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Differences in *ABCA1 R219K* Polymorphisms and Serum Indexes in Alzheimer and Parkinson Diseases in Northern China

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: *ABCA1 R219K* single-nucleotide polymorphisms (SNPs) was related to Alzheimer disease (AD) but not Parkinson disease (PD). Here, we analyzed the associations among *ABCA1 R219K* distribution, serum biomarkers, AD, and PD in a population in northern China.

Material/Methods: We used the Mini-Mental State Examination (MMSE) and the Hoehn and Yahr scale (H-Y) to evaluate AD and PD progression, separately. *ABCA1 R219K* was analyzed by matrix-assisted laser desorption ionization time of flight time mass spectrometry (MALDI-TOF-MS). Serum indexes were determined by enzyme-linked immunosorbent assay (ELISA).

Results: *ABCA1 R219K RR+RK* genotype frequency in AD and PD patients was lower than that in normal controls (NC), while *ABCA1 R219K KK* genotype frequency was significantly higher. *ABCA1 R219K RR* genotype frequency in AD patients and NC was lower than that in PD patients, while *ABCA1 R219K RK+KK* genotype frequency was significantly higher. *ABCA1 R219K RR* genotype was positively correlated to MMSE value in AD patients, while *ABCA1 R219K KK* genotype was negatively correlated to H-Y value in PD patients. Serum factors were significantly different among AD and PD patients and NC. Serum ABCA1, ApoA1, ApoA2, ApoB, HDL, TC, IL-1β, IL-6, and TNF-α were significantly different between AD and PD patients.

Conclusions: *ABCA1 R219K R* allele was the risk factor inducing abnormal serum levels of ApoA2, LDL, and TG in AD patients, and abnormal levels of serum ABCA1, HDL, IL-1β, IL-6, and TNF-α in PD patients, while *ABCA1 R219K K* allele was the risk factor inducing lower ABCA1 in AD patients. IL-1β, IL-6, and TNF-α were negatively correlated to MMSE in AD patients but positively correlated to H-Y in PD patients, while HDL was positively related to H-Y in PD patients.

MeSH Keywords: **Alzheimer Disease • ATP Binding Cassette Transporter 1 • Inflammation • Lipid Metabolism • Parkinson Disease**

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Background

AD is one of the most important age-dependent neurodegenerative diseases in the world. Clinically, AD is defined by slowly progressing loss of cognitive functions, and neuropathologically by the aggregation and deposition of amyloid-β (Aβ) peptide into amyloid plaques in the extracellular brain parenchyma, accompanied by hyperphosphorylated tau in intracellular neurofibrillary tangles [1]. PD is another age-dependent neurodegenerative disease, which is clinically characterized by tremor, rigidity, and slowness of movements, as well as the progressive neuronal loss of substantia nigra (SN) primarily and neuropathologically [2].

Adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) is an important element in reverse cholesterol transport and removal of cholesterol from tissues [3]. ABCA1 was found to participate in the early remodeling process of brain injury, especially apolipoprotein E (ApoE) lipidation and glial cholesterol efflux regulation [4,5]. ABCA1 enhances clearance of Aβ, ameliorating brain injury via the ApoE-mediated pathway, which might be related to the risk of AD [6]. However, there have been few investigations on the relationship between *ABCA1* SNPs and PD.

Most previous investigations focused on the regulation of ABCA1 in lipid metabolism, reporting, for example, that ABCA1 is the major regulator of HDL metabolism [7]. In Tangier disease (TD), ABCA1 leads to low high-density lipoprotein (HDL) levels and macrophage foam cell formation [8]. In mice with *ABCA1* knocked-out, low-density lipoprotein (LDL) level decreased, but triglyceride (TG) increased, suggesting that ABCA1 affects total cholesterol (TC) [9]. There have also been few studies on the relationship of ABCA1 with HDL, LDL, TG, TC, ApoA1, ApoA2, and ApoB in AD and PD patients.

In addition, although clinically and pathologically different, there is evidence of chronic neuroinflammation in the brain in both diseases. Elevated levels of inflammatory cytokines were demonstrated in brain, cerebrospinal fluid (CSF), and basal ganglia of the PD patients, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [10]. These cytokines were found to promote Aβ accumulation and play important roles in AD patients [11]. Cytokines in the peripheral circulation directly enter the central nervous system (CNS) through the regions without blood brain barrier (BBB), especially enhancing permeability of the BBB when there is CNS damage or neuroinflammation [12]. In the change of inflammatory cytokines in peripheral circulation relating to those in CSF, the inflammatory cytokines reflect the extent of the CNS damage. Although some investigations have focused on the relationship between inflammatory cytokines and AD or PD patients, few studies have focused on whether the inflammatory cytokines are potential biomarkers, or whether the SNPs of those cytokines could influence the serum levels in AD and PD patients, especially in populations of different regions.

Therefore, our study focused on the association of *ABCA1 R219K* SNPs with metabolism and inflammation in AD and PD patients in northern China, in order to investigate the pathological and regional differences of *ABCA1 R219K* SNPs, as well as metabolic and inflammatory indexes, between AD and PD patients.

Material and Methods

Patients

Clinical data were collected from 105 AD patients, 116 PD patients, and 100 healthy volunteers from October 2013 to December 2015 in the Neurology Department of Inner Mongolia People's Hospital (China).

There were 105 patients diagnosed with AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke, the Alzheimer's Diseases and Related Disorders Associations (NINCDS-ADRDA), and the Diagnostic and Statistical Manual of Mental Disorders-revised fourth edition (DSM-IV-R). Using radiological evaluation of strategic structures according to previous research [13], we excluded patients with dementia induced by cerebrovascular disease, other neurodegeneration dementias, normal-pressure hydrocephalus (NPH), epilepsia, infection, and systemic metabolic disease, or pseudodementia induced by depression. There were 60 males and 45 females, age 60~80 years old, with an average age of 69.65±4.45 years, with AD course of 0.8~10 years, and average AD course of 3.17±2.24 years.

According to the UK PD Brain Bank Criteria created in 1997 [14] and the new clinical criteria with details described by Reichmann [15], 116 patients were diagnosed with PD and their H-Y stages were evaluated. We excluded patients with Parkinsonism-Plus or secondary Parkinsonism. There were 68 males and 48 females, age 60~80 years old, average age 68.12±5.20 years, with the PD course of 0.5~17 years, and an average PD course of 4.33±2.98 years. The H-Y stage was 1.0~5.0, with an average stage of 2.06±0.51.

We also enrolled 100 healthy volunteers who had health examinations at Inner Mongolia People's Hospital in the period; there were 50 males and 50 females, age 60~80, and average age of 63.66±5.88 years. We excluded volunteers with cognitive impairment or nervous system diseases.

All the AD and PD patients and the volunteers had lived in Inner Mongolia for at least 20 years, and were matched for age

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and sex. Informed consent was obtained from each individual. This study was approved by the Medical Ethics Committee of Inner Mongolia People's Hospital and Renmin Hospital of Wuhan University.

Neuropsychology analysis

All the individuals were assessed by MMSE [16], activity of daily living scale (ADL) [17] (data not shown), clock drawing test (CDT) [18] (data not shown) and Hachinski ischemic scale (HIS) [19] (data not shown).

Sample collections

We collected 10-mL blood samples from each participant under fasting state at 8: 00 a.m.~10: 00 a.m. We used 3 mL of the blood for separating serum after centrifuging at 3000×g for 15 min. The blood and serum samples were stored at –28°C.

Primer design

ABCA1 R219K gene polymorphism was analyzed by real-time fluorescent quantitation polymerase chain reaction (PCR). The primers were designed with Sequenom Assay Design 3.0 software by the Sequenom Company (USA) as follows: forward primer 5'-GTATTTTTGCAAGGCTACCAGTTACATTTGACAA-3', reverse primer 5'-GATTGGCTTCAGGATGTCCATGTTGGAA-3'.

Genomic DNA extraction and analysis

We used the TIANamp Blood DNA Kit (Tiangen Biotech (Beijing) Co., LTD, China) for extracting genomic DNA according to the manufacturer's specifications, followed by storage at –20°C. After purification and quantification by NanoDrop 2000 (Thermo Fisher Scientific, Inc. Shanghai, China), DNA samples were diluted quantitatively and added in a 384-well plate with the designed sequence. The PCR amplification system had a final volume of 20 μl, including genomic DNA (1 uμ), 2×TaqMan Universal PCR Master Mix (Thermo), forward (0.5 μl) and reverse (0.5 μl) primers, and diethyl pyrocarbonate (DEPC) water (8 μl, Thermo). PCR amplification conditions were pre-denaturation at 94°C for 5 min, denaturation at 94°C for 45 s, annealing at 62°C for 45 s, extension at 72°C for 45 s, and final extension at 72°C for 5 min, for a total of 30 cycles. The remaining dNTP was removed by 0.3U alkaline phosphatase (Thermo). After then, the products were spotted into SpectroCHIP chips (Sequenom) and detected by MALDI-TOF-MS (SpectroREADER, Sequenom).

Detection of serum ABCA1, ApoA1, ApoA2, ApoB, HDL, LDL, TC, TG, IL-1β, IL-6, and TNF-α levels

ELISA was used for detection of serum ABCA1, IL-1β, IL-6, and TNF-α levels using the Human ABCA1 ELISA kit (Abbexa, Shanghai Bioleaf Biotech Co., Ltd, China), ApoA1 (Abcam, Shanghai, China), ApoA2 (Abcam), ApoB (Abcam), HDL (Abcam), LDL (Abcam), TC (Abcam), TG (Abcam), IL-1β (Beyotime Biotechnology, Shanghai, China), IL-6 (Beyotime), and TNF-α (Beyotime) ELISA kits.

Statistical analysis

All data were analyzed using SPSS 21.0 software. Deviation from Hardy-Weinberg equilibrium (HWE) was assessed by chi-square test in each case with $P>0.05$. Pearson chi-square or Fisher exact tests were used for comparing genotype and allele frequencies. Logistic regression was used to examine the association of genotypes with AD or PD. The odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the association between the polymorphisms and the risk of AD or PD. Measurable variables are shown as mean ± standard deviations (X±SD) and the comparisons between groups were analyzed by t-test or one-way ANOVA. The Levene test was used to assess homogeneity of variance and the LSD test was used for pairwise comparisons. $P<0.05$ was considered a significant difference.

Results

Clinical data

As shown in Table 1, there was no significant difference in age ($F=4.979$, $P=0.053$) or sex ($\chi^2=0.895$, $P=0.410$), but there was a significant difference in MMSE among AD patients, PD patients, and NC ($F=44.294$, $P<0.001$).

Genotype and allele frequency of *ABCA1 R219K* in AD and PD patients and healthy volunteers

As shown in Figure 1, there were 7 samples with no data and 7 with other data outside of *ABCA1 R219K*, which were all excluded in this study. As shown in Table 2, the *ABCA1 R219K* ($\chi^2=0.048$, $P=0.826$) SNP in NCs and *ABCA1 R219K* ($\chi^2=0.086$, $P=769$) SNP in AD patients were within the range of HWE, while *ABCA1 R219K* ($\chi^2=17.312$, $P<0.05$) SNP in PD patients was not. The distribution of *ABCA1 R219K* genotypes ($\chi^2=6.372$, *P<0.05*) and alleles ($\chi^2=4.576$, $P<0.05$) among the 3 groups were significantly different.

Association of *ABCA1 R219K* genotypes with AD and PD

As shown in Table 3, the distribution of *ABCA1 R219K RR+RK vs. ABCA1 R219K KK* genotypes among the 3 groups were significantly different ($F=7.765$, $P=0.001$). The *ABCA1 R219K RR+RK* genotypes in AD (88.57%) and in PD (89.66%) were lower than that in NC (92.00%), while *ABCA1 R219K KK* genotype in AD

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Table 1. Clinical data of AD and PD patients and healthy volunteers (χ±SD).

Groups	Cases (N)	Male (n)	Female (n)	Average age (years)	MMSE
AD	105	60	45	69.94±4.45	17.38±5.53*
PD	116	68	48	68.94±5.20	26.84±4.72
Control	100	50	50	64.85±5.88	27.96±3.88
F/χ^2	–	1.205		0.758	5.826
P	–	0.644		0.926	0.006

AD – Alzheimer disease; PD – Parkinson disease; MMSE – mini-mental state examination; * comparing to Control group, P<0.05.

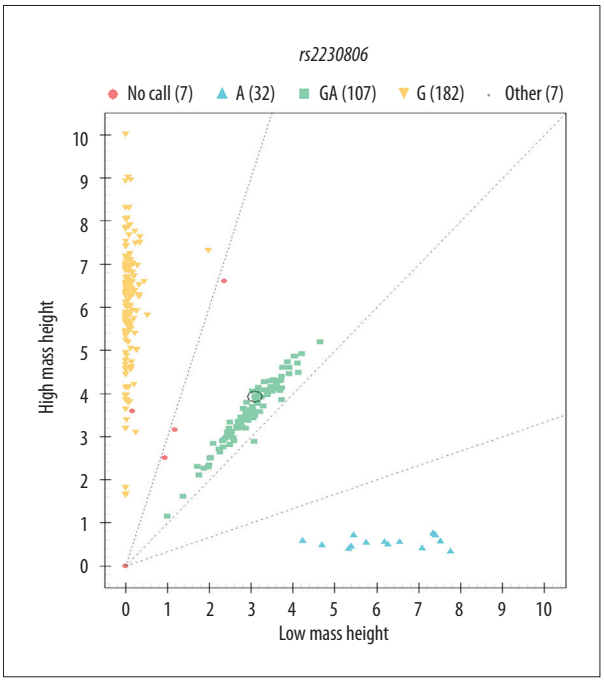

Figure 1. Genotypes distribution of *ABCA1 R219K (G>A)* in AD patients, PD patients, and healthy volunteers.

(11.43%) and PD (10.34%) patients were significantly (P<0.05) higher than in NC (8.00%), but there was no significance between AD and PD patients.

The distribution of *ABCA1 R219K RR vs. ABCA1 R219K RK+KK* genotypes among the 3 groups was significantly different (F=6.372, P=0.002). The *ABCA1 R219K RR* genotype in AD (45.73%) was lower than that in PD patients (69.83%), while *ABCA1 R219K RK+KK* genotypes in AD (54.29%) were significantly (P<0.05) higher than in PD (30.17%). The *ABCA1 R219K RR* genotype in PD patients was higher than in NC (53.00%), while *ABCA1 R219K RK+KK* genotypes in PD patients were significantly (P<0.05) higher than in NC (47.00%). We found no significant difference between AD and NC.

Association of *ABCA1 R219K* genotypes with progression of AD and PD

As shown in Table 4, *ABCA1 R219K* genotypes in AD patients were negatively correlated with MMSE (r=–0.222, 95% CI=–0.386~–0.033, P<0.05), indicating that the AD patients with *ABCA1 R219K RR* genotype had higher MMSE and lower progression. *ABCA1 R219K* genotypes in PD patients was negatively correlated to H-Y (r=–0.489, 95% CI=–0.624~–0.330, P<0.05), indicating that the PD patients with *ABCA1 R219K KK* genotype had lower H-Y and lower progression.

Serum factors in AD, PD, and healthy volunteers

As showed in Table 5 and Figure 2, serum ABCA1, ApoA1, ApoA2, LDL, TC, and TG in AD patients were lower than in NC, while ApoB, HDL, IL-1β, IL-6, and TNF-α in AD were significantly (P<0.05) higher than in NC. Serum ABCA1, TC, and IL-1β in AD were lower than in PD. ApoA1, ApoA2, ApoB, HDL, IL-6, and TNF-α in AD were significantly (P<0.05) higher than in PD patients.

Serum ApoA1, ApoA2, ApoB, and HDL in PD were lower than in NC, while serum ABCA1, IL-1β, IL-6, and TNF-α in PD patients were significantly (P<0.05) higher than in NC. No significance differences were found in serum LDL, TC, and TG between PD and NC.

Correlation of *ABCA1 R219K* genotypes with serum factors in AD patients and healthy volunteers

As shown in Table 6, in AD patients with *ABCA1 R219K RR+RK* genotypes, serum ABCA1, ApoA1, ApoA2, ApoB, HDL, LDL, TC, TG, IL-1β, IL-6, and TNF-α were significantly different compared to NC (P<0.05). In AD patients with *ABCA1 R219K KK* genotype, serum ABCA1, ApoA1, ApoB, HDL, TC, IL-1β, IL-6, and TNF-α were significantly different compared to NC (P<0.05), while serum ApoA2, LDL, and TG were not significantly different.

In AD patients with *ABCA1 R219K RR* genotype, serum ABCA1, ApoA1, ApoA2, ApoB, HDL, TC, IL-1β, IL-6, and TNF-α were

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Table 2. Genotype allele frequency of *ABCA1 R219K* in AD and PD patients and healthy volunteers.

Genes	AD (n/%)	PD (n/%)	Control (n/%)
Cases (N)	105	116	100
RR	48 (45.71)	81 (69.83)	53 (53.00)
RK	45 (42.86)	23 (19.83)	39 (39.00)
KK	12 (11.43)	12 (10.34)	8 (8.00)
R	141 (67.14)	185 (79.74)	145 (72.50)
K	69 (32.86)	47 (20.26)	55 (27.50)
χ^2	0.134	15.769	0.044
P	<0.001	<0.001	<0.001

Table 3. Serum ABCA1, TC, TG, HDL, LDL, ApoA1, ApoB, IL-1β, IL-6 and TNF-α levels in AD, PD and healthy volunteers (χ±SD).

	AD	PD	Control	*F*	*P*
Cases (N)	105	116	100	–	–
ABCA1 (μg/l)	1.72±0.61*	3.85±0.46	3.23±0.32	4.265	<0.001
ApoA1 (g/l)	1.04±0.15*	0.89±0.11*	1.52±0.13	2.950	0.006
ApoA2 (g/l)	0.36±0.05#	0.26±0.04*	0.39±0.04	0.764	0.012
ApoB (g/l)	0.95±0.07#	0.52±0.05*	0.84±0.04	1.925	<0.001
HDL (mmol/l)	1.95±0.26*#	0.95±0.13*	1.37±0.18	4.367	<0.001
LDL (mmol/l)	2.76±0.25	2.89±0.18	2.84±0.21	6.331	0.616
TC (mmol/l)	4.35±0.17	4.51±0.11	4.76±0.09	9.203	0.574
TG (mmol/l)	1.21±0.15	1.37±0.10	1.48±0.12	2.957	0.465
IL-1β (ng/l)	42.96±5.09*#	51.68±5.93*	30.62±7.79	107.50	<0.001
IL-6 (ng/l)	6.34±1.42*	6.09±1.93*	4.26±1.33	9.428	<0.001
TNF-α (ng/l)	28.96±3.90*	26.90±4.04*	18.51±2.60	46.503	<0.001

* Comparing to Control group, *P*<0.05; # comparison between AD and PD groups, *P*<0.05.

significantly different compared to NC (*P*<0.05), while serum LDL and TG were not significantly different between AD and PD patients. In AD patients with *ABCA1 R219K RK+KK* genotypes, serum ABCA1, ApoA1, ApoA2, ApoB, HDL, TC, IL-1β, IL-6, and TNF-α were significantly different compared to NC (*P*<0.05), while serum LDL and TG were not significantly different between AD and PD patients.

Correlation of *ABCA1 R219K* genotypes with serum factors in PD patients and healthy volunteers

As shown in Table 7, in PD patients with *ABCA1 R219K RR+RK* genotypes, serum ABCA1, ApoA1, ApoA2, ApoB, HDL, IL-1β, IL-6, and TNF-α were significantly different compared to NC (*P*<0.05), while serum LDL, TC, and TG were not significantly different between AD and PD patients. In PD patients with *ABCA1 R219K KK* genotype, serum ApoA1, ApoA2, ApoB, HDL, IL-1β, IL-6 and TNF-α were significantly different comparing to NC (*P*<0.05), while serum ABCA1, LDL, TC, and TG were not significantly different between AD and PD patients.

In PD patients with *ABCA1 R219K RR* genotype, serum ABCA1, ApoA1, ApoA2, ApoB, HDL, IL-1β, IL-6, and TNF-α were significantly different compared to NC (*P*<0.05), while serum LDL, TC, and TG were not significantly different between AD and PD patients. In PD patients with *ABCA1 R219K RK+KK* genotypes, serum ApoA1, ApoA2, ApoB, HDL, IL-1β, IL-6, and TNF-α were significantly different compared to NC (*P*<0.05), while serum ABCA1, LDL, TC, and TG were not significantly different between AD and PD patients.

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Table 4. Comparisons on serum factors between AD or PD patients and healthy volunteers with of *R219K* genotypes ABCA1 (χ±SD).

	AD	PD	Control	P_1	P_2
RK+KK					
ABCA1 (μg/l)	1.62±0.35*	3.62±0.35	3.06±0.44	<0.001	0.337
ApoA1 (g/l)	1.10±0.09*	1.34±0.13	1.60±0.14	<0.001	0.472
ApoA2 (g/l)	0.31±0.07	0.32±0.05	0.42±0.06	0.376	0.167
ApoB (g/l)	0.92±0.05	0.85±0.05	0.91±0.03	0.357	0.244
HDL (mmol/l)	2.06±0.17*	1.29±0.14	1.46±0.20	<0.001	0.250
LDL (mmol/l)	2.63±0.19	2.90±0.19	2.66±0.22	0.446	0.411
TC (mmol/l)	4.21±0.12	4.60±0.12	4.89±0.08	0.124	0.306
TG (mmol/l)	1.15±0.10	1.42±0.11	1.39±0.16	0.608	0.279
IL-1β (ng/l)	44.85±3.99*	51.95±4.98*	34.64±6.02	<0.001	<0.001
IL-6 (ng/l)	6.40±1.03*	5.58±1.95*	3.90±1.25	<0.001	<0.001
TNF-α (ng/l)	29.76±4.55*	27.09±3.96*	17.27±3.06	<0.001	<0.001
RR					
ABCA1 (μg/l)	2.32±0.42*#	3.90±0.17	3.46±0.17	<0.001	0.434
ApoA1 (g/l)	1.26±0.15	0.82±0.09*	1.60±0.09	0.472	<0.001
ApoA2 (g/l)	0.37±0.05	0.20±0.04*	0.40±0.04	0.167	<0.001
ApoB (g/l)	0.95±0.07	0.45±0.03*	0.80±0.03	0.244	<0.001
HDL (mmol/l)	1.39±0.23	0.84±0.10*	1.33±0.15	0.250	<0.001
LDL (mmol/l)	2.79±0.30	2.75±0.16	2.95±0.21	0.411	0.385
TC (mmol/l)	4.86±0.23	4.26±0.07	4.43±0.10	0.306	0.313
TG (mmol/l)	1.47±0.16	1.31±0.08	1.50±0.09	0.279	0.386
IL-1β (ng/l)	41.60±2.75*	50.64±7.05*	29.58±7.86	<0.001	<0.001
IL-6 (ng/l)	6.08±1.85*	6.22±1.50*	4.38±1.35	<0.001	<0.001
TNF-α (ng/l)	28.32±3.43*	26.47±4.62*	18.97±2.20	<0.001	<0.001

P_1 – comparison between AD and Control; P_2 – comparison between PD and Control; * comparing to the Control, $P<0.05$; # comparing to AD carrying *R219 RK+KK*, $P<0.05$.

Associations of MMSE in AD patients and H-Y in PD patients with serum factors

As shown in Table 8, serum IL-1β (r=–0.731, 95% CI=–0.801~ –0.650, $P<0.05$), IL6 (r=–0.752, 95% CI=–0.819~ –0.670, $P<0.05$), and TNF-α (r=–0.691, 95% CI=–0.770~–0.600, $P<0.05$) were negatively correlated to MMSE in AD patients. Serum HDL (r=–0.439, 95% CI=–0.576~–0.297, $P<0.05$) was negatively correlated, but IL-1β (r=0.849, 95% CI=0.799~0.886, $P<0.05$), IL6 (r=0.768, 95% CI=0.696~0.828, $P<0.05$), and TNF-α (r=0.851, 95% CI=0.802~0.893, $P<0.05$) were positively correlated to H-Y in PD patients.

Discussion

AD and PD are the most common neurodegenerative diseases clinically. In recent years, more and more attention has focused on SNPs in AD or PD patients. Dopamine β-hydroxylase (DBH) (rs11611115) is a new SNPs found in PD patients by Shao et al. [20]. However, fewer studies have emphasized the common SNPs in different neurodegenerative diseases. ABCA1 is reported to be important in AD [4,21], but its role in PD is unclear. In a northern Chinese population, we analyzed *ABCA1 R219K* in AD and PD, as well as the serum ABCA1, ApoA1, ApoA2, ApoB, HDL, LDL, TC, TG, IL-1β, IL-6, and TNF-α, to investigate the association of these factors with the risk of AD and PD.

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Table 5. Association of MMSE in AD and H-Y in PD patients with serum factors.

	MMSE in AD		H-Y in PD	
	r	*P*	r	*P*
ABCA1 (μg/l)	–	0.268	–	0.204
ApoA1 (g/l)	–	0.134	–	0.545
ApoA2 (g/l)	–	0.462	–	0.708
ApoB (g/l)	–	0.224	–	0.079
HDL (mmol/l)	–	0.314	–	0.136
LDL (mmol/l)	–	0.640	–	0.582
TC (mmol/l)	–	0.337	–	0.251
TG (mmol/l)	–	0.260	–	0.401
IL-1β (ng/l)	–0.436	<0.001	0.598	<0.001
IL-6 (ng/l)	–0.925	<0.001	–	0.186
TNF-α (ng/l)	–	0.219	–	0.337

Based on the homogeneity of sex and age, *ABCA1 R219K* in AD and NC groups were both within HWE, while PD was not. These results indicate that there were factors influencing the distributions of *ABCA1 R219K* in PD patients, such as the small sample size, genetic mutation, genetic drift, and racial differences. Analysis of the distributions of *ABCA1 R219K* showed significant differences among AD and PD patients and healthy volunteers. The *ABCA1 R219K R* allele frequency in AD patients was significantly lower than that in PD patients, while the *ABCA1 R219K K* allele frequency was higher. However, there were no significant differences in *ABCA1 R219K* allele frequencies of AD or PD patients compared to NC. These results suggest that the distribution of *ABCA1 R219K* was different in AD *vs.* PD patients, which has never been reported before.

By analyzing genotypes, ABCA*1 R219K RR+RK vs. ABCA1 R219K KK* genotypes were significantly different in AD and PD patients compared to NC, but no significant difference was found between AD and PD patients. However, *ABCA1 R219K RR vs. ABCA1 R219K RK+KK* genotypes were significantly different between AD and PD patients, as well as between PD patients and NC, but we found no significant difference between AD patients and NC. According to previous studies [22–24], ABCA1 is correlated with the risk of AD, especially late-onset AD (LOAD). According to Sundar et al., *ABCA1 R219K RR* in females with LOAD was lower than in healthy people, and *ABCA1 R219K K* allele frequency in female with LOAD was higher than that in healthy people [22], but this phenomenon was not found in males. Sundar et al. suggested that *ABCA1 R219K R* was the protective allele for LOAD in female. In our study, although no significant difference was found between males and females, the *ABCA1 R219K K* frequency in AD patients was significantly higher than in PD patients, and was higher than that in healthy people, but the difference was not significant, which is in agreement with previous results.

When analyzing the correlation of *ABCA1 R219K* genotypes with progression of AD and PD, the results showed that in AD patients carrying the *ABCA1 R219K RR* genotype, the development of AD was slower, while in those carrying the *ABCA1 R219K RK* or *ABCA1 R219K KK* genotypes, the development of AD was faster, suggesting the *ABCA1 R219K R* allele is protects against AD pathogenesis and development. On the contrary, in PD patients carrying *ABCA1 R219K RR* or *ABCA1 R219K RK* genotypes, the development of PD was faster, while in those carrying the *ABCA1 R219K RR* genotype, the development of PD was slower, suggesting the *ABCA1 R219K K* allele protects against PD pathogenesis and development, which shows the different effects of *ABCA1 R219K* genotypes on AD and PD.

In the past few years, many researchers reported high-level expression of inflammatory factors in the brain of AD and PD patients, suggesting that the inflammatory factors increase the risk of AD and PD [25–28]. Ba et al. [29] found that the risk of AD in patients taking anti-inflammatory drugs was lower. Therefore, the biomarkers in AD and PD are helpful for diagnosis and treatment. Zhang et al. [30] used GTM-1 to treat mice and, by detecting IC3-II and Aβ42 levels in routine blood samples, found that GTM-1 alleviated AD syndrome. In our study, we detected ABCA1, ApoA1, ApoA2, ApoB, HDL, LDL, TC, TG, IL-1β, IL-6, and TNF-α in AD and PD patients compared to healthy volunteers. Firstly, we found that serum ABCA1, ApoA1, ApoA2, LDL, TC, and TG in AD patients were lower than in NCs, while ApoB, HDL, IL-1β, IL-6, and TNF-α in AD patients were higher.

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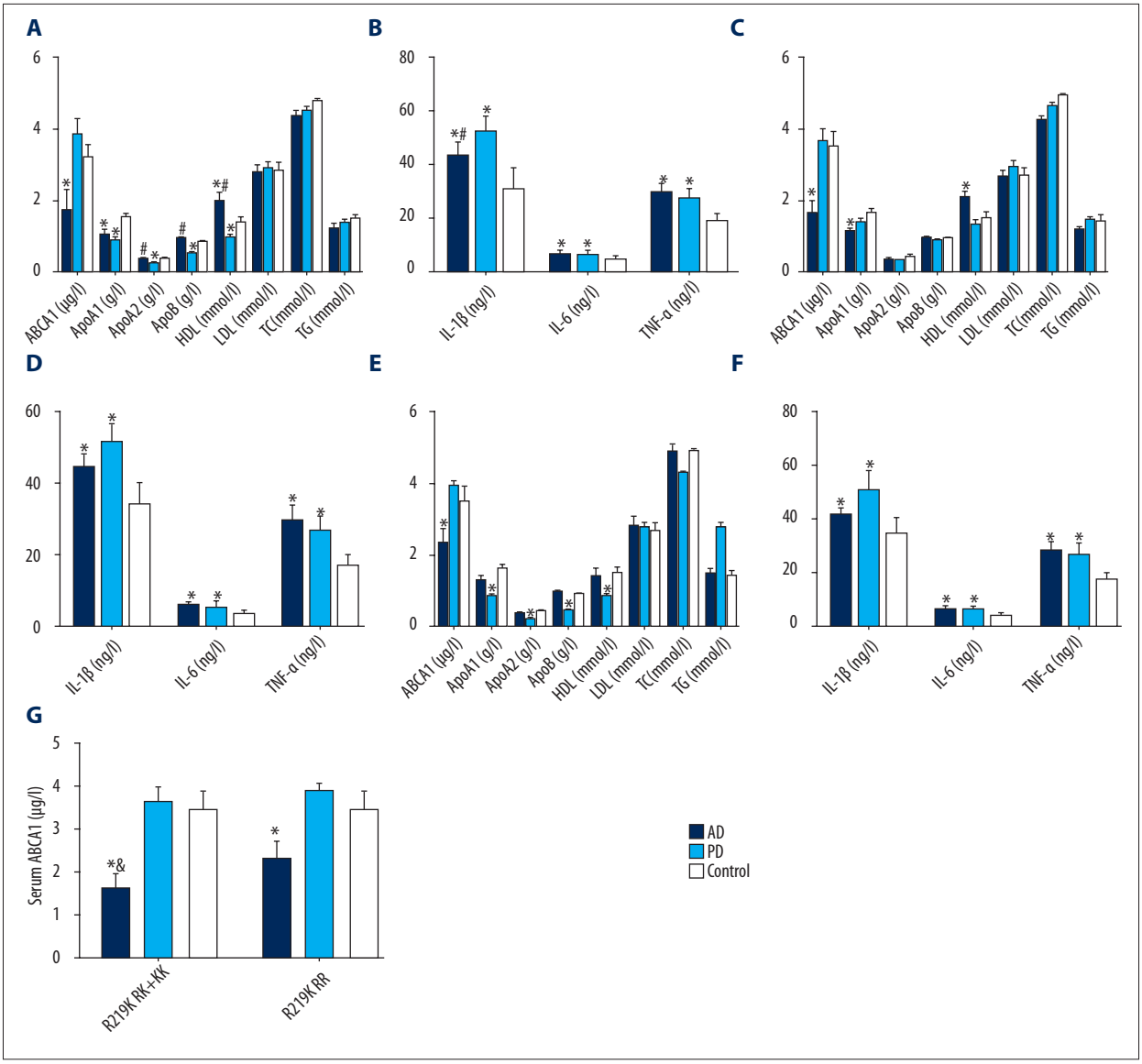

Figure 2. Comparisons of serum ABCA1, ApoA1, ApoA2, ApoB, HDL, LDL, TC, TG, IL-1β, IL-6, and TNF-α among in AD and PD patients and healthy volunteers. (**A**) Serum ABCA1, ApoA1, ApoA2, ApoB, HDL, LDL, TC, and TG; (**B**) Serum IL-1β, IL-6, and TNF-α; (**C**) Serum ABCA1, ApoA1, ApoA2, ApoB, HDL, LDL, TC, and TG in *ABCA1 R219K RK+KK* genotype; (**D**) Serum IL-1β, IL-6, and TNF-α in *ABCA1 R219K RK+KK* genotype; (**E**) Serum ABCA1, ApoA1, ApoA2, ApoB, HDL, LDL, TC, and TG in *ABCA1 R219K RR* genotype; (**F**) Serum IL-1β, IL-6, and TNF-α in *ABCA1 R219K RR* genotype; (**G**) Serum ABCA1 in *ABCA1 R219K RK+KK* genotype *vs. ABCA1 R219K RR* genotype.

Serum ABCA1, TC, and IL-1β were lower than in PD patients, while ApoA1, ApoA2, ApoB, HDL, IL-6, and TNF-α were higher. In AD patients, serum ApoA1, ApoA2, ApoB, and HDL in PD were lower than in NC, while ABCA1, IL-1β, IL-6, and TNF-α in PD patients were higher. These results indicate that there were differences in serum factors between AD and PD patients during the progression.

Based on the difference in *ABCA1 R219K* distribution among AD and PD patients and healthy volunteers, we analyzed the correlation between *ABCA1 R219K* distribution and serum factors. There were differences in serum factors among different *ABCA1 R219K* distributions. In AD patients, serum ApoA2, LDL, and TG levels were significantly different between those carrying *ABCA1 R219K RR+RK vs. KK,* as well as between and those carrying *ABCA1 R219K RR vs. RK+KK*. However, in PD patients, serum ABCA1 was significantly different between those carrying *ABCA1 R219K RR+RK vs. KK* and those carrying *ABCA1 R219K RR vs. RK+KK*. Suggesting that the abnormal levels of serum ApoA2, LDL, and TG in AD patients and abnormal ABCA1

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levels in PD patients might be related to *ABCA1 R219K RR+RK* genotypes, indicating the *ABCA1 R219K R* allele induces abnormal levels of serum ApoA2, LDL, and TG in AD patients and abnormal ABCA1 levels in PD patients.

Further analysis was focused on the correlation of serum factor levels with progression of AD and PD. The results showed that serum IL-1β, IL-6, and TNF-α levels were negatively correlated with MMSE in AD patients. However, serum HDL was negatively correlated and serum IL-1β, IL-6, and TNF-α levels were positively correlated with H-Y in PD. These results suggest that as the clinical grades of AD and PD develop, the levels of inflammatory factors in serum increased, indicating the association between more serious inflammation and decreasing HDL, as the protective protein, in PD patients, as well as indicating worsening inflammation.

However, according to previous research, serum ABCA1 is correlated with progression of AD and PD [24,31]. But in our study, we found that serum ABCA1 was correlated with *ABCA1 R219K* genotypes but not with the progression of AD and PD, which differs from previous research findings.

Cheng et al. [32] reported that serum ApoA1, ApoA2, ApoB, HDL, and IL-6 were correlated with cognitive ability of AD patients, and serum levels of LDL, TG, TC, IL-1β, and TNF-α change as AD progresses. Gao et al. and Swanson et al. found that serum proteins associated with lipid in PD patients were significantly different from those in healthy persons [33,34]. In our study, the protein levels were significantly associated with lipid levels in AD patients compared to healthy persons, including ApoA1, ApoA2, ApoB, HDL, LDL, TC, and TG. For PD patients, only serum ApoA1, ApoA2, ApoB, and HDL were different from levels in healthy persons, while serum LDL, TC, and TG were not. We believe the differences between results of the present study and those of previous studies are related to differences in the populations studied, such as ethnicity and lifestyle.

Conclusions

We found that the distributions of *ABCA1 R219K* genotypes and alleles were different in AD and PD patients and in healthy people in northern China, which contributed to the pathogenesis and development, as well as the abnormal serum inflammatory and lipid factors, in AD and PD.

Conflict of interest

The authors declare no conflict of interest.

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