TNFα G[-308]A, TNFα T[-1031]C
Bialecka et al.	2008	Poland	Caucasian	316	300	TNFα G[-308]A, IL-10 G[-1082]A
Zhou et al.	2008	China	Asian	533	530	IL-1α C[-889]T
Infante et al.	2008	Spain	Caucasian	195	170	IL-1α C[-889]T
				196	170	IL-6 C[-174]G
				193	168	IL-10 G[-1082]A
				194	170	TNFα T[-1031]C
Arman et al.	2010	Turkey	Other*	166	199	IL-1α C[-889]T, IL-1β C[-511]T, IL-1RA VNTR
Pascale et al.	2010	Italy	Caucasian	146	156	IL-1β C[-511]T, TNFα G[-308]A, IL-10 G[-1082]A

* Other represented for Turkish population in Arman's study[25]

https://doi.org/10.1017/S0317167100012695 Published online by Cambridge University Press

the stepdown Bonferroni method to correct the p-values[39]. After correcting, $p<0.05$ was considered significant. All p-values were two-sided. Data was analyzed using the statistical analysis software stata 11.0 (StataCorp, College Station, TX, USA).

Results

After a careful screening of the published literature (Figure), twenty-one studies (Table 1) were identified, all of them were published in the English language. Because of the limited number of studies, some of the rare single-nucleotide polymorphisms (SNPs) (studied by less than three studies) investigated in these studies were excluded. Finally, seven gene polymorphisms: IL-1α -889; IL-1β -511; IL-1RA VNTR; TNFα -308, -1031; IL-10 -1082 and IL-6 -174 polymorphisms were selected for pooling (Table 2). The extracted data for meta-analysis of the seven gene polymorphisms were shown in Table 2.

IL-1α C[-889]T polymorphism (rs1800587)

Ten case-control studies investigating the association of IL-1α C[-889]T polymorphism and PD risk were eligible for our meta-analysis, but one study[21] was excluded because it used the data overlapping with Dodel's study[17]. In the remaining nine studies, three[16,22,23] were conducted in Asian populations, five[17-20,24] in Caucasian populations and one[25] in a Turkish population.

Table 2: Genotype and allele distributions in case and control group

gene polymorphism	Study	Racial descent	Case					Control				
IL-1α C[-889]T			C	T	CC	CT	TT	C	T	CC	CT	TT
	Dodel et al. 2001	Caucasian	302	100	108	86	7	307	87	115	77	5
	McGeer et al. 2002	Caucasian	123	77	36	51	13	134	66	37	60	3
	Schulte et al. 2002	Caucasian	357	157	125	107	25	375	145	141	93	26
	Mattila et al. 2002	Caucasian	76	28	28	20	4	95	51	33	29	11
	Infante et al. 2008	Caucasian	282	108	102	78	15	255	85	97	61	12
	Nishimura et al. 2000	Asian	218	26	97	24	1	199	25	87	25	0
	Wu et al. 2007	Asian	907	79	417	73	3	720	56	334	52	2
	Zhou et al. 2008	Asian	981	85	451	79	3	947	113	422	103	5
	Arman et al. 2009	Other*	233	95	82	69	13	268	130	94	80	25
IL-1β C[-511]T			C	T	CC	CT	TT	C	T	CC	CT	TT
	McGeer et al. 2002	Caucasian	111	89	33	45	22	141	59	44	53	3
	Schulte et al. 2002	Caucasian	361	229	110	141	44	359	175	127	105	35
	Mattila et al. 2002	Caucasian	75	29	25	25	2	78	68	24	30	19
	Pascale et al. 2010	Caucasian	185	107	65	55	26	182	130	56	70	30
	Nishimura et al. 2005	Asian	363	359	91	181	89	266	248	69	128	60
	Wu et al. 2007	Asian	549	437	146	257	90	405	371	105	195	88
	Wahner et al. 2007	Mixed	347	231	106	135	48	362	176	118	126	25
	Arman et al. 2009	Other*	196	136	55	86	25	206	192	61	84	54
TNFα G[-308]A			G	A	GG	GA	AA	G	A	GG	GA	AA
	Krüger et al. 2000	Caucasian	385	89	153	79	5	297	57	127	43	7
	Ross et al. 2004	Caucasian	140	40	60	20	10	139	47	54	31	8
	Bialecka et al. 2008	Caucasian	516	116	203	110	3	410	190	121	168	11
	Pascale et al. 2010	Caucasian	255	37	115	25	6	263	49	109	45	2
	Wu et al. 2007	Asian	648	90	282	84	3	585	67	262	61	3
	Wahner et al. 2007	Mixed	481	97	205	71	13	464	74	201	62	6
IL-10 G[-1082]A			G	A	GG	GA	AA	G	A	GG	GA	AA
	Håkansson et al. 2005	Caucasian	242	276	59	124	76	296	318	76	144	87
	Bialecka et al. 2007	Caucasian	290	392	61	168	112	279	351	63	153	99
	Infante et al. 2008	Caucasian	227	159	66	95	32	191	145	55	81	32
	Pascale et al. 2010	Caucasian	114	178	19	76	51	124	188	27	70	59
TNFα T[-1031]C			T	C	TT	TC	CC	T	C	TT	TC	CC
	Infante et al. 2008	Caucasian	365	23	174	17	3	316	24	147	22	1
	Nishimura et al. 2001	Asian	273	71	112	49	11	274	40	120	34	3
	Wu et al. 2007	Asian	602	136	260	82	27	546	106	228	90	8
IL-6 G[-174]C			G	C	GG	GC	CC	G	C	GG	GC	CC
	Ross et al. 2004	Caucasian	96	84	26	44	20	114	72	32	50	11
	Håkansson et al. 2005	Caucasian	285	231	78	129	51	298	318	68	162	78
	Pascale et al. 2010	Caucasian	257	135	88	81	27	205	135	62	81	27
IL-1RA VNTR			L	2	LL	L2	22	L	2	LL	L2	22
	Mattila et al. 2002	Caucasian	83	21	31	21	0	96	50	32	32	9
	Nishimura et al. 2000	Asian	227	17	105	17	0	216	6	105	6	0
	Arman et al. 2009	Other*	254	74	99	56	9	301	97	120	61	18

* Other represented for Turkish population in Arman's study[25]

https://doi.org/10.1017/S0317167100012695 Published online by Cambridge University Press

A total of 2117 cases and 2029 controls were included. Genotype distribution in the controls of all studies but one[18] was in agreement with HWE. No evidence for publication bias and heterogeneity was found, so a fixed effects model was adopted for the comparisons.

Only one[23] of the nine case-control studies found the T allele was associated with a reduced risk of PD (OR: 0.72, 95%CI: 0.54-0.97, p= 0.033). In our meta-analysis, no significant association was found in any genetic model. Subgroup analysis of studies enrolling Caucasians and Asians separately as well as sensitive analysis produced insignificant results (Table 3).

IL-1β C[-511]T polymorphism (rs16944)

For the association between IL-1β C[-511]T polymorphisms and PD risk, nine studies were retrieved. One of them[16] was excluded because of overlapping data with a latter study[26]. The remaining eight studies included 1920 cases and 1709 controls. Among them, four studies[18-20,35] were conducted in populations of Caucasian, two[22,26] in Asian populations, one[25] in a Turkish population and one[27] recruited individuals of mixed ethnic origin. The genotype frequencies of the control arm in two studies were inconsistent with the HWE[18,25]. There was statistical evidence of heterogeneity in most of the comparisons except the Asian subgroup (Table 2), so fixed effects model or the random effects model was adopted accordingly.

The results of the studies concerning association between IL-1β C[-511]T polymorphism and PD risk were very controversial. McGeer [18] and Schulte[19] found a significant increase of the IL-1β T genotype frequency in PD cases compared with controls(X^2=9.65, p=0.0019[18]; X^2=4.44, p=0.035[19]), Wahner[27] found that the risk of Parkinson's disease doubled in carriers of the TT genotype (OR=2.26; 95%CI: 1.27-4.02). While Mattila[20] and Arman[25] got the opposite results: allele C increased the PD risk (OR=8.8; 95%CI: 2.0-39.7[20] and OR=1.178, 95% CI:0.999-1.388[25]). No significant association was found in Pascale's research[35] and the two Asian studies[22,26].

Our results did not support an effect of IL-1β C[-511]T on the risk of PD, but the pooled estimate was derived from a set of heterogeneous studies. However, no significant association was found in the subgroup analysis of Caucasian groups and Asian groups. The sensitivity analysis after excluding the studies which deviated from HWE did not alter the pattern of the results. Heterogeneity still existed in the analysis of Caucasian and all HWE studies (Table 3).

Table 3: Results of allelic and genotypic association analysis for the seven cytokine gene polymorphisms

Gene polymorphism	Category	Number of studies	Number of cases/controls	Allelic Comparison			Homozygote Comparison			Dominant model			Recessive model		
				OR (95% CI)	P#	P*(I2%)	OR (95% CI)	P#	P*(I2%)	OR (95% CI)	P#	P*(I2%)	OR (95% CI)	P#	P*(I2%)
IL-1α C[-889]T	All	9	2117/2029	1.000(0.890-1.122)	1	0.229(31.1)	1.015(0.736-1.401)	1	0.251(21.6)	1.002(0.872-1.152)	1	0.302(15.8)	0.985(0.721-1.345)	1	0.229(24.1)
	Caucasian	5	803/800	1.118(0.958-1.306)	0.624	0.478(0)	1.211(0.821-1.784)	0.668	0.162(38.9)	1.153(0.946-1.405)	0.624	0.692(0)	1.154(0.793-1.678)	0.668	0.119(45.5)
	Asian	3	1148/1030	0.877(0.710-1.082)	0.816	0.178(42.1)	0.883(0.318-2.448)	1	0.62(0)	0.864(0.619-1.082)	0.816	0.183(41.1)	0.909(0.328-2.523)	1	0.643(0)
	Other§	1	166/199	-	-	-	-	-	-	-	-	-	-	-	-
	HWE	8	1929/2017	0.979(0.867-1.101)	1	0.178(31,3)	0.898(0.640-1.259)	1	0.652(0)	1.000(0.866-1.154)	1	0.22(26.2)	0.855(0.615-1.188)	1	0.775(0)
IL-1β C[-511]T	All	8	1920/1709	0.993(0.785-1.256)	1	0(82.2)	1.018(0.607-1.706)	1	0(82.6)	1.022(0.801-1.304)	1	0.006(64.3)	0.997(0.635-1.565)	1	0(81.6)
	Caucasian	4	593/596	0.998(0.606-1.645)	1	0(87)	1.085(0.337-3.498)	1	0(89.7)	1.012(0.603-1.697)	1	0.005(76.5)	1.090(0.383-3.104)	1	0(85.2)
	Asian	2	872/645	0.908(0.786-1.049)	0.736	0.08(67.5)	0.821(0.614-1.098)	0.736	0.074(68.7)	0.891(0.710-1.118)	0.736	0.169(47.2)	0.864(0.675-1.105)	0.736	0.127(56.9)
	Other§	1	166/199	-	-	-	-	-	-	-	-	-	-	-	-
	Mixed	1	369/389	-	-	-	-	-	-	-	-	-	-	-	-
	HWE	6	1654/1410	0.956(0.746-1.224)	1	0(80.7)	0.933(0.506-1.538)	1	0(78.7)	0.985(0.735-1.319)	1	0.004(70.6)	0.959(0.644-1.428)	1	0.002(73.1)
TNFα G[-308]A	All	6	1447/1321	1.105(0.954-1.279)	0.549	0.471(0)	1.539(0.958-2.471)	0.296	0.323(14.2)	1.072(0.908-1.267)	0.824	0.115(43.5)	1.570(0.983-2.509)	0.295	0.244(25.4)
	Caucasian	4	789/726	1.026(0.850-1.238)	1	0.387(0.9)	1.401(0.821-2.603)	0.594	0.175(39.5)	0.970(0.781-1.206)	1	0.076(56.3)	1.532(0.867-2.707)	0.508	0.118(48.9)
	Asian	1	369/326	-	-	-	-	-	-	-	-	-	-	-	-
	Mixed	1	289/269	-	-	-	-	-	-	-	-	-	-	-	-
	HWE	5	1131/1021	1.102(0.931-1.305)	1	0.335(12.3)	1.309(0.781-2.195)	1	0.431(0)	1.087(0.898-1.318)	1	0.067(54.3)	1.340(0.804-2.234)	1	0.319(14.9)
IL-10 G[-1082]A	All	4	936/949	1.024(0.900-1.165)	1	0.836(0)	1.030(0.793-1.337)	1	0.715(0)	1.021(0.821-1.271)	1	0.868(0)	1.040(0.850-1.271)	1	0.868(0)
TNFα T[-1031]C	All	3	735/653	1.247(1.005-1.547)	0.264	0.091(58.4)	**3.146(1.631-6.070)**	0.008	0.919(0)	1.091(0.852-1.397)	0.824	0.065(63.5)	**3.187(1.657-6.128)**	0.008	0.977(0)
	Caucasian	1	194/170	-	-	-	-	-	-	-	-	-	-	-	-
	Asian	2	541/483	**1.328(1.053-1.675)**	0.034	0.099(63.2)	**3.207(1.614-6.373)**	0.004	0.717(0)	1.170(0.894-1.531)	0.252	0.052(73.4)	**3.238(1.636-6.410)**	0.004	0.886(0)
IL-6 G[-174]C	All	3	544/571	**0.761(0.641-0.903)**	0.008	0.234(31.1)	0.883(0.438-1.777)	0.896	0.031(71.3)	0.755(0.585-0.975)	0.093	0.175(42.7)	0.890(0.659-1.202)	0.896	0.062(64.1)
IL-1RA VNTR	All&	2	237/251	**0.614(0.456-0.826)**	0.004	0.361(0)	**0.300(0.137-0.653)**	0.006	0.168(47.3)	**0.637(0.442-0.917)**	0.015	0.558(0)	**0.334(0.155-0.720)**	0.01	0.180(44.3)
	Caucasian	1	71/52	-	-	-	-	-	-	-	-	-	-	-	-
	Other§	1	166/199	-	-	-	-	-	-	-	-	-	-	-	-

*P value for heterogeneity; # P value[&] was corrected by multiple testing (stepdown Bonferroni method); [&] The over all analysis included the studies of Mattila's[20] and Arman's[25]; §Other represented for Turkish population in Arman's study[25]

https://doi.org/10.1017/S0317167100012695 Published online by Cambridge University Press

TNFα G[-308]A polymorphism (rs1800629)

Six studies evaluating the role of the TNFα G[-308]A polymorphism for PD risk were eligible for meta-analysis. One study[31] was conducted in an Asian population, four[28,30,32,35] in Caucasian populations and one[27] recruited individuals of mixed ethnic origin. In total, 1447 cases and 1321 controls were included. Genotype distribution in one study[32] was not in agreement with HWE. No heterogeneity was found in any of the comparisons, so fixed effects model was adopted.

Even though one study found that GA phenotype was more frequent in patients[28], our meta-analysis did not find any significant association in all the comparisons (Table 3).

IL-10 G[-1082]A polymorphism (rs 1800896)

There were five case-control studies[24,32,34,35,40] investigating the association of IL-10 G[-1082]A polymorphism and PD risk. One[32] was excluded because of overlapping data[40]. The remaining four studies included 936 PD cases and 949 healthy controls, all of which were Caucasian studies. Heterogeneity was absent in all the comparisons, so we adopted the fixed effects model.

In agreement with the three published studies. Our meta-analysis did not find any significant association between this gene polymorphism and PD risk (Table 3).

TNFα T[-1031]C polymorphism (rs1799964)

Three studies[24,29,31] provided data on the association between TNFα T[-1031]C polymorphism and PD, two[29,31] of them enrolled Asian subjects, and one[24] was performed in a Caucasian population. Seven hundred and thirty-five cases and 653 controls were included. Genotype distributions in the controls of all studies were in agreement with HWE. No heterogeneity existed in the any of the comparisons, thus a fixed effects model was applied.

Two Asian studies[29,31] found significant associations between TNFα T[-1031]C polymorphism and PD, while the Caucasian study[24] did not. In our meta-analysis, the overall OR of the C allele for PD was 1.247 (95% CI: 1.005-1.547), however, the p-value of this comparison did not survive multiple test(P=0.264 after correction), both homozygote comparison (OR=3.146, 95% CI: 1.631-6.070, P=0.008) and recessive model (OR=3.187, 95% CI:1.657-6.128, P=0.008) provided evidence of an association between this SNP and PD. A slightly higher and significant risk for PD was observed in the Asian subgroups (C versus T : OR=1.328 95% CI: 1.053-1.675, P=0.034;CC versus TT OR=3.207, 95% CI: 1.614-6.373, P=0.004; CC versus TT+TC: OR=3.238, 95% CI: 1.636-6.410, P=0.004).

IL-6 G[-174]C polymorphism (rs1800795)

Three studies[24,30,33] focused on the potential association between the IL-6 G[-174]C polymorphism and PD. All of them were conducted in Caucasian populations, and a total of 544 cases and 571 controls were included. There was no deviation from HWE. Heterogeneity was considered only in the homozygote comparison, so the random effects model was applied in this comparison.

Only one study[33] found a significantly elevated frequency of the GG genotype in the patient group (P=0.03), while the other two got insignificant results. Our meta-analysis indicated that the C allele has a protective effect (OR=0.761, 95% CI: 0.641-0.903, p=0.008). The OR in the Dominant model was 1.247 (95% CI: 1.005-1.547), however the p-value (p=0.093) of this comparison was not significant after correction.

IL-1RA VNTR

The effect of this polymorphism on the occurrence of PD has been investigated in three studies, among them was one Asian study[16], one Caucasian study[20] and one[25] Turkish study. In total, 359 PD cases and 363 healthy controls were included. Since the allele 2 frequency was very low (4.9%), and genotype 22 was not detected in the Asian study, this study was excluded from the overall analysis (Table 3). No between-study heterogeneity was detected, thus the fixed effects model was adopted.

In our meta-analysis all of the four comparisons provided evidence for a protective role of allele 2 for PD without heterogeneity (OR= 0.614, 95% CI: 0.456-0.826, p=0.004) (Table 3).

Discussion

The current meta-analysis is a comprehensive quantitative evaluation of the relevance to PD of seven cytokine gene polymorphisms. Findings of the meta-analysis indicated a positive association of TNFα -1031 CC genotype in overall analysis, and in the Asian subgroup; C variant, as well as CC genotype, conveyed an increased PD risk. Several arguments reinforce these findings. TNFα -1031C variant was reported to be associated with elevation of TNFα gene transcription[41,42]. Several inflammation-related diseases have been reported to be associated with this SNP, such as Behçet disease and Graves' disease etc.[43,44]. However TNFα -1031C is in strong linkage disequilibrium with the TNFα -863A and TNFα microsatellite (TNFα-2) allele 2, a high producer of TNF,[29]. We could not exclude the possibility that the positive finding was partly attributed to the linkage between these SNPs. Further studies evaluating the combined effect of two or more SNPs by haplotype analysis are needed to detect the real association between this gene polymorphism and PD.

The current report also documented a decreased risk for PD in IL-6-174C carriers. IL-6 has a pro-inflammatory effect. Transgenic mice over expressing IL-6 developed an age-related neurodegeneration[45], the methamphetamine-induced neurotoxicity was attenuated in IL-6 knockout mice[46]. Increased levels of IL-6 were found in the CSF and the diseased brain tissue of PD patients[1,13]. IL-6 (-174) C allele has been associated with decreased IL-6 expression[24]. All these might be explanations for our results. However, studies with larger sample sizes are needed to further confirm the gene effect of IL-6 (-174) polymorphism in PD.

In the last section, our study showed a protective role of IL-1RA VNTR 2 allele. IL-1RA is an anti-inflammatory cytokine. Previous studies reported that the 2 allele was associated with increased IL-1RA production in human monocytes[47]. However, different allele frequencies of this polymorphism were observed in different ethnic populations. According to our analysis and previous studies[48,49], the effect of IL-1RA VNTR polymorphism may not be the same between Caucasian and Asian populations.

Further studies, including subjects of different ethnic background, should be conducted to illustrate the gene effect in PD.

In the present meta-analysis, many efforts have been made to avoid possible sources of bias. We assessed the impact of deviations from the HWE[50]. Sensitivity analysis that excluded those studies inconsistent with the HWE did not change the pattern of the findings. We performed appropriate tests for detecting publication bias using Egger's test[38]. No significant publication bias was found in any of the analyses. While ethnicity can strongly influence the distribution and effect of gene polymorphisms, we did subgroup analysis according to ethnic background. To investigate the effect of these gene polymorphisms, we not only tested the allele prevalence of each gene, but also performed the analysis in three commonly used genetic models. Finally, we performed multiple testing to control for false discovery rate[39].

However, several limitations in our meta-analysis should be addressed. First, due to sparse data on age at onset of the disease and sex across studies, we could not investigate the effect of these factors in the gene-disease interaction. Second, certain alleles of some SNPs are in linkage disequilibrium with each other, such as IL-10 G[-1082]A, IL-10 T[-819]C and IL-10 C[-592]A[51] and TNFα -1031 polymorphism mentioned above. Only two studies[32,40] examined the composite effect of three IL-10 SNP sites. Therefore, future studies should carefully address such interactions, i.e. perform stratified analyses that could be used in a subsequent meta-analysis and evaluate the combined effect of two or more SNPs, perhaps by haplotype analysis.

In conclusion, we found that TNFα -1031, IL-6-174 and IL-1RA VNTR polymorphisms are associated with the probability of PD. However, additional large well-designed studies will be necessary to validate our findings.

References

1. Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol. 2009; 8(4): 382-97.
2. Ogata A, Tashiro K, Pradhan S. Parkinsonism due to predominant involvement of substantia nigra in Japanese encephalitis. Neurology. 2000; 55(4): 602.
3. Ling ZD, Chang Q, Lipton JW, et al. Combined toxicity of prenatal bacterial endotoxin exposure and postnatal 6-hydroxydopamine in the adult rat midbrain. Neuroscience. 2004; 124(3): 619-28.
4. Long-Smith CM, Sullivan AM, Nolan YM. The influence of microglia on the pathogenesis of Parkinson's disease. Prog Neurobiol. 2009; 89(3): 277-87.
5. Imamura K, Hishikawa N, Sawada M, et al. Distribution of major histocompatibility complex class II-positive microglia and cytokine profile of Parkinson's disease brains. Acta Neuropathol. 2003; 106(6): 518-26.
6. Mirza B, Hadberg H, Thomsen P, et al. The absence of reactive astrocytosis is indicative of a unique inflammatory process in Parkinson's disease. Neuroscience. 2000; 95(2): 425-32.
7. Ghosh A, Roy A, Liu X, et al. Selective inhibition of NF-kappaB activation prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease. Proc Natl Acad Sci USA. 2007; 104(47): 18754-9.
8. Wang T, Zhang W, Pei Z, et al. Reactive microgliosis participates in MPP+-induced dopaminergic neurodegeneration: role of 67 kDa laminin receptor. FASEB J. 2006; 20(7): 906-15.
9. Chen H, Zhang SM, Hernan MA, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Arch Neurol. 2003; 60(8): 1059-64.
10. Chen H, Jacobs E, Schwarzschild MA, et al. Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease. Ann Neurol. 2005; 58(6): 963-7.
11. Blum-Degen D, Muller T, Kuhn W, et al. Interleukin-1 beta and interleukin-6 are elevated in the cerebrospinal fluid of Alzheimer's and de novo Parkinson's disease patients. Neurosci Lett. 1995; 202(1-2): 17-20.
12. Mogi M, Harada M, Riederer P, et al. Tumor necrosis factor-alpha (TNF-alpha) increases both in the brain and in the cerebrospinal fluid from parkinsonian patients. Neurosci Lett. 1994; 165(1-2): 208-10.
13. Mogi M, Harada M, Kondo T, et al. Interleukin-1 beta, interleukin-6, epidermal growth factor and transforming growth factor-alpha are elevated in the brain from parkinsonian patients. Neurosci Lett. 1994; 180(2): 147-50.
14. Mogi M, Togari A, Kondo T, et al. Caspase activities and tumor necrosis factor receptor R1 (p55) level are elevated in the substantia nigra from parkinsonian brain. J Neural Transm. 2000; 107(3): 335-41.
15. Gayle DA, Ling Z, Tong C, et al. Lipopolysaccharide (LPS)-induced dopamine cell loss in culture: roles of tumor necrosis factor-alpha, interleukin-1beta, and nitric oxide. Brain Res Dev Brain Res. 2002; 133(1): 27-35.
16. Nishimura M, Mizuta I, Mizuta E, et al. Influence of interleukin-1beta gene polymorphisms on age-at-onset of sporadic Parkinson's disease. Neurosci Lett. 2000; 284(1-2): 73-6.
17. Dodel RC, Lohmuller F, Du Y, et al. A polymorphism in the intronic region of the IL-1alpha gene and the risk for Parkinson's disease. Neurology. 2001; 56(7): 982-3.
18. McGeer PL, Yasojima K, McGeer EG. Association of interleukin-1 beta polymorphisms with idiopathic Parkinson's disease. Neurosci Lett. 2002; 326(1): 67-9.
19. Schulte T, Schols L, Muller T, et al. Polymorphisms in the interleukin-1 alpha and beta genes and the risk for Parkinson's disease. Neurosci Lett. 2002; 326(1): 70-2.
20. Mattila KM, Rinne JO, Lehtimaki T, et al. Association of an interleukin 1B gene polymorphism (-511) with Parkinson's disease in Finnish patients. J Med Genet. 2002; 39(6): 400-2.
21. Moller JC, Depboylu C, Kolsch H, et al. Lack of association between the interleukin-1 alpha (-889) polymorphism and early-onset Parkinson's disease. Neurosci Lett. 2004; 359(3): 195-7.
22. Wu YR, Chen CM, Hwang JC, et al. Interleukin-1 alpha polymorphism has influence on late-onset sporadic Parkinson's disease in Taiwan. J Neural Transm. 2007; 114(9): 1173-7.
23. Zhou YT, Yang JF, Zhang YL, et al. Protective role of interlekin-1 alpha gene polymorphism in Chinese Han population with sporadic Parkinson's disease. Neurosci Lett. 2008; 445(1): 23-5.
24. Infante J, Garcia-Gorostiaga I, Sanchez-Juan P, et al. Inflammation-related genes and the risk of Parkinson's disease: a multilocus approach. Eur J Neurol. 2008; 15(4): 431-3.
25. Arman A, Isik N, Coker A, et al. Association between sporadic Parkinson disease and interleukin-1beta -511 gene polymorphisms in the Turkish population. Eur Cytokine Netw. 21(2): 116-121.
26. Nishimura M, Kuno S, Kaji R, et al. Glutathione-S-transferase-1 and interleukin-1beta gene polymorphisms in Japanese patients with Parkinson's disease. Mov Disord. 2005; 20(7): 901-2.
27. Wahner AD, Sinsheimer JS, Bronstein JM, et al. Inflammatory cytokine gene polymorphisms and increased risk of Parkinson disease. Arch Neurol. 2007; 64(6): 836-40.
28. Kruger R, Hardt C, Tschentscher F, et al. Genetic analysis of immunomodulating factors in sporadic Parkinson's disease. J Neural Transm. 2000; 107(5): 553-62.
29. Nishimura M, Mizuta I, Mizuta E, et al. Tumor ncrosis factor gene polymorphisms in patients with sporadic Parkinson's disease. Neurosci Lett. 2001; 311(1): 1-4.
30. Ross OA, O'Neill C, Rea IM, et al. Functional promoter region polymorphism of the proinflammatory chemokine IL-8 gene associates with Parkinson's disease in the Irish. Hum Immunol. 2004; 65(4): 340-6.

31. Wu YR, Feng IH, Lyu RK, et al. Tumor necrosis factor-alpha promoter polymorphism is associated with the risk of Parkinson's disease. Am J Med Genet B Neuropsychiatr Genet. 2007; 144B(3): 300-4.
32. Bialecka M, Klodowska-Duda G, Kurzawski M, et al. Interleukin-10 (IL10) and tumor necrosis factor alpha (TNF) gene polymorphisms in Parkinson's disease patients. Parkinsonism Relat Disord. 2008; 14(8): 636-40.
33. Hakansson A, Westberg L, Nilsson S, et al. Interaction of polymorphisms in the genes encoding interleukin-6 and estrogen receptor beta on the susceptibility to Parkinson's disease. Am J Med Genet B Neuropsychiatr Genet. 2005; 133B(1): 88-92.
34. Hakansson A, Westberg L, Nilsson S, et al. Investigation of genes coding for inflammatory components in Parkinson's disease. Mov Disord. 2005; 20(5): 569-73.
35. Pascale E, Passarelli E, Purcaro C, et al. Lack of association between IL-1beta, TNF-alpha, and IL-10 gene polymorphisms and sporadic Parkinson's disease in an Italian cohort. Acta Neurol Scand. 2011; 124(3):176-81.
36. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med. 1997; 127(9): 820-6.
37. Xue H, Lin B, Ni P, et al. Interleukin-1B and interleukin-1 RN polymorphisms and gastric carcinoma risk: a meta-analysis. J Gastroenterol Hepatol. 25(10): 1604-17.
38. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109): 629-34.
39. Holm S. A simple sequentially rejective multiple test procedure. Scand J Statist. 1979; 6: 65-70.
40. Bialecka M, Klodowska-Duda G, Kurzawski M, et al. Interleukin-10 gene polymorphism in Parkinson's disease patients. Arch Med Res. 2007; 38(8): 858-63.
41. Park YJ, Park H, Park MH. TNF-alpha promoter polymorphisms and extended HLA and TNF-alpha haplotypes in Koreans based on 100 families. Tissue Antigens. 2004; 63(1): 75-9.
42. Higuchi T, Seki N, Kamizono S, et al. Polymorphism of the 5'-flanking region of the human tumor necrosis factor (TNF)-alpha gene in Japanese. Tissue Antigens. 1998; 51(6): 605-12.
43. Li N, Zhou Z, Liu X, et al. Association of tumour necrosis factor alpha (TNF-alpha) polymorphisms with Graves' disease: A meta-analysis. Clin Biochem. 2008; 41(10-11): 881-6.
44. Touma Z, Farra C, Hamdan A, et al. TNF polymorphisms in patients with Behcet disease: a meta-analysis. Arch Med Res. 41(2):142-6.
45. Heyser CJ, Masliah E, Samimi A, et al. Progressive decline in avoidance learning paralleled by inflammatory neurodegeneration in transgenic mice expressing interleukin 6 in the brain. Proc Natl Acad Sci USA. 1997; 94(4): 1500-5.
46. Ladenheim B, Krasnova IN, Deng X, et al. Methamphetamine-induced neurotoxicity is attenuated in transgenic mice with a null mutation for interleukin-6. Mol Pharmacol. 2000; 58(6): 1247-56.
47. Danis VA, Millington M, Hyland VJ, et al. Cytokine production by normal human monocytes: inter-subject variation and relationship to an IL-1 receptor antagonist (IL-1Ra) gene polymorphism. Clin Exp Immunol. 1995; 99(2): 303-10.
48. Serdaroglu G, Alpman A, Tosun A, et al. Febrile seizures: interleukin 1beta and interleukin-1 receptor antagonist polymorphisms. Pediatr Neurol. 2009; 40(2): 113-6.
49. Chou IC, Lin WD, Wang CH, et al. Interleukin (IL)-1beta, IL-1 receptor antagonist, IL-6, IL-8, IL-10, and tumor necrosis factor alpha gene polymorphisms in patients with febrile seizures. J Clin Lab Anal. 24(3): 154-9.
50. Trikalinos TA, Salanti G, Khoury MJ, et al. Impact of violations and deviations in Hardy-Weinberg equilibrium on postulated gene-disease associations. Am J Epidemiol. 2006; 163(4): 300-9.
51. Thakkinstian A, Dmitrienko S, Gerbase-Delima M, et al. Association between cytokine gene polymorphisms and outcomes in renal transplantation: a meta-analysis of individual patient data. Nephrol Dial Transplant. 2008; 23(9): 3017-23.