Genetics and Molecular Research

Role of *ADH2* and *ALDH2* gene polymorphisms in the development of Parkinson's disease in a Chinese population

C.C. Zhao[1,2], H.B. Cai[2], H. Wang[2] and S.Y. Pan[1]

[1]Department of Neurology, Nanfang Hospital, Southern Medical University, Guangzhou, China
[2]Department of Neurology, Second Hospital of Lanzhou University, Lanzhou, China

Corresponding author: S.Y. Pan
E-mail: suyuepanyp@163.com

Genet. Mol. Res. 15 (3): gmr.15038606
Received March 7, 2016
Accepted April 15, 2016
Published September 2, 2016
DOI http://dx.doi.org/10.4238/gmr.15038606

Copyright © 2016 The Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution ShareAlike (CC BY-SA) 4.0 License.

ABSTRACT. In this study, we investigated the role of *ADH2* Arg47His and *ALDH2* Glu487Lys genetic polymorphisms in the development of Parkinson's disease in a Chinese population. Between January 2013 and May 2014, 115 patients with Parkinson's disease and 214 healthy controls were recruited in our study. Genotyping of *ADH2* Arg47His and ALDH2 Glu487Lys polymorphisms was performed by the polymerase chain reaction-restriction fragment length polymorphism method. In the dominant model, the GA + AA genotype of *ALDH2* Glu487Lys was found to be significantly associated with elevated risk of Parkinson's disease when compared with the GG genotype [odds ratio = 1.71, 95% confidence interval (CI) = 1.02-2.84]. In the recessive model, the AA genotype of *ALDH2* Glu487Lys showed a 4.87-fold increase (95%CI = 1.54-18.03) in the risk of Parkinson's disease when compared

to the GG and GA genotypes. However, no significant association was found between the *ADH2* Arg47His polymorphism and risk of Parkinson's disease in the co-dominant, dominant, or recessive models. In conclusion, our study suggests that the *ALDH2* polymorphism could influence the development of Parkinson's disease in the Chinese population studied here.

Key words: Parkinson's disease; *ADH2* Arg47His; *ALDH2* Glu487Lys; Polymorphism

INTRODUCTION

Parkinson's disease is a common neurodegenerative disease, and its incidence is second to that of Alzheimer's disease (Liu et al., 2016). It was estimated that the prevalence of Parkinson's disease is approximately 1-2% in people above 65 years of age, and approximately 4% in people above 80 years of age (Elbaz et al., 2016; Evans et al., 2016). The development of Parkinson's disease is attributable to various environmental and lifestyle factors such as old age, brain trauma, sleep behavior disorders, mental illness, vitamins, flavonoids, calorie intake, alcohol consumption, metals consumed via food and fatty acids, and coffee consumption (Elbaz et al., 2016; Evans et al., 2016). Moreover, familial aggregation and co-aggregation of Parkinson's disease have indicated that genetic factors also play an important role in the development of Parkinson's disease. Previous studies have shown that genes encoding β-site APP cleaving enzyme 1, myeloid cells 2, cyclooxygenase-2, aldehyde dehydrogenase 2, neuronal nitric oxide synthase, and bone marrow stromal cell antigen 1, all contribute to the development of this disease (Dai et al., 2015; Goudarzian et al., 2015; Gupta et al., 2015; Wang et al., 2015a,b; Zhang et al., 2015).

Previous studies have also shown that alcohol intake is negatively associated with the development of Parkinson's disease (Zhang et al., 2014; Kenborg et al., 2015). Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are two important enzymes for ethanol metabolism in the human body (Asakage et al., 2007; Dakeishi et al., 2008; Kang et al., 2009; Lee et al., 2015). ADH catalyzes the conversion of ethanol to acetaldehyde, which is a highly active and toxic substance. ALDH catalyzes the conversion of acetaldehyde dehydrogenase to acetic acid, which enters the Krebs cycle, and is metabolized to CO_2 and H_2O, which are then excreted from the body (Asakage et al., 2007; Dakeishi et al., 2008; Kang et al., 2009; Lee et al., 2015). *ADH2* and *ALDH2* are genetic variants of *ADH* and *ALDH*. *ADH2* Arg47His and *ALDH2* Glu487Lys genetic polymorphisms could alter the activity of the wild-type proteins, and thus influence ethanol metabolism (Kang et al., 2009; Lai et al., 2013). In our study, we investigated the role of *ADH2* Arg47His and *ALDH2* Glu487Lys genetic polymorphisms in the development of Parkinson's disease in a Chinese population.

MATERIAL AND METHODS

Subjects

A hospital-based case-control design was adopted in this study. Between January 2013 and May 2014, 115 patients with Parkinson's disease were recruited from the

Department of Neurology of the Second Hospital of Lanzhou University. The diagnosis of Parkinson's disease was based on the UK Parkinson's disease Society Brain Bank Criteria (Hughes et al., 1992). The exclusion criteria were as follows: individuals who had a history of secondary Parkinson's disease, Parkinsonism-plus syndrome, cerebrovascular diseases, brain trauma, malignant brain tumors, chronic or acute infections, and end-stage liver or kidney diseases.

Over the same period, 214 healthy controls were also recruited to the study. These subjects were individuals who were either visiting the outpatient clinics, or receiving regular health check-ups in the Department of Neurology of the Second Hospital of Lanzhou University. All controls subjects were free of Parkinson's disease, chronic or acute infections, end-stage liver or kidney diseases, cerebrovascular diseases, brain trauma, malignant brain tumors, as well as other nervous system diseases.

The demographic and clinical data from the patients and control subjects were collected from their medical records. This information included gender, age, family history of Parkinson's disease, alcohol consumption, and tobacco smoking. Written informed consents were obtained from all subjects prior to their enrollment in our study. All procedures performed in our study received approval from the Ethics Committee of the Second Hospital of Lanzhou University.

DNA extraction and genotyping analysis

Peripheral blood (5 mL) was drawn from each subject for analysis, and the blood samples were collected in vacuum tubes containing 5% ethylenediaminetetraacetic acid. DNA extraction was carried out with the TIANamp Blood DNA Kit (Tiangen, Beijing, China), following the manufacturer protocol. Genotyping of the *ADH2* Arg47His and *ALDH2* Glu487Lys polymorphisms was performed by polymerase chain reaction (PCR)-restriction fragment length polymorphism. The primer sequences were designed using the Primer Premier 5.0 software. The forward and reverse primer sequences for *ADH2* were 5'-AATCTTTTCTGAATCTGAACAG-3' and 5'-GAAGGGGGGTCACCAGGTTG-3', respectively. The forward and reverse primer sequences for *ALDH2* were 5'-GTTTGGAGCCCA GTAACCCTT-3' and 5'-CCCACACTCACAGTTTTGAATT-3', respectively. The PCR products of *ADH2* Arg47His and *ALDH2* Glu487Lys were digested with *Mae*III and *Eco*RI restriction enzymes, respectively. PCR was performed in a 25-μL reaction mixture, which contained 2.0 μL DNA, 20 pmol of each primer, 2.5 mM deoxynucleotide mixture, 2.5 μL 10X PCR buffer solution, and 1.25 U Taq DNA polymerase. The cycling conditions for *ADH2* Arg47His were as follows: denaturation at 97°C for 5 min; 35 cycles of denaturation at 94°C for 1 min, annealing at 57°C for 1 min, and extension at 72°C for 30 s; and a final extension at 72°C for 10 min. The cycling conditions for *ALDH2* Glu487Lys were as follows: denaturation at 97°C for 5 min; 55 cycles of 94°C for 30 s, 55.5°C for 30 s, and 72°C for 30 s; and a final extension at 72°C for 7 min. The PCR products and digestive products were detected by electrophoresis on a 3% agarose gel.

The PCR-amplified products of *ADH2* Arg47His and *ALDH2* Glu487Lys were 108 bp in size. For the *ADH2* gene, the restriction fragment length was 60 bp for the GG genotype and 95 bp for the AA genotype; heterozygotes exhibited both fragments. For the *ALDH2* polymorphism, the restriction fragment length was 119 bp for the GG genotype and 98 bp for the AA genotype; both fragments were present in the GA genotype.

Statistical analysis

Student *t*-tests were performed to analyze the continuous variables, and χ^2 tests were performed to analyze the categorical variables. Departure of frequencies of the *ADH2* Arg47His and *ALDH2* Glu487Lys genotypes from the Hardy-Weinberg equilibrium (HWE) was estimated by performing the Pearson χ^2 test and comparing the acute and theoretical frequency values. The association between the *ADH2* Arg47His and *ALDH2* Glu487Lys polymorphisms and Parkinson's disease was assessed by multiple-logistic regression analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to express the results. Three genetic models (co-dominant, dominant, and recessive) were included in this study. The SPSS 16.0 software (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analysis; $P < 0.05$ was considered statistically significant.

RESULTS

The demographic variables of the patients with Parkinson's disease and control subjects in this study are presented in Table 1. There were no significant differences between the patients and controls in terms of age ($\chi^2 = 0.458$, $P = 0.498$), gender ($\chi^2 = 0.224$, $P = 0.636$), alcohol consumption ($\chi^2 = 0.616$, $P = 0.433$), and tobacco smoking ($\chi^2 = 0.462$, $P = 0.497$). However, we found that the patients with Parkinson's disease were more likely to have a family history of Parkinson's disease than were the controls ($\chi^2 = 13.309$, $P < 0.001$).

Table 1. Demographic variables of patients with Parkinson's disease and controls.

Variables	Patients	%	Controls	%	Chi-square test	P value
Age (years)						
<65	45	39.13	92	42.99		
≤65	70	60.87	122	57.01	0.458	0.498
Gender						
Females	49	42.61	97	45.33		
Males	66	57.39	117	54.67	0.224	0.636
Family history of Parkinson's disease						
No	108	93.91	214	100.00		
Yes	7	6.09	0	0.00	13.309	<0.001
Alcohol consumption						
No	78	67.83	154	71.96		
Yes	37	32.17	60	28.04	0.616	0.433
Tobacco smoking						
No	72	62.61	142	66.36		
Yes	43	37.39	72	33.64	0.462	0.497

The distributions of the *ADH2* Arg47His and *ALDH2* Glu487Lys genotypes are presented in Table 2. The GG, GA, and AA genotypes of ADH2 Arg47His accounted for 34.783, 47.826, and 17.391% of the patients with Parkinson's disease, respectively. These genotypes accounted for 34.112, 50.467, and 15.421% of the control subjects, respectively (Table 2). In patients with Parkinson's disease, the frequencies of the GG, GA, and AA genotypes of *ALDH2* Glu487Lys were 61.739, 27.826 and 10.435%, respectively; these genotypes appeared in 73.364, 24.300, and 2.336% of the controls. Results of χ^2 tests revealed a significant difference in the *ALDH2* Glu487Lys polymorphism ($\chi^2 = 11.317$, $P = 0.003$) between the patients with Parkinson's disease and the controls. However, no significant

difference was observed in the genotype frequencies of *ADH2* Arg47His between the two study groups (χ^2 = 0.296, P = 0.863). The genotype frequencies of *ADH2* Arg47His (χ^2 = 0.451, P = 0.502) and *ALDH2* Glu487Lys (χ^2 = 0.079, P = 0.779) were confirmed to be in Hardy-Weinberg equilibrium in the control subjects.

Table 2. *ADH2* Arg47His and *ALDH2* Glu487Lys genotype frequencies of the study groups.

Variables	Patients	%	Controls	%	Chi-square test	P value	Chi-square test for HWE	P value for HWE
ADH2 Arg47His								
GG	40	34.783	73	34.112				
GA	55	47.826	108	50.467				
AA	20	17.391	33	15.421	0.296	0.863	0.451	0.502
ALDH2 Glu487Lys								
GG	71	61.739	157	73.364				
GA	32	27.826	52	24.300				
AA	12	10.435	5	2.336	11.317	0.003	0.079	0.779

We also performed unconditional logistic regression analyses, and observed that the GA genotype of *ALDH2* Glu487Lys significantly increased the risk of Parkinson's disease when compared to the GG genotype (OR = 5.312, 95%CI = 1.656-19.824; P = 0.001; Table 3). In the dominant model, the GA + AA genotype of *ALDH2* Glu487Lys was significantly associated with an elevated risk of Parkinson's disease when compared to the GG genotype (OR = 1.710, 95%CI = 1.022-2.845; P = 0.029). In the recessive model, the AA genotype of *ALDH2* Glu487Lys showed a 4.874-fold (95%CI = 1.542-18.035; P = 0.002) higher risk of Parkinson's disease when compared to that shown by the GG and GA genotypes. However, we observed no significant association between the *ADH2* Arg47His polymorphism and Parkinson's disease in the co-dominant, dominant, or recessive models.

Table 3. Relationship between *ADH2* Arg47His and *ALDH2* Glu487Lys polymorphisms and risk of Parkinson's disease.

Variables	Patients	%	Controls	%	OR (95%CI)	P value
ADH2 Arg47His						
Co-dominant model						
GG	40	34.783	73	34.112	1.0 (Ref.)	-
GA	55	47.826	108	50.467	0.919 (0.532-1.552)	0.702
AA	20	17.391	33	15.421	1.087 (0.527-2.233)	0.825
Dominant model						
GG	40	34.783	73	34.112	1.0 (Ref.)	-
GA+AA	75	65.217	141	65.888	0.974 (0.592-1.617)	0.903
Recessive model						
GG+GA	95	82.609	181	84.579	1.0 (Ref.)	-
AA	20	17.391	33	15.421	1.141 (0.592-2.188)	0.667
ALDH2 Glu487Lys						
Co-dominant model						
GG	71	61.739	157	73.364	1.0 (Ref.)	-
GA	32	27.826	52	24.300	1.364 (0.783-2.362)	0.247
AA	12	10.435	5	2.336	5.312 (1.656-19.824)	0.001
Dominant model						
GG	71	61.739	157	73.364	1.0 (Ref.)	-
GA+AA	44	38.261	57	26.636	1.710 (1.022-2.845)	0.029
Recessive model						
GG+GA	103	89.565	209	97.664	1.0 (Ref.)	-
AA	12	10.435	5	2.336	4.874 (1.542-18.035)	0.002

[1]Adjusted for age, gender and family history of Parkinson's disease.

DISCUSSION

In the present study, we evaluated the relationship between *ADH2* Arg47His and *ALDH2* Glu487Lys polymorphisms and Parkinson's disease. Our results indicated that the *ALDH2* Glu487Lys polymorphism increases the risk of Parkinson's disease in the Chinese population studied here.

Previous studies have shown that *ALDH2* plays an important role in the detoxification of trans-4-hydroxy-2-nonenal, which is a product of lipid peroxidation. In addition, *ALDH2* also contributes to detoxification of the dopamine metabolite 3,4-dihydroxyphenylacetaldehyde. It has been shown that during this detoxification process, the enzyme encoded by this gene can catalyze the transformation of toxic acetaldehyde products to acetic acid (Meyer et al., 2004; Brichac et al., 2007; Leiphon and Picklo, 2007). Meyer et al. (2004) and Vermeer et al. (2012) reported that trans-4-hydroxy-2-nonenal and 3,4-dihydroxyphenylacetaldehyde are associated with disease of the central nervous system. Furthermore, Casida et al. (2014) indicated that the dopamine metabolite 3,4-dihydroxyphenylacetaldehyde is mainly detoxified by *ALDH*, and that *ALDH* may play an important role in the pathogenesis of Parkinson's disease.

Polymorphisms in *ALDH2* can influence the expression and function of this protein, and consequently increase susceptibility of the individual to a variety of diseases of the central nervous system (Hao et al., 2011; Yao et al., 2011; Li et al., 2015). In a study conducted by Li et al. (2015), which included 369 Chinese patients with cerebral infarction and 247 healthy Chinese subjects, it was shown that the A allele in *ALDH2* may be a significant risk factor for cerebral infarction in Chinese females (Li et al., 2015). Notably, Yao et al. (2011) stated that the A allele in *ALDH2* is an independent protective variable for patients who have had stroke and have a history of heavy alcohol consumption. Further, in a meta-analysis by Hao et al. (2011), it was shown that the GA and AA genotypes in *ALDH2* increased the risk of Alzheimer's disease. However, some studies reported contradicting results (Zhou et al., 2010; Komatsu et al., 2014). For example, in a study by Zhou et al. (2010), it was found that *ALDH2* does not influence the development of Alzheimer's disease. Similarly, in a study by Komatsu et al. (2014), involving 201 patients with Alzheimer's disease and 130 control subjects, it was shown that *ALDH2* does not affect susceptibility to Alzheimer's disease.

Until date, only two studies have examined the relationship between *ALDH2* and risk of Parkinson's disease (Fitzmaurice et al., 2014; Zhang et al., 2015). Fitzmaurice et al. (2014) indicated that ALDH inhibition is a critical mechanism for Parkinson's disease attributable to environmental toxicants. In addition, Zhang et al. (2015) conducted a cohort study involving 584 patients with Parkinson's disease and 582 control subjects, and revealed that the *ALDH2* s4767944 polymorphism promotes susceptibility to this disease. The exact molecular mechanisms underlying the pathogenesis of Parkinson's disease remain to be elucidated in future studies.

Two limitations of the present study should be taken into consideration when interpreting the results. First, the sample size in this study was relatively small, which may have reduced the statistical power of identifying differences between the two groups that were studied. Second, influence of other genes on *ALDH2* was not considered in this study. Further studies with larger sample sizes are needed to verify our results.

In conclusion, our results suggest that the *ALDH2* polymorphism influences the development of Parkinson's disease in the Chinese population studied here, whereas the *ADH2* polymorphism does not. Further studies with larger sample sizes are required to confirm the relationship between *ADH2* and *ALDH2* polymorphisms and risk of Parkinson's disease.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

Asakage T, Yokoyama A, Haneda T, Yamazaki M, et al. (2007). Genetic polymorphisms of alcohol and aldehyde dehydrogenases, and drinking, smoking and diet in Japanese men with oral and pharyngeal squamous cell carcinoma. *Carcinogenesis* 28: 865-874. http://dx.doi.org/10.1093/carcin/bgl206

Brichac J, Ho KK, Honzatko A, Wang R, et al. (2007). Enantioselective oxidation of trans-4-hydroxy-2-nonenal is aldehyde dehydrogenase isozyme and Mg^{2+} dependent. *Chem. Res. Toxicol.* 20: 887-895. http://dx.doi.org/10.1021/tx7000509

Casida JE, Ford B, Jinsmaa Y, Sullivan P, et al. (2014). Benomyl, aldehyde dehydrogenase, DOPAL, and the catecholaldehyde hypothesis for the pathogenesis of Parkinson's disease. *Chem. Res. Toxicol.* 27: 1359-1361. http://dx.doi.org/10.1021/tx5002223

Dai Y, Wu Y and Li Y (2015). Genetic association of cyclooxygenase-2 gene polymorphisms with Parkinson's disease susceptibility in Chinese Han population. *Int. J. Clin. Exp. Pathol.* 8: 13495-13499.

Dakeishi M, Murata K, Sasaki M, Tamura A, et al. (2008). Association of alcohol dehydrogenase 2 and aldehyde dehydrogenase 2 genotypes with fasting plasma glucose levels in Japanese male and female workers. *Alcohol Alcohol.* 43: 143-147. http://dx.doi.org/10.1093/alcalc/agm173

Elbaz A, Carcaillon L, Kab S and Moisan F (2016). Epidemiology of Parkinson's disease. *Rev. Neurol.* 172: 14-26. http://dx.doi.org/10.1016/j.neurol.2015.09.012

Evans JR, Cummins G, Breen DP, Foltynie T, et al. (2016). Comparative epidemiology of incident Parkinson's disease in Cambridgeshire, UK. *J. Neurol. Neurosurg. Psychiatry* jnnp-2015-312581. http://dx.doi.org/10.1136/jnnp-2015-312581

Fitzmaurice AG, Rhodes SL, Cockburn M, Ritz B, et al. (2014). Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease. *Neurology* 82: 419-426. http://dx.doi.org/10.1212/WNL.0000000000000083

Goudarzian M, Khaligh A, Fourozan R, Jamal Mirmoosavi S, et al. (2015). The rs1572931 polymorphism of the RAB7L1 gene promoter is associated with reduced risk of Parkinson's disease. *Neurol. Res.* 37: 1029-1031. http://dx.doi.org/10.1179/1743132815Y.0000000085

Gupta SP, Kamal R, Mishra SK, Singh MK, et al. (2015). Association of polymorphism of neuronal nitric oxide synthase gene with risk to Parkinson's disease. *Mol. Neurobiol.*

Hao PP, Chen YG, Wang JL, Wang XL, et al. (2011). Meta-analysis of aldehyde dehydrogenase 2 gene polymorphism and Alzheimer's disease in East Asians. *Can. J. Neurol. Sci.* 38: 500-506. http://dx.doi.org/10.1017/S0317167100011938

Hughes AJ, Daniel SE, Kilford L and Lees AJ (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J. Neurol. Neurosurg. Psychiatry* 55: 181-184. http://dx.doi.org/10.1136/jnnp.55.3.181

Kang TS, Woo SW, Park HJ, Lee Y, et al. (2009). Comparison of genetic polymorphisms of CYP2E1, ADH2, and ALDH2 genes involved in alcohol metabolism in Koreans and four other ethnic groups. *J. Clin. Pharm. Ther.* 34: 225-230. http://dx.doi.org/10.1111/j.1365-2710.2008.00986.x

Kenborg L, Lassen CF, Ritz B, Andersen KK, et al. (2015). Lifestyle, family history, and risk of idiopathic Parkinson disease: a large Danish case-control study. *Am. J. Epidemiol.* 181: 808-816. http://dx.doi.org/10.1093/aje/kwu332

Komatsu M, Shibata N, Ohnuma T, Kuerban B, et al. (2014). Polymorphisms in the aldehyde dehydrogenase 2 and dopamine b hydroxylase genes are not associated with Alzheimer's disease. *J Neural Transm (Vienna)* 121: 427-432. http://dx.doi.org/10.1007/s00702-013-1112-z

Lai CL, Li YP, Liu CM, Hsieh HS, et al. (2013). Inhibition of human alcohol and aldehyde dehydrogenases by cimetidine and assessment of its effects on ethanol metabolism. *Chem. Biol. Interact.* 202: 275-282. http://dx.doi.org/10.1016/j.cbi.2012.11.016

Lee SL, Lee YP, Wu ML, Chi YC, et al. (2015). Inhibition of human alcohol and aldehyde dehydrogenases by aspirin and salicylate: assessment of the effects on first-pass metabolism of ethanol. *Biochem. Pharmacol.* 95: 71-79. http://dx.doi.org/10.1016/j.bcp.2015.03.003

Leiphon LJ and Picklo MJ, Sr. (2007). Inhibition of aldehyde detoxification in CNS mitochondria by fungicides. *Neurotoxicology* 28: 143-149. http://dx.doi.org/10.1016/j.neuro.2006.08.008

Li QY, Zhao NM, Ma JJ, Duan HF, et al. (2015). ALDH2*2 allele is a negative risk factor for cerebral infarction in Chinese women. *Biochem. Genet.* 53: 260-267. http://dx.doi.org/10.1007/s10528-015-9686-9

Liu CC, Li CY, Lee PC and Sun Y (2016). Variations in incidence and prevalence of Parkinson's disease in Taiwan: a population-based nationwide study. *Parkinsons Dis.* 2016: 8756359. http://dx.doi.org/10.1155/2016/8756359

Meyer MJ, Mosely DE, Amarnath V and Picklo MJ, Sr. (2004). Metabolism of 4-hydroxy-trans-2-nonenal by central nervous system mitochondria is dependent on age and NAD+ availability. *Chem. Res. Toxicol.* 17: 1272-1279. http://dx.doi.org/10.1021/tx049843k

Vermeer LM, Florang VR and Doorn JA (2012). Catechol and aldehyde moieties of 3,4-dihydroxyphenylacetaldehyde contribute to tyrosine hydroxylase inhibition and neurotoxicity. *Brain Res.* 1474: 100-109. http://dx.doi.org/10.1016/j.brainres.2012.07.048

Wang L, Cheng L, Li NN, Yu WJ, et al. (2015a). Genetic analysis of SLC41A1 in Chinese Parkinson's disease patients. *Am. J. Med. Genet. Part B* 168: 706-711.

Wang S, Xu YF, Ding XY, Liu ZR, et al. (2015b). Association between bone marrow stromal cell antigen 1 gene polymorphisms and the susceptibility to Parkinson's disease: a meta-analysis. *Neurosci. Lett.* 599: 120-124. http://dx.doi.org/10.1016/j.neulet.2015.05.026

Yao CT, Cheng CA, Wang HK, Chiu SW, et al. (2011). The role of ALDH2 and ADH1B polymorphism in alcohol consumption and stroke in Han Chinese. *Hum. Genomics* 5: 569-576. http://dx.doi.org/10.1186/1479-7364-5-6-569

Zhang D, Jiang H and Xie J (2014). Alcohol intake and risk of Parkinson's disease: a meta-analysis of observational studies. *Mov. Disord.* 29: 819-822. http://dx.doi.org/10.1002/mds.25863

Zhang X, Ye YL, Wang YN, Liu FF, et al. (2015). Aldehyde dehydrogenase 2 genetic variations may increase susceptibility to Parkinson's disease in Han Chinese population. *Neurobiol. Aging* 36: 2660. e9-13.

Zhou S, Huriletemuer, Wang J, Zhang C, et al. (2010). Absence of association on aldehyde dehydrogenase 2 (ALDH2) polymorphism with Mongolian Alzheimer patients. *Neurosci. Lett.* 468: 312-315. http://dx.doi.org/10.1016/j.neulet.2009.11.022