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Article

ABC Transporters, APOE, CYP46A1 and LRP1 Gene Polymorphisms as Markers of Dementia Development in Patients with Hyperlipidemia

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Abstract

In an aging society, solving problems associated with the diagnosis and treatment of dementia-related diseases represents a serious challenge. The aim of the study was to evaluate the possibility of applying molecular biology methods to test polymorphisms recognized in global literature as potentially useful in assessing the risk of developing dementia in a group of patients with hyperlipidemia. A sample of 203 patients- 109 diagnosed with both dementia and hyperlipidemia and 94 with hyperlipidemia were genotyped. Additional data about cognitive decline and neuropsychological assessment were collected. Among all the studied polymorphisms, the frequency of the *ABCA1* rs2230806 polymorphism differed between the analyzed groups. The GG genotype ($p=0.0002$, $RR=3.22$, $CI=1.63\div 6.37$) and the G allele ($p=0.0007$, $RR=1.53$, $CI=1.19\div 1.97$) were more frequent in patients diagnosed with dementia, specifically in those with Alzheimer's disease. Furthermore, the GG genotype was more common in individuals with a shorter disease duration and lower scores on the MoCA scale, and consequently, with greater cognitive function deficits during early stages of the diagnostic process. *ABCA1* rs2230806 genotyping is a potential marker for the early identification of dementia risk in patients with hyperlipidemia, which supports the validity of exploring options for incorporating diagnostics based on molecular biology methods.

Keywords: *ABCA1*; *ABCB1*; APOE; CYP46A1; LRP; dementia; hyperlipidemia; polymorphism; markers

1. Introduction

The World Health Organization (WHO) defines dementia as a set of symptoms of a progressive or chronic nature, in the course of which cognitive functions deteriorate to a greater extent than in the case of the biological aging process. Nearly 10 million new cases were diagnosed every year [1]. In 2021 cardiovascular disease- ischemic heart disease and stroke were respectively first and third cause of death worldwide [2]. It is reviewed in existing literature that shared risk factors such as BMI, hypertension, diabetes, dyslipidemia can be affected by genetics. Numerous convergent genes are involved in disease progress of both morbid conditions [3]. Growing importance of molecular diagnostics in clinical practice might be a useful tool to understand pathogenesis and simultaneously a chance to modify lifestyle before prodromal phases. According to the latest report based on analysis

nearly half million cases hyperlipidemia diagnosed in younger age results in higher risk in all-cause dementia (HR 1.46 in diagnosis <50 years) [4]. Moreover, lifestyle modification after CVD diagnosis reduces the risk of developing dementia [5]. Conclusions from observational studies and genotyping trials provide evidence that genetic markers are needed in public health policy for prevention.

Table 1 presents the genes selected for analysis based on their alignment in lipid metabolism processes and the development of dementia.

Table 1. Genes under investigation, role in lipid metabolism and dementia.

Gene	Role in lipid metabolism	Involvement in dementia	References
<i>ABCA1</i>	Regulation of cholesterol, support ApoE lipidation	Influence for ApoE lipidation affect APP processing and A β cumulation	[6,8]
<i>ABCA7</i>	Regulation of lipid metabolism, apolipoproteins lipidation	Phagocytic elimination of A β , suppression of A β PP proteolysis	[6–8]
<i>ABCB1</i>	Efflux transporter, pharmacoresistance, detoxification, homeostasis maintaince in CNS	Transport of A β from neural processes to blood circulation	[6]
<i>APOE</i>	Lipid transporter protein	APOE E4 variant accelerate the accumulation, aggregation, and deposition of A β in the brain	[9]
<i>CYP46A1</i>	Conversion cholesterol into form 24S-OHC capable of crossing blood-brain barrier	Decreased function leads to an increased production of A β and tau proteins	[10–12]
<i>LRP1</i>	Internalization of lipoproteins into neurons, apoE receptor	A β deposition, tau regulation, brain homeostasis	[13,14]

To follow this line, we conduct *ABCA1*, *ABCB7*, *ABCB1*, *APOE*, *CYP46A1* and *LRP1* genotyping to compare allele frequency in three groups of patients diagnosed in 1) dementia with coexisting hyperlipidemia, 2) hyperlipidemia, 3) healthy controls, to clarify their role in dementia development and assess their potential for use as early markers of dementia among patients with dyslipidemia.

2. Results

2.1. Baseline Characteristics

A total of 285 participants, 90 with dementia and hyperlipidemia patients, 94 with hypercholesterolemia and 101 individuals as allele frequency control group were included in the study. No significant difference was observed in sex distribution. Patients with both dementia and

hyperlipidemia were older than with hyperlipidemia (70.8 ($\pm$ 11.5) vs. 64.1 ($\pm$ 12.9). Dementia & hyperlipidemia participants had a lower burden of comorbidities. Both diabetes and hypertension were more frequently observed in the hyperlipidemia group ($p<0.05$). The mean age of dementia diagnosis was 65.8 ($\pm$ 9.8), duration is average 7.8 ($\pm$ 2.4). MMSE and MoCA scores were respectively 18.1 ($\pm$ 4.0) and 19.0 ($\pm$ 4.1). In hyperlipidemia & dementia group laboratory workup shows significantly increased cholesterol, HDL, LDL and triglycerides levels ($p<0.05$ in all parameters).

Table 2. Attributes of the sample.

Parameter	Dementia & hyperlipidemia (n=109)	Hyperlipidemia (n=94)	p-value
Male / Female, sex	47/62 (43.1%/56.9%)	37/57 (39.4%/60.6%)	p=0.588
Age, y	70.8 ($\pm$ 11.5)	64.1 ($\pm$ 12.9)	p <0.05
Weight, kg	78.0 (70.0÷86.5)	79.5 (68.0÷95.5)	p=0.420
Diabetes	13 (11.9%)	27 (28.7%)	p <0.05
Hypertension	20 (18.4%)	68 (72.3%)	p <0.05
Age of dementia diagnosis, y	65.8 ($\pm$ 9.8)	-	
Dementia duration, y	7.8 ($\pm$ 2.4)	-	
MMSE score	18.1 ($\pm$ 4.0)	-	
MoCA score	19.0 ($\pm$ 4.1)	-	
Total cholesterol, mg/dl	231.0 (220.0÷244.0)	146.0 (118.0÷168.0)	p <0.05
HDL cholesterol, mg/dl	55.0 (49.0÷64.0)	43.0 (32.0÷56.0)	p <0.05
LDL cholesterol, mg/dl	140.7 ($\pm$ 21.3)	77.3 ($\pm$ 34.6)	p <0.05
Triglicerydes, mg/dl	195.2 ($\pm$ 53.1)	130.7 ($\pm$ 75.5)	p <0.05

Data expressed as n (%) mean (SD) or median (first÷third quartile). SI conversion: cholesterol to mmol/l, multiplied by 0.0259; triglycerides to mmol/l, by 0.0113.

2.2. Polymorphisms

First, we assessed differences in genotype frequency in all experiment groups: dementia& hyperlipidemia, non-demented with hyperlipidemia and controls (Table 3). The distribution of *ABCA1* (rs2422493), *ABCA7*, *ABCB1*, *APOE*, *CYP46A1* and *LRP1* genotypes were not significantly different. The *ABCA1* (rs2230806) genotypes were not evenly distributed between groups ($p=0.004$). Further analysis confirmed the existence of differences in the distribution of genotypes between dementia & hyperlipidemia versus hyperlipidemia, with a more frequent prevalence of the GG genotype ($p=0.0002$, RR=3.22, CI=1.63÷ 6.37) and G allele ($p=0.0007$, RR=1.53, CI=1.19÷1.97) in patients with dementia. This genotype was also related to an increased risk of Alzheimer disease diagnosis ($p=0.006$). We also compared the occurrence of genotypes in males and females, but no differences were observed.

Table 3. Genotype frequency.

Gene	rs code	Participants	Genotype frequency			P-value
ABCA1	rs2230806		AA	GA	GG	0.004
		Dementia & hyperlipidemia	39 (35.8%)	36 (33.0%)	34 (31.2%)	
		Hyperlipidemia	45 (47.8%)	40 (42.6%)	9 (9.6%)	

		Controls	37 (36.6%)		44 (43.6%)		20 (19.8%)	
ABCA1	rs2422493		CC		CT		TT	
		Dementia & hyperlipidemia	34 (31.2%)		51 (46.8%)		24 (22.0%)	
		Hyperlipidemia	20 (21.3%)		56 (59.6%)		18 (19.1%)	
		Controls	20 (19.8%)		49 (48.5%)		32 (31.7%)	
ABCA7	rs4147929		AA		AG		GG	
		Dementia & hyperlipidemia	3 (2.8%)		35 (32.1%)		71 (65.1%)	
		Hyperlipidemia	2 (2.1%)		30 (31.9%)		62 (66.0%)	
		Controls	3 (3.0%)		23 (22.8%)		75 (74.2%)	
ABCA7	rs3752246		CC		CG		GG	
		Dementia & hyperlipidemia	71 (65.1%)		36 (33.0%)		2 (1.9%)	
		Hyperlipidemia	64 (68.1%)		29 (30.8%)		1 (1.1%)	
		Controls	77 (76.2%)		23 (22.8%)		1 (1.0%)	
ABCA7	rs3764650		GG		GT		TT	
		Dementia & hyperlipidemia	1 (0.9%)		17 (15.6%)		91 (83.5%)	
		Hyperlipidemia	1 (1.1%)		11 (11.7%)		82 (87.2%)	
		Controls	-		10 (9.9%)		91 (90.1%)	
ABCB1	rs1045642		CC		CT		TT	
		Dementia & hyperlipidemia	27 (24.8%)		55 (50.4%)		27 (24.8%)	
		Hyperlipidemia	28 (29.8%)		44 (46.8%)		22 (23.4%)	
		Controls	19 (18.8%)		52 (51.5%)		30 (29.7%)	
ABCB1	rs1128503		CC		CT		TT	
		Dementia & hyperlipidemia	38 (34.9%)		48 (44.0%)		23 (21.1%)	
		Hyperlipidemia	38 (40.4%)		48 (43.6%)		15 (16.0%)	
		Controls	30 (29.7%)		47 (46.5%)		24 (23.8%)	
ABCB1	rs2032582		GG		GT		TT	
		Dementia & hyperlipidemia	36 (33.6%)		51 (47.7%)		20 (18.7%)	
		Hyperlipidemia	44 (46.8%)		37 (39.4%)		13 (13.8%)	
		Controls	34 (33.7%)		49 (48.5%)		18 (17.8%)	
APOE	rs429358		E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4
	rs7412	Dementia & hyperlipidemia	-	16 (14.7%)	5 (4.6%)	77 (70.6%)	7 (6.4%)	4 (3.7%)

		Hyperlipidemia	1 (1.1%)	6 (6.3%)	1 (1.1%)	67 (71.3%)	19 (20.2%)	-		
		Controls	1 (1.0%)	7 (6.9%)	1 (1.0%)	86 (85.2%)	6 (5.9%)	-		
CYP46A1	rs754203		AA		AG		GG			
		Dementia & hyperlipidemia	51 (46.8%)		52 (47.7%)		6 (5.5%)			
		Hyperlipidemia	44 (46.8%)		35 (37.2%)		15 (16.0%)		0.148	
		Controls	48 (47.5%)		40 (39.6%)		13 (12.9%)			
LRP1	rs1799986		CC		CT		TT			
		Dementia & hyperlipidemia	75 (68.8%)		31 (28.4%)		3 (2.8%)		0.224	
		Hyperlipidemia	73 (77.6%)		17 (18.1%)		4 (4.3%)			
		Controls	65 (64.4%)		32 (31.6%)		4 (4.0%)			

Next, we conducted an analysis to evaluate the influence of investigated genotypes on age of dementia diagnosis and duration of disease. Patients with *ABCA1* (rs2230806) GG variant presented shorter dementia duration compared to AA and GA genotypes (p=0.0001 and p=0.0004 respectively). Moreover, individuals with *ABCA1* (rs2230806) GG genotype achieved lower scores on MoCA scale during first examination (p=0.01) (Figure 1).

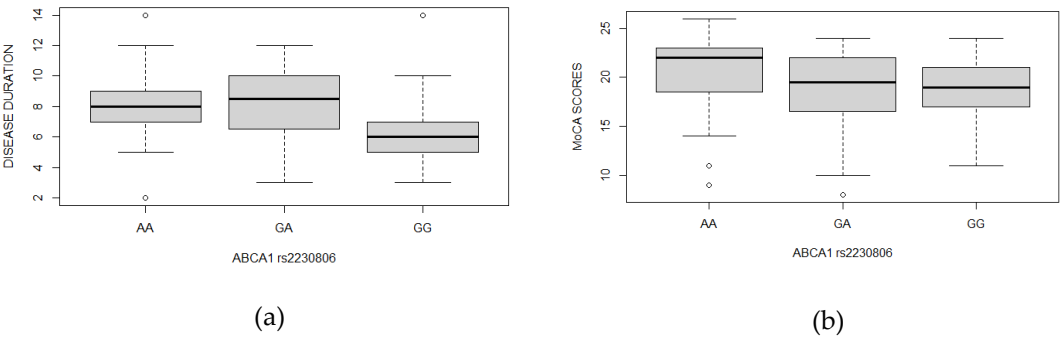


Figure 1. (a) Box-plot illustrates the distribution of individual *ABCA1* (rs2230806) genotypes and the duration of the disease; (b) Box plot illustrates the relationship between the distribution of *ABCA1* (rs2230806) genotypes and MoCa scores.

An analysis of the impact of the polymorphisms studied on total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides levels was not conducted due to the long-term use of statins by patients in the hyperlipidemia group.

3. Discussion

The aim of this study was to assess the usefulness of *ABCA1*, *ABCB7*, *ABCB1*, *APOE*, *CYP46A1* and *LRP1* genotyping as promising dementia risk factors among a wide group of patients with hyperlipidemia diagnosed first. Our findings indicate that *ABCA1* (rs2230806) is a suitable candidate. Analysis of other investigated polymorphisms did not reveal differences between the compared groups.

ABCA1 transporter is ATP binding cassette family protein involved in cholesterol efflux and metabolism. Its expression is regulated by several factors, including cholesterol itself, which provides ligands for liver X receptors that stimulate *ABCA1* transcription [15]. This transporter plays a crucial

role in various diseases including dyslipidemia, coronary heart disease, type 2 diabetes, and potential implications for neurological disorders [16].

Apart from critical role in HDL formation and lipid distribution at the plasma membranes, dysregulation of apolipoprotein lipidation associated with the occurrence of genetic polymorphism increases the risk of dementia developing by promoting the formation of A β through the activation of secretase action on the transmembrane amyloid precursor protein [17,18]. At the neurovascular unit without deficits, ABCA1 works alongside ABCB1 to facilitate A β clearance from the brain. While ABCB1 directly transports A β into the blood circulation, ABCA1 neutralizes A β aggregation capacity in an ApoE-dependent manner [19].

The most common context for rs2030806 polymorphism analysis is the risk of coronary artery disease (CAD). Studies have shown that the G allele of rs2230806 is significantly more frequent in coronary artery disease patients, potentially increasing CAD risk [20]. Moreover a meta-analysis revealed that rs2230806 A allele carriers had higher HDL-C levels and lower LDL-C and triglyceride levels compared to non-carriers [21]. Recent research highlights a strong association between cardiovascular disease (CVD) and Alzheimer's disease (AD). Individuals with subclinical CVD are at higher risk for dementia and AD. Common risk factors for both conditions include hypertension, high LDL cholesterol, low HDL cholesterol, and diabetes [22]. In light of these evidence analysis in relation of neurodegeneration is required. Studies using mice lacking brain *ABCA1* have shown increased neuroinflammation, astrogliosis, and cortical neuronal death [23]. Other survey on mouse models confirmed that *ABCA1* haplodeficiency results in increased A β levels and cognitive deficits, but the scale is significantly greater in individuals with the ApoE4 variant [24]. It is worth to be noted that *ABCA1* is transcriptionally regulated by Liver X Receptors (LXR) and Retinoic X Receptors (RXR), presenting potential therapeutic targets for neurodegenerative disorders [25–27].

Contrary to the presented results of studies on mice findings from published genetic association studies between *ABCA1* and Alzheimer's disease are inconclusive. In Hungarian report the minor A allele of rs2230806 has been linked to a modest protective effect against Alzheimer's disease [28]. Similarly, in the Chinese Han population, individuals with the A allele achieved better scores on the MMSE cognitive impairment assessment scale and have significantly higher concentration of HDL fraction than non-carriers [29]. According to Wavrant-De Vrièze et al. AG and GG genotypes are associated with the onset of Alzheimer disease, however coincidence with ApoE variant is noteworthy [30]. Sundar et al. indicate a gender-specific association between the *ABCA1* rs2230806 polymorphism and late-onset Alzheimer's disease (LOAD), because women with A allele exhibited 1,75- fold higher risk of the disease [31].

We found significant difference in *ABCA1* (rs2230806) genotype distribution between the involved groups hyperlipidemia & dementia and hyperlipidemia. Moreover, GG genotype is related to AD incidence. Patients with GG genotype in comparison to other variants had shorter dementia duration and lower scores on MoCA test during the first examination. Until now, many publications have confirmed that the best risk marker for dementia is the *APOE* E4 variant; however, the vast majority have relied on comparative studies of healthy individuals and those with dementia. In our study, both groups of participants included patients with hyperlipidemia as an underlying condition, and the differentiating criterion was the presence or absence of dementia. Considering the essential role of *APOE* as a primary lipid transporter, this enhanced the credibility of the conducted experiment.

Currently, neuropathological examination of brain, neuroimaging and biomarkers widely accepted for the diagnosis of dementia, including the measurement of tau protein, phosphorylated tau protein, and A β 1-42 which requires the performance of an invasive procedure to collect cerebrospinal fluid, can provide high diagnostic accuracy in diagnosis of dementia [32]. Some promising plasma phosphorylated tau protein and A β 42/A β 40 ratio biomarkers were also reported recently [33,34].

However, molecular testing lately has become a basic diagnostic tool in primary care and has a promising potential to be used in different clinical cases. It is significant to consider the usefulness of genetic markers as screening factors in the targeted group of patients.

Limitations

The conducted study is characterized by several limitations, primarily related to the sample size and the polymorphisms selected based on a review of global literature, which have been reported as involved in both lipid metabolism disorders and dementia-related diseases. However, the study was intended as a preliminary analysis of the potential for identifying gene polymorphisms that should be considered as markers for dementia development in a dedicated patient group. Increasing the number of cases, conducting the analysis across different populations, and significantly expanding the number of polymorphisms tested, for example, through panel tests, would substantially enhance the reliability of the obtained data. In our study, we also did not take into account laboratory test results, particularly those related to lipid metabolism, due to differences in statin use between the two study groups. Cautious planning and implementation of extended lipid parameter diagnostics would undoubtedly add value by narrowing the patient group in which molecular test results could directly influence clinical decisions.

4. Materials and Methods

4.1. Study Population

The study protocol included 203 patients: 109 diagnosed with both dementia and hyperlipidemia hospitalized in Department of Psychiatry Wrocław Medical University and 94 with hyperlipidemia from 4 Military Hospital with Polyclinic in Wrocław. Moreover 101 healthy volunteers as genotype frequency control group were enrolled. Dementia was diagnosed in line with Alzheimer's Association criteria while hypercholesterolemia according to defined LDL-C levels and risk of cardiovascular disease. Exclusion criteria were: 1) brain injuries 2) acquired causes of dementia 3) liver or kidney disease 4) secondary causes of dyslipidemia 5) long-term fat-elimination diet. Patients were informed about the details of the study and signed fixed consent forms for participation in molecular tests and clinical data processing without personalities. Questionnaires completed by authorized representatives in each department include demographic data (sex, age), anthropometric data (weight), laboratory results (cholesterol, LDL, HDL, triglycerides), comorbidities (diabetes, hypertension) age of diagnosis, duration of dementia, neuropsychological assessment including MMSE (Mini-Mental State Examination and MoCA (Montreal Cognitive Assessment) results collected at the early stage of diagnosing cognitive impairment, which subsequently progressed to dementia.. The study protocol was approved by the Local Ethics Committee of the Wrocław Medical University(141/2019).

4.2. Genotyping

One blood EDTA sampling was completed to extract DNA in the commercial kit (Omega Bio-tek, Georgia) for the genetic survey. The participants were genotyped for the *ABCA1* (rs2230806, rs2422493), *ABCA7* (rs4147929, rs3752246 rs3764650), *ABCB1* (rs1045642, rs1128503, rs2032582) *APOE*, (rs429358, rs7412), *CYP46A1* (rs754203), *LRP1* (rs1799986) using AmpliSNiP Dementia Screening Panel (qPCR) (Amplicon, Poland) on Biometra TOptical 96 system (Analytic Jena, Germany).

4.3. Laboratory Markers

Total cholesterol, triglycerides, HDL cholesterol were measured during standard diagnostic process in hospital using the enzymatic colorimetric method on a biochemical analyzer using commercially available kits (Roche Diagnostics, Germany). LDL-C concentrations were calculated using the Friedewald formula (in case of triglycerides ≥ 400 mg/dl measured directly).

4.4. Statistical Analysis

The statistical analysis was performed using the Statistica Ver. 13.3. (TIBCO Software Inc.). The normality of the distribution was evaluated using the Shapiro-Wilk test. The homogeneity of variance was assessed with Levene’s test. Variables with a normal distribution were presented as the mean ± standard deviation, while different distribution as the median along with the first (Q1) and third (Q3) quartile. Qualitative data were expressed as an average percentage. Chi square or the Fisher exact test were performed to compare categorical data. ANOVA, Kruskal-Wallis or Mann-Whitney test were settled to compare continuous variables. P value below 0.05 was considered as significant.

5. Conclusions

The results of our research confirm the impact of the *ABCA1* gene polymorphism rs2230806 on an increased risk of developing dementia among patients with hyperlipidemia. This polymorphism is also associated with the duration of the disease and MoCA scale results in the early stages of diagnosing mild cognitive impairment, which over time progressed to dementia. The *ABCA1* gene is involved in the regulation of cholesterol transport and phospholipid balance in cells, while rs2230806 polymorphism leading to downregulation of gene activity play a significant role in the development of atherosclerosis and other age-related diseases, it may suggest that changes also occur within the central nervous system, promoting the onset of dementia. However, due to the relatively small sample size in this experiment, it is necessary to expand the study group in order to confirm the utility of *ABCA1* rs2230806 genotyping as a predictive marker for the onset of dementia in individuals with hyperlipidemia.

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Institutional Review Board Statement: The study was performed in accordance with the Declaration of Helsinki and received approval from the Ethics Committee at Wrocław Medical University (141/2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author.

Conflicts of Interest: Author Janusz Piechota was employed by the company Amplicon Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

24S-OHC	24(S)-Hydroxycholesterol
AD	Alzheimer disease
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
Aβ	Amyloid β

BMI	Body mass index
CAD	Coronary artery disease
CNS	Central nervous system
CVD	Cardiovascular disease
HDL	High density lipoprotein
LDL	Low density lipoprotein
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
WHO	World Health Organization

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