



Role of *ADH1B* rs1229984 and *ALDH2* rs671 gene polymorphisms in the development of Alzheimer's disease

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ABSTRACT. In the present study, we investigated the association between *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms and the development of Alzheimer's disease in a Chinese population. Genotyping of the *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms was carried out by polymerase chain reaction-restriction fragment length polymorphism. Logistic regression analyses revealed that the AA genotype of *ADH1B* rs1229984 was associated with an increased risk of Alzheimer's disease (OR = 2.54, 95%CI = 1.19-5.41). In addition, *ADH1B* rs1229984 was also associated with elevated risk of Alzheimer's disease in both dominant (OR = 1.78, 95%CI = 1.09-2.93) and recessive (OR = 2.33, 95%CI = 1.18-4.57) models. For *ALDH2* rs671, the AA genotype was correlated with an increased risk of Alzheimer's disease as compared to the GG genotype (OR = 4.57, 95%CI = 1.60-14.01). The *ALDH2* rs671 polymorphism was associated with Alzheimer's in both dominant (OR = 1.79, 95%CI = 1.08-2.97) and recessive (OR = 4.17, 95%CI = 1.49-12.67) models. In conclusion,

we observed that *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms increased the risk of Alzheimer's disease in all the genetic models.

Key words: *ADH1B*; *ALDH2*; Polymorphism; Alzheimer's disease

INTRODUCTION

Alzheimer's disease is a chronic neurodegenerative disease that usually starts slowly, but worsens over time. It is estimated that the prevalence of Alzheimer's disease is approximately 1-2% in people above 65 years of age (Campion et al., 1999), and 25-35% in people above 80 years of age (Hebert et al., 2003). The pathogenesis of Alzheimer's disease involves many environmental factors such as age, brain trauma or tumors, infection, and poisoning (Ting et al., 2016). A study conducted in 11,884 twins has shown that genetic predisposition accounts for 58-79% of Alzheimer's disease cases (Gatz et al., 2006). Previous studies have indicated that genetic polymorphisms in protein tyrosine kinase 2 β , presenilin 2, apolipoprotein E, cytochrome 46A1, disrupted-in-schizophrenia-1, 3-hydroxy-3-methylglutaryl-CoA reductase, and sortilin receptor 1 all play essential roles in the development of this disease (Chang et al., 2016; Huang et al., 2016; Jia et al., 2016; Li et al., 2016; Suzuki et al., 2016; Zhang et al., 2016; Zheng et al., 2016).

Previous studies have reported that alcohol consumption is associated with risk of Alzheimer's disease (Piazza-Gardner et al., 2013; Berntsen et al., 2015; Ilomaki 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). *ADH1B* and *ALDH2* are two common ADH and ALDH proteins, and polymorphisms in *ADH1B* rs1229984 and *ALDH2* rs671 could cause alterations in enzymatic activities of these proteins, thus leading to the development of nervous system diseases including Alzheimer's disease (Song et al., 2014; Hu et al., 2015; Yoshimasu et al., 2015; Zhang et al., 2015). Therefore, we investigated the association between *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms and the development of Alzheimer's disease in a Chinese population.

MATERIAL AND METHODS

Patients

Alzheimer's disease patients (N = 115) and control subjects (N = 236) were recruited from the Department of Neurology at the Remin Hospital of Wuhan University between October 2013 and April 2015. Alzheimer's disease was diagnosed based on NINCDS-ADRDA criteria proposed by the Department of Health and Human Services Task Force on Alzheimer's Disease (McKhann et al., 1984). Patients with a history of brain tumor, secondary Alzheimer's disease were excluded from this study

Over the same period, control subjects were recruited from patients who visit the outpatient clinics in the Department of Pneumology, Department of Dermatology, and Department of Orthopedics at the Remin Hospital of Wuhan University. Control subjects were confirmed to be without histories of brain tumor, Alzheimer's disease, neurological diseases, and end-stage liver or kidney diseases.

The general characteristics of Alzheimer's disease patients and control subjects were collected from a questionnaire, which was filled during face-to-face interviews by doctors or nurses. Information obtained from the study participants included gender, age, body mass index, family history of Alzheimer's disease, tobacco smoking, and alcohol drinking. A written informed consent was obtained from study subjects prior to their enrollment, and all study procedures were approved by the Ethics Committee of the Remin Hospital of Wuhan University.

Of the investigated patients and controls, the mean ages were 68.54 ± 9.30 and 67.10 ± 9.59 years, respectively. There were 41 (35.65%) females and 74 (64.35%) males in the Alzheimer's disease group. In the control group, there were 87 (36.86%) females and 149 (63.14%) males.

DNA extraction and genotyping analysis

Peripheral blood (5 mL) from each subject was drawn and collected into vacuum tubes with 5% ethylenediaminetetraacetic acid (EDTA). DNA extraction was performed using the TIANamp Blood DNA Kit (Tiangen, Beijing, China), following the manufacturer protocol. Genotyping of *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms was carried out via polymerase chain reaction (PCR)-restriction fragment length polymorphism analysis. The forward and reverse primer sequences for *ADH1B* rs1229984 were 5'-AATCTTTTGTGAATCTGAACAG-3' and 5'-GAAGGGGGGTCACCAGGTTG-3', respectively. The forward and reverse primers for *ALDH2* Glu487Lys were 5'-GTCAACTGCTATGATGTGTTTGG-3' and 5'-CCACCAGCAGACCCTCAAG-3', respectively. The restriction enzymes used for *ADH1B* rs1229984 and *ALDH2* rs671 digestion were *Mae*III and *Eco*RI, respectively. The genotypes of *ADH1B* rs1229984 and *ALDH2* rs671 were determined using 3% agarose gel electrophoresis and EB staining.

Statistical analysis

Data are reported as percentages of total (categorical variables) or as means \pm SD (continuous variables). The Student *t*-test was used to determine differences in means, and Pearson χ^2 or Fisher exact tests were used to assess inter-group differences. Allele frequencies were calculated by the gene-counting method, and each genotype was tested for departure from Hardy-Weinberg equilibrium (HWE) in the control population using χ^2 tests. Logistic regression analysis was performed in order to determine the odds ratios (OR) and 95% confidence intervals (95%CI) associated with risk to Alzheimer's disease, and the controls were used as the reference group. Statistical significance was set at $P < 0.05$.

RESULTS

As confirmed using the χ^2 test, patients with Alzheimer's disease were more likely to have a family history of Alzheimer's disease ($\chi^2 = 20.70$, $P < 0.001$), and have no habit of alcohol consumption ($\chi^2 = 4.58$, $P = 0.03$) (Table 1). However, no significant difference was observed between the Alzheimer's disease patients and controls with regards to age ($\chi^2 = 0.62$, $P = 0.43$), gender ($\chi^2 = 0.05$, $P = 0.83$), BMI ($\chi^2 = 0.23$, $P = 0.63$), and tobacco smoking ($\chi^2 = 0.25$, $P = 0.62$).

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

Variables	Patients (N = 115)	%	Controls (N = 236)	%	χ^2 test	P value
Age (years)						
<65	37	32.17	86	36.44		
≥ 65	78	67.83	150	63.56	0.62	0.43
Gender						
Females	41	35.65	87	36.86		
Males	74	64.35	149	63.14	0.05	0.83
BMI						
<24	77	66.96	164	69.49		
≥ 24	38	33.04	72	30.51	0.23	0.63
Family history of Alzheimer's disease						
No	93	80.87	226	95.76		
Yes	22	19.13	10	4.24	20.70	<0.001
Alcohol consumption						
No	88	76.52	154	65.25		
Yes	27	23.48	82	34.75	4.58	0.03
Tobacco smoking						
No	66	57.39	142	60.17		
Yes	49	42.61	94	39.83	0.25	0.62

The genotype distributions of *ADH1B* rs1229984 and *ALDH2* rs671 in the two study groups are shown in Table 2. Statistical analysis using the χ^2 test revealed significant differences in the genotype distributions of *ADH1B* rs1229984 ($\chi^2 = 7.55$, $P = 0.02$) and *ALDH2* rs671 ($\chi^2 = 11.65$, $P = 0.003$) between Alzheimer's disease patients and controls (Table 2). We found that genotype distributions of *ADH1B* rs1229984 and *ALDH2* rs671 were in agreement with HWE in controls. However, the genotype distribution of *ALDH2* rs671 was in HWE in the patient group.

Table 2. Genotype distributions of *ADH1B* rs1229984 and *ALDH2* rs671 in the two study groups.

Variables	Patients (N = 115)	%	Controls (N = 236)	%	χ^2 test	P value	HWE in patients		HWE in controls	
							χ^2 test	P value	χ^2 test	P value
<i>ADH1B</i> rs1229984										
GG	40	30.4	73	37.5						
GA	55	49.7	108	52.8						
AA	20	19.9	33	9.7	7.55	0.02	0.30	0.86	0.02	0.88
<i>ALDH2</i> rs671										
GG	72	62.61	177	75.00						
GA	30	26.09	52	22.03						
AA	13	11.30	7	2.97	11.65	0.003	9.80	0.002	1.67	0.20

Logistic regression analysis revealed that the AA genotype of *ADH1B* rs1229984 was associated with an increased risk of Alzheimer's disease (OR = 2.54, 95%CI = 1.19-5.41), and that *ADH1B* rs1229984 was associated with elevated risk of Alzheimer's disease in both dominant (OR = 1.78, 95%CI = 1.09-2.93) and recessive (OR = 2.33, 95%CI = 1.18-4.57) models (Table 3). For *ALDH2* rs671, the AA genotype was correlated with increased risk of Alzheimer's disease as compared with the GG genotype (OR = 4.57, 95%CI = 1.60-14.01). Finally, the *ALDH2* rs671 polymorphism was associated with development of Alzheimer's disease in both dominant (OR = 1.79, 95%CI = 1.08-2.97) and recessive (OR = 4.17, 95%CI = 1.49-12.67) models.

Table 3. Association between *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms and Alzheimer's disease risk.

Variables	Patients (N = 115)	%	Controls (N = 236)	%	OR (95%CI) ¹	P value
<i>ADH1B</i> rs1229984						
Codominant						
GG	35	30.43	89	37.71	1.0 (Ref.)	-
GA	57	49.57	125	52.97	1.16 (0.68-1.98)	0.56
AA	23	20.00	23	9.75	2.54 (1.19-5.41)	0.01
Dominant						
GG	35	30.43	89	37.71	1.0 (Ref.)	-
GA+AA	103	89.57	147	62.29	1.78 (1.09-2.93)	0.01
Recessive						
GG+GA	92	80.00	214	90.68	1.0 (Ref.)	-
AA	23	20.00	23	9.75	2.33 (1.18-4.57)	0.01
<i>ALDH2</i> rs671						
Codominant model						
GG	72	62.61	177	75.00	1.0 (Ref.)	-
GA	30	26.09	52	22.03	1.42 (0.80-2.47)	0.19
AA	13	11.30	7	2.97	4.57 (1.60-14.01)	0.01
Dominant						
GG	72	62.61	177	75.00	1.0 (Ref.)	-
GA+AA	43	37.39	59	25.00	1.79 (1.08-2.97)	0.02
Recessive						
GG+GA	102	88.70	229	97.03	1.0 (Ref.)	-
AA	13	11.30	7	2.97	4.17 (1.49-12.67)	0.02

¹Adjusted for gender, age, family history of Alzheimer's disease, and alcohol consumption.

The interactions between the two gene polymorphisms and alcohol consumption with respect to risk of Alzheimer's disease are illustrated in Table 4. We observed that *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms are significantly associated with family history of Alzheimer's disease and alcohol consumption in the risk of this disease.

Table 4. Interaction between *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms and drinking status in risk of Alzheimer's disease.

Variables	<i>ADH1B</i> rs1229984		<i>ALDH2</i> rs671	
	Spearman correlation coefficient	P value	Spearman correlation coefficient	P value
Age (years)	0.047	0.36	0.036	0.49
Gender	0.063	0.22	0.059	0.32
BMI	0.061	0.27	0.040	0.42
Family history of Alzheimer's disease	0.172	<0.001	0.265	<0.001
Alcohol consumption	0.131	0.02	0.160	0.04
Tobacco smoking	0.035	0.48	0.045	0.37

DISCUSSION

Polymorphisms in *ADH1B* rs1229984 and *ALDH2* rs671 may influence the expression and function of proteins in enzyme metabolism, because the single nucleotide polymorphism could change the expression and quantities of protein in individuals. In the present study, we observed that the AA genotype of *ADH1B* rs1229984 or *ALDH2* rs671 was associated with the risk to Alzheimer's disease in a Chinese population.

Previous studies have reported on the relationship between alcohol consumption and Alzheimer's disease, and have indicated that low levels of alcohol consumption could protect

against dementia and reduce the mortality rate of mild Alzheimer's disease (Berntsen et al., 2015; Ilomaki et al., 2015). However, one large-scale study has reported that frequent alcohol consumption is associated with elevated risk of dementia (Langballe et al., 2015). Ethanol is not toxic to the human body; however, the acetaldehyde oxidized from ethanol is toxic. ADH and ALDH oxidize ethanol to acetaldehyde, which is then converted to acetate in the liver. The enzymatic activities of ADH and ALDH could influence the level of acetaldehyde in the human body. Therefore, polymorphisms in *ADH1B* and *ALDH2* could lead to differences in ethanol metabolism between individuals, and affect the accumulation of acetaldehyde in the human body.

Previous studies have reported that *ALDH2* polymorphism is associated with development of Alzheimer's disease; however, the results were inconsistent among studies (Kamino et al., 2000; Shin et al., 2005; Wang et al., 2008; Zhou et al., 2010; Hao et al., 2011; Komatsu et al., 2014). Kamino et al. (2000) carried out a case-control study with 447 patients and age- and gender-matched controls, and indicated that *ALDH2* deficiency is a risk for late-onset Alzheimer's disease in the Japanese population. However, some studies reported opposite results. Shin et al. (2005) reported that the AA genotype of *ALDH2* does not play an important role in the etiology of dementia in the Korean population. Similarly, Zhou et al. (2010) reported that *ALDH2* does not play a role in the development of Alzheimer's disease in the Mongolian population. Komatsu et al. (2014) also did not find any significant association between *ALDH2* polymorphism and risk of Alzheimer's disease in the Japanese population. In a recent meta-analysis with 821 Alzheimer's disease patients and 1380 healthy controls, it was suggested that the GA and AA genotypes of *ALDH2* increase the risk of Alzheimer's disease in East Asian men (Hao et al., 2011). This was in agreement with our results, which showed that the AA genotype of *ALDH2* rs671 increased the risk of Alzheimer's development. It is possible that the discrepancies between individual studies are due to differences in populations, sample sizes, as well as case selection.

To date, no studies have reported on the association between *ADH1B* polymorphism and risk of Alzheimer's disease. Therefore, here we show for the first time the role of *ADH1B* rs1229984 in Alzheimer's disease. However, the exact molecular mechanisms underlying the pathogenesis of Alzheimer's disease remain to be elucidated in future studies.

Two limitations should be noted in our study. First, the study subjects were all recruited from one hospital within China, which may not be representative of the global population. Second, the sample sizes of this study were relatively small, which may reduce the statistical power of our analyses.

In conclusion, we observed that *ADH1B* and *ALDH2* polymorphisms increased the risk of Alzheimer's disease development. Therefore, *ADH1B* and *ALDH2* genetic polymorphisms may be risk factors for Alzheimer's disease.

Conflicts of interest

The authors declare no conflict of interest.

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REFERENCES

- Asakage T, Nakao K, Ebihara Y, Fujishiro Y, et al. (2007). A clinical study of post-cricoid carcinoma. *Acta Otolaryngol.* 559 (Suppl.): 118-122. doi: 10.1080/03655230701599354.
- Berntsen S, Kragstrup J, Siersma V, Waldemar G, et al. (2015). Alcohol consumption and mortality in patients with mild Alzheimer's disease: a prospective cohort study. *BMJ Open* 5: e007851. <http://dx.doi.org/10.1136/bmjopen-2015-007851>
- Campion D, Dumanchin C, Hannequin D, Dubois B, et al. (1999). Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. *Am. J. Hum. Genet.* 65: 664-670. <http://dx.doi.org/10.1086/302553>
- Chang XL, Tan L, Tan MS, Wang HF, et al. (2016). Association of HMGCR polymorphism with late-onset Alzheimer's disease in Han Chinese. *Oncotarget* 7: 22746-22751.
- 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. doi: 10.1093/alcalc/agn173.
- Gatz M, Reynolds CA, Fratiglioni L, Johansson B, et al. (2006). Role of genes and environments for explaining Alzheimer disease. *Arch. Gen. Psychiatry* 63: 168-174. <http://dx.doi.org/10.1001/archpsyc.63.2.168>
- 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>
- Hebert LE, Scherr PA, Bienias JL, Bennett DA, et al. (2003). Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch. Neurol.* 60: 1119-1122. <http://dx.doi.org/10.1001/archneur.60.8.1119>
- Hu MC, Lee SY, Wang TY, Chang YH, et al. (2015). Interaction of DRD2TaqI, COMT, and ALDH2 genes associated with bipolar II disorder comorbid with anxiety disorders in Han Chinese in Taiwan. *Metab. Brain Dis.* 30: 755-765. <http://dx.doi.org/10.1007/s11011-014-9637-x>
- Huang CC, Liu ME, Kao HW, Chou KH, et al. (2016). Effect of Alzheimer's disease risk variant rs3824968 at SORL1 on regional gray matter volume and age-related interaction in adult lifespan. *Sci. Rep.* 6: 23362. <http://dx.doi.org/10.1038/srep23362>
- Iilomaki J, Jokanovic N, Tan EC and Lonroos E (2015). Alcohol consumption, dementia and cognitive decline: an overview of systematic reviews. *Curr. Clin. Pharmacol.* 10: 204-212. <http://dx.doi.org/10.2174/157488471003150820145539>
- Jia F, Liu Z, Song N, Du X, et al. (2016). The association between CYP46A1 rs4900442 polymorphism and the risk of Alzheimer's disease: A meta-analysis. *Neurosci. Lett.* 620: 83-87. <http://dx.doi.org/10.1016/j.neulet.2016.03.048>
- Kamino K, Nagasaka K, Imagawa M, Yamamoto H, et al. (2000). Deficiency in mitochondrial aldehyde dehydrogenase increases the risk for late-onset Alzheimer's disease in the Japanese population. *Biochem. Biophys. Res. Commun.* 273: 192-196. <http://dx.doi.org/10.1006/bbrc.2000.2923>
- Kang WJ, Ko MH, Lee DS and Kim S (2009). Bioimaging of geographically adjacent proteins in a single cell by quantum dot-based fluorescent resonance energy transfer. *Proteomics Clin. Appl.* 3: 1383-1388. doi: 10.1002/prca.200900077.
- 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.* 121: 427-432. <http://dx.doi.org/10.1007/s00702-013-1112-z>
- Langballe EM, Ask H, Holmen J, Stordal E, et al. (2015). Alcohol consumption and risk of dementia up to 27 years later in a large, population-based sample: the HUNT study, Norway. *Eur. J. Epidemiol.* 30: 1049-1056. <http://dx.doi.org/10.1007/s10654-015-0029-2>
- Lee YS, Yi HS, Suh YG, Byun JS, et al. (2015). Blockade of retinol metabolism protects T cell-induced hepatitis by increasing migration of regulatory T cells. *Mol. Cells* 38: 998-1006. doi: 10.14348/molcells.2015.0218.
- Li YQ, Tan MS, Wang HF, Tan CC, et al. (2016). Common variant in PTK2B is associated with late-onset Alzheimer's disease: A replication study and meta-analyses. *Neurosci. Lett.* 621: 83-87. <http://dx.doi.org/10.1016/j.neulet.2016.04.020>
- McKhann G, Drachman D, Folstein M, Katzman R, et al. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34: 939-944. <http://dx.doi.org/10.1212/WNL.34.7.939>
- Piazza-Gardner AK, Gaffud TJ and Barry AE (2013). The impact of alcohol on Alzheimer's disease: a systematic review. *Aging Ment. Health* 17: 133-146. <http://dx.doi.org/10.1080/13607863.2012.742488>
- Shin IS, Stewart R, Kim JM, Kim SW, et al. (2005). Mitochondrial aldehyde dehydrogenase polymorphism is not associated with incidence of Alzheimer's disease. *Int. J. Geriatr. Psychiatry* 20: 1075-1080. <http://dx.doi.org/10.1002/gps.1401>

- Song K, Kim S, Na JY, Park JH, et al. (2014). Rutin attenuates ethanol-induced neurotoxicity in hippocampal neuronal cells by increasing aldehyde dehydrogenase 2. *Food Chem. Toxicol.* 72: 228-233. <http://dx.doi.org/10.1016/j.fct.2014.07.028>
- Suzuki A, Shibata N, Kasanuki K, Nagata T, et al. (2016). Genetic association between presenilin 2 polymorphisms and Alzheimer's disease and dementia of Lewy body type in a Japanese population. *Dement. Geriatr. Cogn. Dis. Extra* 6: 90-97. <http://dx.doi.org/10.1159/000444080>
- Ting SK, Hao Y, Chia PS, Tan EK, et al. (2016). Clinicopathological correlation of psychosis and brain vascular changes in Alzheimer's disease. *Sci. Rep.* 6: 20858. <http://dx.doi.org/10.1038/srep20858>
- Wang B, Wang J, Zhou S, Tan S, et al. (2008). The association of mitochondrial aldehyde dehydrogenase gene (ALDH2) polymorphism with susceptibility to late-onset Alzheimer's disease in Chinese. *J. Neurol. Sci.* 268: 172-175. <http://dx.doi.org/10.1016/j.jns.2007.12.006>
- Yoshimasu K, Mure K, Hashimoto M, Takemura S, et al. (2015). Genetic alcohol sensitivity regulated by ALDH2 and ADH1B polymorphisms is strongly associated with depression and anxiety in Japanese employees. *Drug Alcohol Depend.* 147: 130-136. <http://dx.doi.org/10.1016/j.drugalcdep.2014.11.034>
- Zhang LL, Wang YQ, Fu B, Zhao SL, et al. (2015). Aldehyde dehydrogenase 2 (ALDH2) polymorphism gene and coronary artery disease risk: a meta-analysis. *Genet. Mol. Res.* 14: 18503-18514. <http://dx.doi.org/10.4238/2015.December.23.38>
- Zhang XY, Wang HF, Tan MS, Wan Y, et al. (2016). Association of DISC1 polymorphisms with late-onset Alzheimer's disease in Northern Han Chinese. *Mol. Neurobiol.* [Epub ahead of print]
- Zheng L, Duan J, Duan X, Zhou W, et al. (2016). Association of Apolipoprotein E (ApoE) polymorphism with Alzheimer's disease in Chinese population. *Curr. Alzheimer Res.* 13: 912-917. <http://dx.doi.org/10.2174/1567205013666160401115307>
- Zhou S, Huriletmuer, 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>