Neuroscience Letters 664 (2018) 79–83

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research paper

ABCA1 rs2230805 and rs2230806 common gene variants are associated with Alzheimer's disease

Ágnes Fehér*, Zsófia Giricz, Anna Juhász, Magdolna Pákáski, Zoltán Janka, János Kálmán

University of Szeged, Department of Psychiatry, Szeged, Hungary

ARTICLE INFO

Keywords:
Alzheimer's disease
ATP-binding cassette transporter subfamily A member 1 (*ABCA1*)
Single nucleotide polymorphism (SNP)
Association study

ABSTRACT

The ATP-binding cassette, sub-family A, member 1 gene (*ABCA1*) is a relevant positional and functional candidate gene for Alzheimer's disease (AD). A case-control association study of genetic variations covering the *ABCA1* locus was performed in relation to AD risk in a Hungarian sample. Five single nucleotide polymorphisms (rs2422493: C-477T, rs2740483: G-17C, rs2230805: G474A/L158L, rs2230806: G656A/R219 K and rs2066718: G2311A/V771 M) were genotyped in 431 AD patients and 302 cognitively healthy, elderly controls. In single marker analysis, significant associations were found in the case of rs2230805 and rs2230806 polymorphisms: the minor A allele containing genotypes for both polymorphisms were more frequent in the control compared to the AD group. Haplotype analysis revealed that rs2230805, rs2230806 and rs2066718 polymorphisms created a linkage disequilibrium (LD) block with a strong LD between rs2230805 and rs2230806 polymorphisms. In the haplotype risk association tests, A-A-G haplotype of the rs2230805-rs2230806-rs2066718 polymorphisms was found to be nominally significantly more frequent in the control group. After correcting *p* values for multiple testing, only the effects of the rs2230805 and rs2230806 polymorphisms remained significant in the recessive model suggesting a modest protective effect of their minor alleles in AD, which should be interpreted with considerable caution, until further studies elucidate their role in AD pathology.

1. Introduction

The non-familial late-onset (> 65 years of age at-onset) form of Alzheimer's disease (AD) is most likely caused by a complex interaction of genetic and environmental factors. The most predictive genetic risk factor for late-onset AD is the ε4 variant of the apolipoprotein E (*APOE*; MIM#107741) gene. The *APOE* ε2/ε3/ε4 isoforms (defined by rs429358 and rs7412 polymorphisms) influence the lipid compounds of the cell membrane and thereby the cleavage of the amyloid-β protein precursor (AβPP) creates aggregation prone amyloid-ß (Aß) peptides [25]. The common genetic variants that have been associated with late-onset AD other than *APOE* ε4 allele have small effect sizes and still a great portion of the predicted heritability for AD remains unrevealed [14].

The ATP-binding cassette, sub-family A, member 1 gene (*ABCA1*; MIM# 600046) is a positional and functional candidate gene for AD. The *ABCA1* gene is located near to an AD linkage peak on chromosome 9 at position q22 [2,18,19]. The encoded product of the *ABCA1* gene is a membrane-associated transporter that functions as an efflux pump for cholesterol and phospholipids from cell membranes to lipid-free apolipoprotein A-I (apoA-I) and apoE in the cellular lipid removal pathway [13,28].

Controlling apoE lipidation, ABCA1 likely has a role in the pathogenesis of AD, which is supported by a number of studies reporting significant impact of ABCA1 on Aβ deposition and clearance in AD model mice [11]. AβPP transgenic mice lacking the *ABCA1* gene have increased Aβ deposition and cognitive decline with diminished levels of soluble apoE, while transgenic mice overexpressing *ABCA1* in the brain have fewer Aβ plaques [11].

In humans, genetic studies further support the involvement of *ABCA1* in AD. The strongest indication for investigating the relationship between lipid metabolism and neurodegeneration came from the association of *APOE* gene variants and the risk for late-onset AD. Genetic variations of the *ABCA1* gene have been studied extensively in relation to cholesterol metabolism and neurodegeneration after two important discoveries. Mutations in the *ABCA1* gene were reported as the primary cause of Tangier disease characterized by extremely low levels of high density lipoprotein [3,4,24]. Non-synonymous common genetic variation in the *ABCA1* gene was found to be associated with altered lipoprotein levels and a modified risk for coronary artery disease [6].

Several case-control association studies attempted to reveal the

* Corresponding author at: University of Szeged, Department of Psychiatry, 57 Kálvária Ave, Szeged, H-6724, Hungary.
E-mail addresses: feher.agnes@med.u-szeged.hu, feherag@gmail.com (Á. Fehér).

https://doi.org/10.1016/j.neulet.2017.11.027
Received 29 May 2017; Received in revised form 1 November 2017; Accepted 9 November 2017
Available online 10 November 2017
0304-3940/

relationship between *ABCA1* common polymorphisms and AD susceptibility; however, despite the biological plausibility of this locus as a modulator of AD risk, contradictory results were reported (*positive findings:* [10,20,22,26,27,31–33] *negative results:* [5,12,15] *meta-analyses:* [9,30]). In a recent study all *ABCA1* coding regions were sequenced and found to have a significantly higher proportion of rare non-synonymous variants in the control compared the AD group suggesting a protective effect [16].

The present association study was designed to give further data on five potentially relevant single nucleotide polymorphisms (SNPs) in a well-defined Hungarian sample. SNPs selected for this study consisted of two promoter polymorphisms (rs2422493: C-477T and rs2740483: G-17C), and three gene variants – synonymous (rs2230805: G474A/L158L) and non-synonymous (rs2230806: G656A/R219 K and rs2066718: G2311A/V771 M) – in the coding region. Applying single-marker and haplotype analyses, we aimed to evaluate the possible association of the above mentioned *ABCA1* genetic variations with the susceptibility to late-onset AD either alone or in epistasis with *APOE* ε2/ε3/ε4 polymorphism.

2. Subjects and methods

Our case-control study population consisted of 431 patients with late-onset AD (74.6 ± 6.8 years of age (mean ± SD), men 34.5%) and 302 cognitively healthy, elderly control individuals (74.1 ± 7.2 years of age (mean ± SD), men 35.5%) of Hungarian Caucasian descent. Demographic characteristics of the investigated groups are presented in Table 1. The AD patients were recruited from the Memory Clinic of the Department of Psychiatry, University of Szeged, Hungary. All diagnoses of late-onset AD were set according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria [17]. No patient had a family history raising suspicion of familial AD and the minimum age at onset was 65 years.

Global cognitive performance was measured by the Mini-Mental State Examination (MMSE). The mean MMSE score in the AD group was 17.5 ± 5.6 (mean ± SD), while in the control group MMSE scores were higher than 28 points and none of the control individuals had any verified symptoms of dementia. The clinical evaluation of all study participants was set without any prior knowledge of genetic background. All recruitment and protocols were conducted with written informed consent and with the approval of the Ethics Committee of the Hungarian Council on Science and Health (ETT-TUKEB).

Blood was drawn by venous puncture, and genomic DNA was extracted from whole blood by standard procedures using the Roche High Pure PCR Template Preparation Kit (Roche Holding AG, Basel, Switzerland). Genotyping of the investigated polymorphisms was performed by applying commercial TaqMan single-nucleotide polymorphism assays (Thermo Fisher Scientific/Applied Biosystems/Waltham, Massachusetts, USA). The polymerase chain reaction amplification was conducted in single-plex reactions in 96-well plates with a total volume of 20 μl using the following amplification protocol: 95 °C for 10 min, and 40 cycles of 92 °C for 15 s, and 60 °C for 1 min. Fluorescence measurements were performed using the CFX96 Touch Real-Time PCR Detection System (Bio-Rad Laboratories, Inc., Hercules, CA).

Controls and AD patients were analyzed using *t*-test for continuous parameters (MMSE and age), whereas Fisher's exact and Pearson chi-square tests were used when categorical parameters (gender, allele and genotype frequencies) were compared. Binary logistic regression model was used to test for interaction between the *ABCA1* and *APOE* polymorphisms, and to calculate odds ratios (ORs) with 95% confidence intervals (CIs). To exclude Type I errors, we carried out Bonferroni's correction for multiple testing for 5 single-marker genotype comparisons in the genotypic model, 2 single-marker genotype comparisons in the recessive model for rs2230805 and rs2230806, and 5 haplotype comparisons.

All SNPs were tested for deviation from Hardy-Weinberg equilibrium (HWE) by Pearson chi-square test. The software Haploview 4.2 was used to conduct linkage disequilibrium (LD) calculations, haplotype analyses and to create LD blocks [1]. Power analysis was performed using G*Power 3.0 software [8], and the effect size was determined according to the method published by Cohen [7]. Based on the calculated effect sizes (w = 0.207 for rs2230805 and w = 0.173 for rs2230806), our study sample has 99% power at the significance level of 0.05 to detect differences in rs2230805 and rs2230806 genotype frequencies between AD and control groups. Given the calculated effect sizes (w = 0.106 for rs2422493, w = 0.124 for rs2740483, w = 0.1181 for rs2066718) comparing the different genotype frequencies between the two investigated groups, our study population has a power of 73% for rs2422493, 86% for rs2740483 and 82% for rs2066718 at the significance level of 0.05.

3. Results

A total of 733 samples were analyzed, including 431 AD patients and 302 elderly, cognitively healthy controls. Comparing the background parameters, no significant differences were found between AD cases and controls in mean age or in the distribution of genders, while MMSE mean scores were shown to differ significantly. Genotype frequencies were in agreement with HWE for both AD patients and controls. As shown in Table 1, the APOE ε3/ε4 and ε4/ε4 genotypes were significantly over-represented in the AD group as compared to the control group (χ^2 = 75.995 (5) p < 0.001).

Genotype frequencies of the investigated *ABCA1* gene variants are summarized in Table 2. Genotype distributions of the rs2422493, rs2740483 and rs2066718 polymorphisms did not differ significantly between the AD and control groups (rs2422493: χ^2 = 1.954 (2) p = 0.376; rs2740483: χ^2 = 2.958 (2) p = 0.228; rs2066718: χ^2 = 2.358 (2) p = 0.308). The frequency of the rs2230805 G/G genotype was significantly higher in the AD than in the control group (χ^2 = 7.787 (2) p = 0.020, corrected: p = 0.100). Compared to the controls, the rs2230806 G/G genotype was more frequent in the AD group (χ^2 = 5.245 (2) p = 0.073, corrected: p = 0.365).

As the minor A allele containing genotypes (A+) occurred more frequently in the control group for both rs2230805 and rs2230806 polymorphisms, a recessive model was also applied, and significant differences were found when G/G and A+ genotype frequencies were compared between cases and controls (Fisher's exact test: rs2230805: p = 0.011, corrected: p = 0.022; rs2230806: p = 0.024, corrected: p = 0.048).

The presence of the rs2230805 A allele significantly decreased the risk for AD considering G/G genotype carriers as reference category (OR = 0.674; 95% CI: 0.501-0.906; p = 0.009). Similarly, the A+ genotype of the rs2230806 polymorphism also showed a significantly

Table 1
Demographic characteristics and APOE genotype frequencies of the investigated groups.

	AD patients	Controls
age (years; mean ± SD)	74.6 ± 6.8	74.1 ± 7.2
sex (male/female (%))	34.5%/65.5%	35.5%/64.5%
MMSE (scores; mean ± SD)	17.5 ± 5.6	> 28
APOE genotypes*		
ε2/ε2 n (%)	0 (0.0%)	4 (1.3%)
ε2/ε3 n (%)	19 (4.4%)	28 (9.3%)
ε2/ε4 n (%)	10 (2.3%)	6 (2.0%)
ε3/ε3 n (%)	200 (46.4%)	209 (69.2%)
ε3/ε4 n (%)	169 (39.2%)	54 (17.9%)
ε4/ε4 n (%)	33 (7.7%)	1 (0.3%)

AD: Alzheimer's disease, MMSE: Mini Mental State Examination, APOE genotypes(*): apolipoprotein E genotypes defined by rs429358 and rs7412 polymorphisms.

Table 2
Genotype frequencies of the investigated *ABCA1* polymorphisms.

Chromosomal localization	Polymorphisms	AD patients	Controls
9:104928714	rs2422493		
	C/C	124 (28.8%)	75 (24.8%)
	C/T	196 (45.5%)	152 (50.4%)
	T/T	111 (25.7%)	75 (24.8%)
9:104928254	rs2740483		
	G/G	231 (53.6%)	155 (51.3%)
	G/C	158(36.7%)	126 (41.7%)
	C/C	42 (9.7%)	21 (7.0%)
9:104861748	rs2230805		
	G/G	245 (56.8%)	142 (47.0%)
	G/A	151 (35.0%)	136 (45.0%)
	A/A	35 (8.2%)	24 (8.0%)
9:104858586	rs2230806		
	G/G	231(53.6%)	136 (45.0%)
	G/A	163 (37.8%)	134 (44.4%)
	A/A	37 (8.6%)	32 (10.6%)
9:104826974	rs2066718		
	G/G	394 (91.4%)	281 (93.0%)
	G/A	37 (8.6%)	20 (6.6%)
	A/A	n.d.	1 (0.4%)

AD: Alzheimer's disease, *ABCA1*: ATP-binding cassette transporter subfamily A member 1, n.d.: not detected

decreased risk for AD when G/G genotype was the reference category (OR = 0.709; 95% CI: 0.528-0.953; $p = 0.023$). None of the investigated polymorphisms showed epistasis with *APOE* ε4 allele on AD risk in the logistic regression model ($p > 0.05$).

As shown in the LD plot for the genotyped *ABCA1* polymorphisms in Fig. 1, strong LD was detected between the rs2422493 and rs2740483 (D': 0.941; r^2: 0.322) and between the rs2230805 and rs2230806 polymorphisms (D': 0.92; r^2: 0.766); whereas moderate LD was found between the SNPs rs2230806 and rs2066718 (D': 0.766; r^2: 0.058). Two haplotype blocks were observed: rs2422493-rs2740483 (block 1) and rs2230805-rs2230806- rs2066718 (block 2). The most common

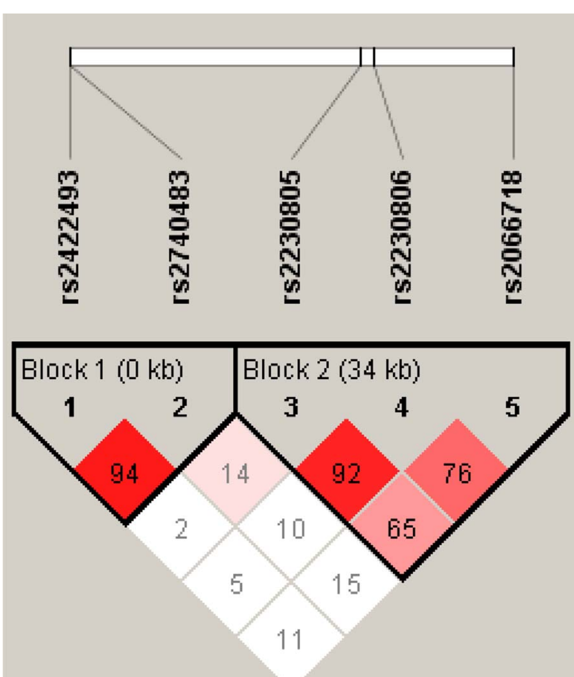

Fig. 1. Linkage disequilibrium characteristics of the investigated *ABCA1* polymorphisms: schematic representation of D' coefficients by pairs of SNPs. Haplotype blocks are rs2422493-rs2740483 (block 1) and rs2230805-rs2230806-rs2066718 (block 2).

Table 3
Haplotype frequencies of the investigated *ABCA1* rs2422493-rs2740483 (block 1) and rs2230805-rs2230806-rs2066718 (block 2) polymorphisms.

Haplotypes[a]	AD patients	Controls	Chi-square	P value
Block1				
T-G	47.8%	49.6%	0.543	0.461
C-C	27.4%	27.5%	0.006	0.937
C-G	24.8%	22.9%	0.563	0.453
Block 2				
G-G-G	69.8%	65.8%	2.464	0.117
A-A-G	20.9%	26.2%	5.77	0.016
G-A-G	3.8%	3.4%	0.000	0.983
A-A-A	3.6%	3.3%	0.116	0.733
A-G-G	1.9%	1.3%	1.672	0.196

AD: Alzheimer's disease, *ABCA1:* ATP-binding cassette transporter subfamily A member 1.

[a] Haplotypes of the *ABCA1* rs2422493-rs2740483 (block 1) and rs2230805-rs2230806-rs2066718 (block 2) polymorphisms. Chi-squares and p values for comparisons of the haplotype frequencies were determined by using the software Haploview 4.2 p.

haplotypes were T-G in block 1, and G-G-G and A-A-G in block 2 in both the AD and control groups.

In the haplotype risk association tests, block 1 showed no association with AD risk, but in block 2 a nominally significant association was found, as presented in Table 3. The G-G-G haplotype of the block 2 polymorphisms was more frequent, but not significantly, in the AD than in the control group ($\chi^2 = 0.154$ (1) $p = 0.116$; corrected $p = 0.580$), while the A-A-G haplotype had a significantly higher occurrence in the control group ($\chi^2 = 0.0307$ (1) $p = 0.016$, corrected: $p = 0.080$).

4. Discussion

We investigated the association between genetic variations in the *ABCA1* gene and AD susceptibility applying single-marker and haplotype analyses of five markers in the promoter and in the coding regions. Single marker case-control analysis revealed significant associations for rs2230805 and rs2230806 polymorphisms in the recessive model, which remained significant after correcting *p* values with Bonferroni's correction for multiple testing.

The minor A allele containing genotypes of the rs2230805 polymorphism were over-represented in controls compared to AD cases, therefore the presence of the A allele lessened the susceptibility to AD considering G/G genotype carriers as reference. Similarly, the presence of the rs2230806 minor A allele occurred more frequently in the control sample and associated with decreased AD risk when G/G genotype was the reference category. The genotype distributions of the rs2422493, rs2740483 and rs2066718 polymorphisms were similar in the AD and control groups without a statistically significant difference. No interactions were observed between *APOE* and the investigated *ABCA1* polymorphisms on diagnosis of AD.

Pairwise LD estimation revealed two haplotype blocks: rs2422493-rs2740483 (block 1) and rs2230805-rs2230806-rs2066718 (block 2) with strong (between rs2422493 and rs2740483, and between rs2230805 and rs2230806 polymorphisms), and moderate LD (between rs2230806 and rs2066718 polymorphisms) in our sample. In haplotype analysis a nominally significant association was found in the case of block 2. The A-A-G haplotype frequency was significantly higher in the control compared to the AD group; however, it did not remain significant after correcting for multiple testing. These results are in line with the single-marker findings that the minor alleles of the strongly linked rs2230805 and rs2230806 polymorphisms were found to be over-represented among controls in the single-marker analysis as well.

This is the first study investigating the Hungarian population, and according to the power estimation our medium sample size proved to be sufficient to detect differences in the genotype frequencies of the investigated *ABCA1* polymorphisms between AD and control samples.

The *ABCA1* genotype distributions observed in our control sample are comparable to earlier reports on other control populations of Caucasian origin [12,23,31,32].

Regarding the two investigated promoter SNPs (rs2422493 and rs2740483), two previous reports did not detect significant association with susceptibility to AD [22,27], while another study showed an association of the rs2422493 T/T genotype with the disease [31]. Significant interaction effects on AD risk were also detected for rs2422493 with polymorphisms in genes involved in cholesterol synthesis and transport [21,23].

Our two positive findings include the strongly linked markers rs2230805 and rs2230806. The synonymous coding variant rs2230805 (G474A/L158L) is located in the last exon of the only putative alternative splice-form of *ABCA1* comprised 5 exons with as yet unknown function [20]. It is not clear if rs2230805 polymorphism differentially affects the binding of common splicing factors. Similarly to our results, a significant association was found between the common allele and the risk for AD in a large comprehensive Swedish study [20]. The putative risk variant also had a modest, but significant effect on cerebrospinal fluid (CSF) levels of Aβ42 with the same tendency as *APOE* ε4 allele, which is also associated with both increased risk and reduced CSF Aβ42 levels [20].

The most extensively studied rs2230806 non-synonymous polymorphism is a nucleotide variation in exon 7 (G656A) which results in an amino acid change at position 219 (R219K). Inconsistent results were reported for this SNP; the conclusions ranged from no association to the minor allele increasing the risk [22,26,27] or decreasing the risk [20,29,33] for the development of AD. Our findings strengthen the results reporting a protective effect on AD risk for the minor allele.

Similar to our findings, no effect on AD susceptibility of the rs2066718 non-synonymous polymorphism in exon 16 (G2311A/V771M) was observed in a previous study [31]. On the other hand, reports of conflicting results can also be found, although both positive findings were detected only in a subset of the investigated samples [10,15].

5. Conclusion

In conclusion, our findings of a decreased susceptibility to AD for the minor alleles of the rs2230805 and rs2230806 strongly linked common polymorphisms suggest a modest protective effect and support the involvement of *ABCA1* gene in AD pathology. The findings and conclusions of our study should be interpreted with caution in light of our medium sample size, limited number of investigated markers and previous inconsistent results until further replication and functional assays provide convergent support.

Conflict of interest

The authors have no conflict of interest to report

Acknowledgments

The authors are grateful to the participants of this study for their cooperation. This project was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences and by a grant from (M. P. & J. K.) the Hungarian *Research* and *Technology Innovation Fund* through the Hungarian Brain Research Program (KTIA_13_NAP-A-II/16).

References

[1] J.C. Barrett, B. Fry, J. Maller, M.J. Daly, Haploview: analysis and visualization of LD and haplotype maps, Bioinformatics 21 (2005) 263–265.
[2] D. Blacker, L. Bertram, A.J. Saunders, T.J. Moscarillo, M.S. Albert, H. Wiener, et al., Results of a high-resolution genome screen of 437 Alzheimer's disease families, Hum. Mol. Genet. 12 (2003) 23–32.
[3] M. Bodzioch, E. Orso, J. Klucken, T. Langmann, A. Bottcher, W. Diederich, W. Drobnik, S. Barlage, C. Buchler, M. Porsch-Ozcurumez, W.E. Kaminski, H.W. Hahmann, K. Oette, G. Rothe, C. Aslanidis, K.J. Lackner, G. Schmitz, The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease, Nat. Genet. 22 (1999) 347–351.
[4] A. Brooks-Wilson, M. Marcil, S.M. Clee, L.H. Zhang, K. Roomp, M. van Dam, et al., Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency, Nat. Genet. 22 (1999) 336–345.
[5] I. Cascorbi, C. Fluh, C. Remmler, S. Haenisch, F. Faltraco, M. Grumbt, M. Peters, A. Brenn, D.R. Thal, R.W. Warzok, S. Vogelgesang, Association of ATP-binding cassette transporter variants with the risk of Alzheimer's disease, Pharmacogenomics 14 (2013) 485–494.
[6] S.M. Clee, A.H. Zwinderman, J.C. Engert, K.Y. Zwarts, H.O. Molhuizen, K. Roomp, et al., Common genetic variation in ABCA1 is associated with altered lipoprotein levels and a modified risk for coronary artery disease, Circulation 103 (2001) 1198–1205.
[7] J. Cohen, Statistical Power Analysis for the Behavioral Sciences, 2nd ed., Lawrence Erlbaum Associates Inc., Hillsdale, New Jersey, 1998, pp. 216–226.
[8] F. Faul, E. Erdfelder, A.G. Lang, A. Buchner, G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences, Behav. Res. Methods 39 (2007) 175–191.
[9] M. Jiang, L. Lv, H. Wang, X. Yang, H. Ji, F. Zhou, W. Zhu, L. Cai, X. Gu, J. Sun, Q. Dong, Meta-analysis on association between the ATP-binding cassette transporter A1 gene (ABCA1) and Alzheimer's disease, Gene 510 (2012) 147–153.
[10] H. Katzov, K. Chalmers, J. Palmgren, N. Andreasen, B. Johansson, N.J. Cairns, M. Gatz, G.K. Wilcock, S. Love, N.L. Pedersen, A.J. Brookes, K. Blennow, P.G. Kehoe, J.A. Prince, Genetic variants of ABCA1 modify Alzheimer disease risk and quantitative traits related to beta-amyloid metabolism, Hum. Mutat. 23 (2004) 358–367.
[11] R. Koldamova, N.F. Fitz, I. Lefterov, ATP-binding cassette transporter A1: from metabolism to neurodegeneration, Neurobiol. Dis. (2014) 13–21 (Pt A).
[12] H. Kolsch, D. Lutjohann, F. Jessen, K. Von Bergmann, S. Schmitz, H. Urbach, W. Maier, R. Heun, Polymorphism in ABCA1 influences CSF 24S-hydroxycholesterol levels but is not a major risk factor of Alzheimer's disease, Int. J. Mol. Med. 17 (2006) 791–794.
[13] D. Kuhnke, G. Jedlitschky, M. Grube, M. Krohn, M. Jucker, I. Mosyagin, I. Cascorbi, L.C. Walker, H.K. Kroemer, R.W. Warzok, S. Vogelgesang, MDR1-P-Glycoprotein (ABCB1) Mediates Transport of Alzheimer's amyloid-beta peptides – implications for the mechanisms of Abeta clearance at the blood-brain barrier, Brain Pathol. 17 (2007) 347–353.
[14] J.C. Lambert, C.A. Ibrahim-Verbaas, D. Harold, A.C. Naj, R. Sims, C. Bellenguez, et al., Meta-analysis of 74, 046 individuals identifies 11 new susceptibility loci for Alzheimer's disease, Nat. Genet. 45 (2013) 1452–1458.
[15] Y. Li, K. Tacey, L. Doil, R. van Luchene, V. Garcia, C. Rowland, S. Schrodi, D. Leong, K. Lau, J. Catanese, J. Sninsky, P. Nowotny, P. Holmans, J. Hardy, J. Powell, S. Lovestone, L. Thal, M. Owen, J. Williams, A. Goate, A. Grupe, Association of ABCA1 with late-onset Alzheimer's disease is not observed in a case-control study, Neurosci. Lett. 366 (2004) 268–271.
[16] M.K. Lupton, P. Proitsi, K. Lin, G. Hamilton, M. Daniilidou, M. Tsolaki, J.F. Powell, The role of ABCA1 gene sequence variants on risk of Alzheimer's disease, J. Alzheimers Dis. 38 (2014) 897–906.
[17] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, E.M. Stadlan, 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 (1984) 939–944.
[18] A. Myers, F. Wavrant De-Vrieze, P. Holmans, M. Hamshere, R. Crook, D. Compton, H. Marshall, D. Meyer, S. Shears, J. Booth, D. Ramic, H. Knowles, J.C. Morris, N. Williams, N. Norton, R. Abraham, P. Kehoe, H. Williams, V. Rudrasingham, F. Rice, P. Giles, N. Tunstall, L. Jones, S. Lovestone, J. Williams, M.J. Owen, J. Hardy, A. Goate, Full genome screen for Alzheimer disease: stage II analysis, Am. J. Med. Genet. 114 (2002) 235–244.
[19] M.A. Pericak-Vance, J. Grubber, L.R. Bailey, D. Hedges, S. West, L. Santoro, B. Kemmerer, J.L. Hall, A.M. Saunders, A.D. Roses, G.W. Small, W.K. Scott, P.M. Conneally, J.M. Vance, J.L. Haines, Identification of novel genes in late-onset Alzheimer's disease, Exp. Gerontol. 35 (2000) 1343–1352.
[20] C.A. Reynolds, M.G. Hong, U.K. Eriksson, K. Blennow, A.M. Bennet, B. Johansson, B. Malmberg, S. Berg, F. Wiklund, M. Gatz, N.L. Pedersen, J.A. Prince, A survey of ABCA1 sequence variation confirms association with dementia, Hum. Mutat. 30 (2009) 1348–1354.
[21] E. Rodriguez-Rodriguez, I. Mateo, J. Infante, J. Llorca, I. Garcia-Gorostiaga, J.L. Vazquez-Higuera, P. Sanchez-Juan, J. Berciano, O. Combarros, Interaction between HMGCR and ABCA1 cholesterol-related genes modulates Alzheimer's disease risk, Brain Res. 1280 (2009) 166–171.
[22] E. Rodriguez-Rodriguez, I. Mateo, J. Llorca, C. Sanchez-Quintana, J. Infante, I. Garcia-Gorostiaga, P. Sanchez-Juan, J. Berciano, O. Combarros, Association of genetic variants of ABCA1 with Alzheimer's disease risk, Am. J. Med. Genet. B Neuropsychiatr. Genet. (2007) 964–968 144B.
[23] E. Rodriguez-Rodriguez, J.L. Vazquez-Higuera, P. Sanchez-Juan, I. Mateo, A. Pozueta, A. Martinez-Garcia, A. Frank, F. Valdivieso, J. Berciano, M.J. Bullido, O. Combarros, Epistasis between intracellular cholesterol trafficking-related genes (NPC1 and ABCA1) and Alzheimer's disease risk, J. Alzheimers Dis. 21 (2010) 619–625.
[24] S. Rust, M. Rosier, H. Funke, J. Real, Z. Amoura, J.C. Piette, J.F. Deleuze, H.B. Brewer, N. Duverger, P. Denefle, G. Assmann, Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1, Nat. Genet. 22

(1999) 352–355.
[25] M. Stefani, G. Liguri, Cholesterol in Alzheimer's disease: unresolved questions, Curr. Alzheimer Res. 6 (2009) 15–29.
[26] Y.M. Sun, H.L. Li, Q.H. Guo, P. Wu, Z. Hong, C.Z. Lu, Z.Y. Wu, The polymorphism of the ATP-binding cassette transporter 1 gene modulates Alzheimer disease risk in Chinese Han ethnic population, Am. J. Geriatr. Psychiatry 20 (2012) 603–611.
[27] P.D. Sundar, E. Feingold, R.L. Minster, S.T. DeKosky, M.I. Kamboh, Gender-specific association of ATP-binding cassette transporter 1 (ABCA1) polymorphisms with the risk of late-onset Alzheimer's disease, Neurobiol. Aging 28 (2007) 856–862.
[28] S.E. Wahrle, H. Jiang, M. Parsadanian, R.E. Hartman, K.R. Bales, S.M. Paul, D.M. Holtzman, Deletion of Abca1 increases Abeta deposition in the PDAPP transgenic mouse model of Alzheimer disease, J. Biol. Chem. 280 (2005) 43236–43242.
[29] F. Wang, J. Jia, Polymorphisms of cholesterol metabolism genes CYP46 and ABCA1 and the risk of sporadic Alzheimer's dise ase in Chinese, Brain Res. 1147 (2007) 34–38.
[30] X.F. Wang, Y.W. Cao, Z.Z. Feng, D. Fu, Y.S. Ma, F. Zhang, X.X. Jiang, Y.C. Shao, Quantitative assessment of the effect of ABCA1 gene polymorphism on the risk of Alzheimer's disease, Mol. Biol. Rep. 40 (2013) 779–785.
[31] F. Wavrant-De Vrieze, D. Compton, M. Womick, S. Arepalli, O. Adighibe, L. Li, J. Perez-Tur, J. Hardy, ABCA1 polymorphisms and Alzheimer's disease, Neurosci. Lett. 416 (2007) 180–183.
[32] M.A. Wollmer, J.R. Streffer, D. Lutjohann, M. Tsolaki, V. Iakovidou, T. Hegi, T. Pasch, H.H. Jung, K. Bergmann, R.M. Nitsch, C. Hock, A. Papassotiropoulos, ABCA1 modulates CSF cholesterol levels and influences the age at onset of Alzheimer's disease, Neurobiol. Aging 24 (2003) 421–426.
[33] Z. Xiao, J. Wang, W. Chen, P. Wang, H. Zeng, W. Chen, Association studies of several cholesterol-related genes (ABCA1 CETP and LIPC) with serum lipids and risk of Alzheimer's disease, Lipids Health Dis. 11 (2012) 163.