

Received: 02 June 2025 / Accepted: 19 August 2025 / Published online: 31 October 2025

DOI 10.34689/SH.2025.27.5.001

UDC 616.43



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GENETIC VARIANTS IN LIPID-ASSOCIATED GENES IN THE KAZAKHSTANI COHORT WITH ATHEROSCLEROSIS AND HYPERTRIGLYCERIDEMIA

Makhabbat S. Bekbossynova¹, <https://orcid.org/0000-0003-2834-617X>

Zhanel Zh. Mirmanova², <https://orcid.org/0000-0002-0284-3891>

Tomiris K. Shakhmarova², <https://orcid.org/0009-0008-6884-3908>

Ayaulym E. Chamoieva², <https://orcid.org/0000-0003-0877-3537>

Madina R. Zhalbinova², <https://orcid.org/0000-0001-9704-8913>

Nazare N. Satvaldina², <https://orcid.org/0000-0002-0611-4485>

Dauren A. Yerezhepov², <https://orcid.org/0000-0002-4161-1348>

Saule E. Rakhimova^{2,3}, <https://orcid.org/0000-0002-8245-2400>

Ulykbek E. Kairov^{2,3}, <https://orcid.org/0000-0001-8511-8064>

Asset Zh. Daniyarov², <https://orcid.org/0000-0003-3886-718X>

Tatyana V. Ivanova-Razumova¹, <https://orcid.org/0000-0002-6471-1587>

Saltanat A. Andossova¹, <https://orcid.org/0000-0001-7259-183X>

Aliya I. Sailybayeva¹, <https://orcid.org/0000-0002-1489-3837>

Sadyk R. Khamitov¹, <https://orcid.org/0000-0001-6296-0507>

Ainur R. Akilzhanova^{2,3,4}, <https://orcid.org/0000-0001-6161-8355>

¹ “University Medical Center” Corporate Fund, Heart Center, Nazarbayev University, Astana, Republic of Kazakhstan;

² Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Republic of Kazakhstan;

³ Eurasian Society of Personalized Medicine, Astana, Republic of Kazakhstan;

⁴ The Academy of Public Administration under the President of the Republic of Kazakhstan, Astana, Republic of Kazakhstan.

Abstract

Introduction. Cardiovascular diseases, including atherosclerosis (AS), are the leading cause of morbidity and mortality worldwide, including in Kazakhstan. Lipid metabolism disorders, in particular, hypertriglyceridemia, which is recognized as an independent risk factor, play an important role in the development of AS. Genetic features associated with genes regulating lipid and carbohydrate metabolism (*GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*) have a significant impact on the formation of dyslipidemia and determine individual metabolic characteristics. Studying the prevalence and effects of these genetic variants in the Kazakh population is particularly important, given its underrepresentation in global genetic research.

Aim. The objective of this study was to study the frequency of genetic polymorphisms in genes involved in the regulation of lipid metabolism (*GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*) in a group of Kazakhstani patients with hypertriglyceridemia and atherosclerosis. Additionally, we analyzed the relationship of the identified genetic variants with the biochemical parameters of the lipid profile.

Materials and methods. The study analyzed data from 402 patients with cardiovascular diseases, 144 of whom had hypertriglyceridemia. To identify the genetic determinants of lipid metabolism disorders, full-exome sequencing was performed with a focus analysis of the *GCKR*, *SLC22A5*, *LPL*, and *FLCN* genes. The identified genetic variants were annotated and classified according to the recommendations of ACMG/AMP. The association of genetic polymorphisms with lipid profile parameters in patients with AS was studied.

Results. Sequencing of the entire exome of patients with varying degrees of cardiovascular risk revealed genetic variations affecting triglyceride metabolism. Elevated triglyceride levels were reported in patients of all risk categories, with the highest frequency in very high-risk individuals (82 patients). Analysis of the lipid profile showed that total cholesterol was significantly higher in the high-risk group compared with the low-risk group (228.8 ± 35.2 versus 207.8 ± 30.3 mg/dl; $p=0.0467$). The level of HDL-C showed an inverse relationship with the level of risk, being the lowest in the very high-risk group (44.6 ± 10.5 versus 50.1 ± 9.9 mg/dl; $p=0.0411$). Although LDL and non-lipoprotein cholesterol did not show statistically significant differences, there was a tendency to increase them. Triglycerides also tended to increase, but without achieving statistical significance ($p>0.05$). There was a significant decrease in apolipoprotein A at high risk ($p<0.0001$). The distribution

of APOE genotypes (p.T388C) was similar in all risk groups, with a predominance of the TT genotype ($\approx 58-67\%$) and a rare occurrence of the CC genotype ($\leq 5.3\%$), without statistically significant differences ($p > 0.05$).

Conclusions. The study did not reveal a statistically significant association between APOE (p.T388C) and GCKR genotypes with cardiovascular risk. Larger-scale studies are required, taking into account additional factors and an increased sample size.

Keywords: atherosclerosis, hypertriglyceridemia, cardiovascular disease, APOE, GCKR.

For citation:

Bekbosynova M.S., Mirmanova Zh.Zh., Shakhmarova T.K., Chamoieva A.E., Zhalbinova M.R., Satvaldina N.N., Yerezhepov D.A., Rakhimova S.E., Kairov U.E., Daniyarov A.Zh., Ivanova-Razumova T.V., Andossova S.A., Sailybayeva A.I., Khamitov S.R., Akilzhanova A.R. Genetic variants in lipid-associated genes in the Kazakhstani cohort with atherosclerosis and hypertriglyceridemia // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (5), pp. 7-15. doi 10.34689/SH.2025.27.5.001

Резюме

**ГЕНЕТИЧЕСКИЕ ВАРИАНТЫ В ЛИПИД-АССОЦИИРОВАННЫХ
ГЕНАХ В КАЗАХСТАНСКОЙ КОГОРТЕ ПАЦИЕНТОВ
С АТЕРОСКЛЕРОЗОМ И ГИПЕРТРИГЛИЦЕРИДЕМИЕЙ**

Махаббат С. Бекбосынова¹, <https://orcid.org/0000-0003-2834-617X>

Жанель Ж. Мирманова², <https://orcid.org/0000-0002-0284-3891>

Томирис К. Шахмарова², <https://orcid.org/0009-0008-6884-3908>

Аяулым Е. Чамойева², <https://orcid.org/0000-0003-0877-3537>

Мадина Р. Жалбинова², <https://orcid.org/0000-0001-9704-8913>

Назерке Н. Сатвалдина², <https://orcid.org/0000-0002-0611-4485>

Даурен А. Ережепов², <https://orcid.org/0000-0002-4161-1348>

Сауле Е. Рахимова^{2,3}, <https://orcid.org/0000-0002-8245-2400>

Улыкбек Е. Каиров^{2,3}, <https://orcid.org/0000-0001-8511-8064>

Асет Ж. Данияров², <https://orcid.org/0000-0003-3886-718X>

Татьяна В. Иванова-Разумова¹, <https://orcid.org/0000-0002-6471-1587>

Салтанат А. Андосова¹, <https://orcid.org/0000-0001-7259-183X>

Алия И. Сайлыбаева¹, <https://orcid.org/0000-0002-1489-3837>

Садык Р. Хамитов¹, <https://orcid.org/0000-0001-6296-0507>

Айнур Р. Акильжанова^{2,3,4}, <https://orcid.org/0000-0001-6161-8355>

¹ Корпоративный фонд «University Medical Center», Центр сердца, Назарбаев Университет, Казахстан, г. Астана, Республика Казахстан;

² Центр наук о жизни, National Laboratory Astana, Назарбаев Университет, г. Астана, Республика Казахстан, г. Астана, Республика Казахстан;

³ Евразийское Общество Персонализированной Медицины, г. Астана, Республика Казахстан;

⁴ Академия государственного управления при Президенте Республики Казахстан.

Введение. Сердечно-сосудистые заболевания, в том числе атеросклероз (АС), являются основной причиной заболеваемости и смертности во всем мире, включая Казахстан. Важную роль в развитии АС играют нарушения липидного обмена, в частности, гипертриглицеридемия, которая признана самостоятельным фактором риска. Генетические особенности, связанные с генами, регулирующими метаболизм липидов и углеводов (*GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*), оказывают значительное влияние на формирование дислипидемий и определяют индивидуальные метаболические характеристики. Изучение распространенности и влияния этих генетических вариантов в казахстанской популяции особенно важно, учитывая ее ограниченное представительство в глобальных генетических исследованиях.

Целью данного исследования было изучить частоты встречаемости генетических полиморфизмов в генах, участвующих в регуляции липидного обмена (*GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*), в группе казахстанских пациентов с гипертриглицеридемией и атеросклерозом. Дополнительно мы анализировали взаимосвязь выявленных генетических вариантов с биохимическими параметрами липидного профиля.

Материал и методы. В рамках исследования были проанализированы данные 402 пациентов с сердечно-сосудистыми заболеваниями, из которых 144 имели гипертриглицеридемию. Для выявления генетических детерминант нарушений липидного обмена было выполнено полноэкзомное секвенирование с анализом генов *GCKR*, *SLC22A5*, *LPL* и *FLCN*. Выявленные генетические варианты были аннотированы и классифицированы в

соответствии с рекомендациями ACMG/AMP. Проведена оценка ассоциации генетических полиморфизмов с нарушениями липидного профиля в казахстанской популяции пациентов с сердечно-сосудистыми заболеваниями.

Результаты. Секвенирование полного экзона пациентов с различной степенью сердечно-сосудистого риска выявило генетические вариации в генах, влияющие на метаболизм триглицеридов. Повышенные уровни триглицеридов были зафиксированы у пациентов всех категорий риска, с наибольшей частотой у лиц с очень высоким риском (82 пациента). Анализ липидного профиля показал, что общий холестерин был статистически значимо выше в группе высокого риска по сравнению с низким ($228,8 \pm 35,2$ против $207,8 \pm 30,3$ мг/дл; $p=0,0467$). Уровень ХС-ЛПВП демонстрировал обратную зависимость от уровня риска, будучи самым низким в группе очень высокого риска ($44,6 \pm 10,5$ против $50,1 \pm 9,9$ мг/дл; $p=0,0411$). Хотя уровни ЛПНП не показали статистически значимых различий, наблюдалась тенденция к их увеличению. Триглицериды также имели тенденцию к росту, но без достижения статистической значимости ($p>0,05$). Было отмечено существенное снижение аполипопротеина А в группе высокого риска ($p<0,0001$). Распределение генотипов АРОЕ (р.Т388С) было схожим во всех группах риска, с преобладанием генотипа ТТ ($\approx 58\text{--}67\%$) и редкой встречаемостью генотипа СС ($\leq 5,3\%$), без статистически значимых различий ($p>0,05$).

Выводы. Исследование не выявило статистически значимой связи между генотипами АРОЕ (р.Т388С) и GCKR с сердечно-сосудистым риском. Требуются более масштабные исследования с учетом дополнительных факторов и увеличенным размером выборки.

Ключевые слова. атеросклероз, гиперлипидемия, сердечно-сосудистое заболевание, АРОЕ, GCKR

Для цитирования:

Бекбосынова М.С., Мирманова Ж.Ж., Шахмарова Т.К., Чамойева А.Е., Жалбинова М.Р., Сатвалдина Н.Н., Ережепов Д.А., Рахимова С.Е., Каиров У.Е., Данияров А.Ж., Иванова-Разумова Т.В., Андосова С.А., Сайлабаева А.И., Хамитов С.Р., Акильжанова А.Р. Генетические варианты в липид-ассоциированных генах в казахстанской когорте пациентов с атеросклерозом и гипертриглицеридемией // Наука и Здравоохранение. 2025. Vol.27 (5), С.7-15. doi 10.34689/SH.2025.27.5.001

Түйіндеме

ГИПЕРТРИГЛИЦЕРИДЕМИЯ ЖӘНЕ АТЕРОСКЛЕРОЗЫ БАР ҚАЗАҚСТАНДЫҚ КОГОРТАДАҒЫ ЛИПИДТЕРМЕН БАЙЛАНЫСТЫ ГЕНДЕРДЕГІ ГЕНЕТИКАЛЫҚ НҰСҚАЛАР

Махаббат С. Бекбосынова¹, <https://orcid.org/0000-0003-2834-617X>

Жанель Ж. Мирманова², <https://orcid.org/0000-0002-0284-3891>

Томирис К. Шахмарова², <https://orcid.org/0009-0008-6884-3908>

Аяулым Е. Чамойева², <https://orcid.org/0000-0003-0877-3537>

Мадина Р. Жалбинова², <https://orcid.org/0000-0001-9704-8913>

Назерке Н. Сатвалдина², <https://orcid.org/0000-0002-0611-4485>

Даурен А. Ережепов², <https://orcid.org/0000-0002-4161-1348>

Сауле Е. Рахимова^{2,3}, <https://orcid.org/0000-0002-8245-2400>

Улыкбек Е. Каиров^{2,3}, <https://orcid.org/0000-0001-8511-8064>

Асет Ж. Данияров², <https://orcid.org/0000-0003-3886-718X>

Татьяна В. Иванова-Разумова¹, <https://orcid.org/0000-0002-6471-1587>

Салтанат А. Андосова¹, <https://orcid.org/0000-0001-7259-183X>

Алия И. Сайлабаева¹, <https://orcid.org/0000-0002-1489-3837>

Садык Р. Хамитов¹, <https://orcid.org/0000-0001-6296-0507>

Айнур Р. Акильжанова^{2,3,4}, <https://orcid.org/0000-0001-6161-8355>

¹ «University Medical Center» корпоративтік қоры, Жүрек орталығы, Назарбаев Университет, Астана қ., Қазақстан Республикасы;

² Өмір туралы ғылымдар орталығы, National Laboratory Astana, Назарбаев Университет, Астана қ., Қазақстан Республикасы;

³ Еуразиялық Дербес Медицина Қоғамы, Астана қ., Қазақстан Республикасы;

⁴ Қазақстан Республикасы Президентінің жанындағы Мемлекеттік басқару академиясы.

Кіріспе. Жүрек-қан тамырлары аурулары, оның ішінде атеросклероз (АС) бүкіл әлемде, соның ішінде Қазақстанда аурушандық пен өлімнің негізгі себебі болып табылады. Липидтер алмасуының бұзылуы, атап айтқанда, тәуелсіз қауіп факторы ретінде танылған гипертриглицеридемия АС дамуында маңызды рөл атқарады. Липидтер мен көмірсулардың метаболизмін реттейтін гендермен байланысты генетикалық ерекшеліктер (GCKR,

SLC22A5, LPL, FLCN, LDLR, APOE) дислипидемияның пайда болуына айтарлықтай әсер етеді және жеке метаболикалық сипаттамаларды анықтайды. Қазақстандық популяциядағы осы генетикалық нұсқалардың таралуы мен әсерін зерттеу оның жаңандық генетикалық зерттеулердегі шектеулі өкілдігін ескере отырып, ерекше маңызды.

Зерттеудің мақсаты. Бұл зерттеудің мақсаты липидтер алмасуын реттеуге қатысатын гендердегі (GCKR, SLC22A5, LPL, FLCN, LDLR, APOE), гипертриглицеридемиясы және атеросклерозы бар қазақстандық пациенттер тобындағы генетикалық полиморфизмдердің пайда болу жиілігін зерттеу болды. Сонымен қатар, біз анықталған генетикалық нұсқалардың липидті профильдің биохимиялық параметрлерімен байланысын талдадық.

Зерттеудің әдістері. Зерттеу барысында жүрек-қан тамырлары аурулары бар 402 пациенттің деректері талданды, олардың 144 гипертриглицеридемия анықталды. Липидтер алмасуының бұзылуының генетикалық детерминанттарын анықтау үшін GCKR, SLC22A5, LPL және FLCN гендеріне бағытталған талдау толық экзом секвенилеу мәліметтерден жасалды. Анықталған генетикалық нұсқалар ACMG/AMP нұсқауларына сәйкес түсіндірілді және жіктелді. Жүрек-қан тамырлары аурулары бар пациенттердің липидті бейіні бұзылған генетикалық полиморфизмдер қауымдастығы бағаланды.

Зерттеудің нәтижелері. Жүрек-қан тамырлары қауіп әртүрлі пациенттердің бүкіл экзомның реттілігінің триглицеридтердің метаболизміне әсер ететін гендерде генетикалық вариацияларды анықтады. Триглицеридтердің жоғарылауы барлық қауіп санаттарындағы пациенттерде тіркелді, бұл өте жоғары қауіпті адамдарда ең жоғары жиілік (82 пациент). Липидті профильді талдау жалпы холестериннің төмен деңгейімен салыстырғанда жоғары қауіп тобында статистикалық тұрғыдан айтарлықтай жоғары екенін көрсетті ($228,8 \pm 35,2$ қарсы $207,8 \pm 30,3$ мг/дл; $p=0,0467$). HDL деңгейі қауіп деңгейіне кері байланысты көрсетті, бұл өте жоғары қауіп тобындағы ең төмен ($44,6 \pm 10,5$ қарсы $50,1 \pm 9,9$ мг / дл; $p=0,0411$). LDL және липопротеиндік емес холестерин статистикалық маңызды айырмашылықтарды көрсетпесе де, олардың өсу тенденциясы байқалды. Триглицеридтер де өсуге бейім болды, бірақ статистикалық маңыздылыққа жете алмады ($p>0,05$). Аполипопротеинінің жоғары тәуекелмен айтарлықтай төмендеуі байқалды ($p<0,0001$). APOE генотиптерінің таралуы (P.T388C) барлық қауіп топтарында ұқсас болды, TT генотипінің басым болуы ($\approx 58-67\%$) және CC генотипінің сирек кездесуі ($\leq 5,3\%$), статистикалық маңызды айырмашылықтар жоқ ($p>0,05$).

Қорытынды. Зерттеуде жүрек-қан тамырлары қауіп бар APOE (P.T388C) және GCKR генотиптері статистикалық маңызды байланыс анықталмады. Бұл бірлестіктерді растау немесе жоққа шығару үшін қосымша факторларды және үлгінің ұлғаюын ескере отырып, үлкен зерттеулер қажет.

Түйін сөздер. атеросклероз, гипертриглицеридемия, жүрек-қан тамырлары ауруы, APOE, GCKR

Дәйексөз үшін:

Бекбосынова М.С., Мирманова Ж.Ж., Шахмарова Т.К., Чамойева А.Е., Жалбинова М.Р., Сатвалдина Н.Н., Ережепов Д.А., Рахимова С.Е., Каиров У.Е., Данияров А.Ж., Иванова-Разумова Т.В., Андосова С.А., Сайлабаева А.И., Хамитов С.Р., Акильжанова А.Р. Гипертриглицеридемия және атеросклерозы бар қазақстандық когортадағы липидтермен байланысты гендердегі генетикалық нұсқалар // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), Б. 7-15. doi 10.34689/SH.2025.27.5.001

Introduction

Atherosclerosis (AS) remains the leading cause of cardiovascular morbidity and mortality worldwide and in Kazakhstan. Disorders of fat metabolism play a key role in its development. In addition to the already well-known risk factor - elevated levels of low-density lipoproteins (LDL), hypertriglyceridemia is essential. This condition, characterized by high triglyceride levels, contributes to endothelial dysfunction, inflammation of the vascular wall, and accelerated formation of atherosclerotic plaques. Thus, elevated triglycerides are recognized as an independent and controllable risk factor for cardiovascular diseases, especially in the context of atherosclerosis [1].

Genetic determinants play a significant role in the formation of dyslipidemia. Variants in the genes regulating lipid and carbohydrate metabolism (GCKR, SLC22A5, LPL, FLCN, LDLR, APOE) affect the lipid profile and metabolism [2]. Polymorphisms in GCKR and LPL are associated with increased triglyceride levels and the development of hypertriglyceridemia, whereas changes in LDLR, APOB, and PCSK9 are associated with familial

hypercholesterolemia. Additionally, variations in APOE and SLC22A5 affect the regulation of lipid and energy metabolism, which also affects cholesterol and triglyceride levels [3, 4].

Thus, studying the prevalence of genetic variants in genes involved in lipid metabolism is important for understanding the mechanisms of hypertriglyceridemia formation and its role in the development of atherosclerosis. The present study aimed to analyze such genes (GCKR, SLC22A5, LPL, FLCN, LDLR, APOE) in a cohort of patients from Kazakhstan with atherosclerosis and hypertriglyceridemia. The population of Kazakhstan is still underrepresented in international genetic research. Given the high prevalence of risk factors for cardiovascular diseases such as obesity, metabolic syndrome, and familial hyperlipidemia, it is necessary to study ethnically specific genetic variants that may influence risk patterns in different populations. Identification of common genetic variants associated with hyperlipidemia and their relationship to biochemical parameters of lipid metabolism in patients with varying degrees of risk of developing AS in the Kazakh

cohort was performed. The purpose of this study was to determine the prevalence of genetic variants in genes involved in lipid metabolism and their relationship to the lipid and metabolic profile in the Kazakh population with atherosclerosis.

Materials and methods

Patients

The study was performed according to the Declaration of Helsinki and was approved by the local Ethics Committee CF "University Medical Center", Astana, Kazakhstan (protocol №3/2023/PE from 14 July 2023). Every participant provided written informed consent before enrollment in the study and blood samples for DNA extraction.

The study included 402 patients with cardiovascular diseases aged from 23 to 65 years. Based on triglyceride

levels, patients with levels above normal were assigned to a separate group. As a result, 144 such patients were identified. They were divided into atherosclerosis risk categories in accordance with the ESC/EAS 2019 recommendations: low risk — 19 patients, high risk — 43 patients, and very high risk — 82 patients. Additionally, stratification was performed by gender and average age in each group [Fig. 1], [5].

Genomic DNA (gDNA) was extracted from whole blood using the Illustra blood GenomicPrep Mini Spin Kit. DNA concentration was determined spectrophotometrically on a NanoDrop 2000 instrument. DNA quality was assessed by electrophoresis in 1% agarose gel, and quantitative analysis was performed using a Qubit 2.0 fluorimeter.

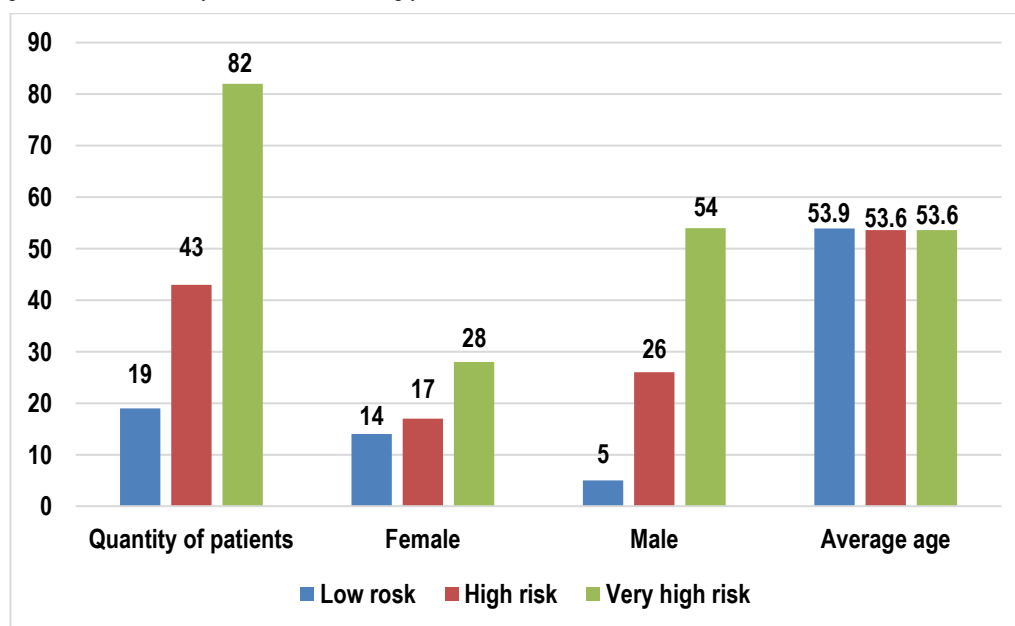


Figure 1. Distribution of patients by cardiovascular risk, quantity of patients, gender, and average age.

Preparation of DNA libraries

DNA libraries for whole exome sequencing were prepared using the Illumina DNA Prep with Enrichment protocol. The libraries were sequenced by high-throughput sequencing on a NovaSeq6000 instrument. Electrophoresis on a BioAnalyzer 2100 using the Agilent DNA 1000 Kit was employed to assess the quality of the libraries. The DNA concentration in libraries was determined by a fluorimetric method using Qubit 2.0 and Qubit TM ds High Sensitivity Assay kit.

To identify genetic factors associated with lipid metabolism disorders analysis of genes involved in lipid metabolism was performed. The focus of the study was on the *GCKR*, *SLC22A5*, *LPL*, and *FLCN* genes, which have been previously associated with the risk of hyperlipidemia and cardiometabolic disorders through population-based and genomic analyses.

A brief description of the functions of each gene follows:

GCKR (glucokinase regulatory protein) - this gene affects glucose and triglyceride metabolism by controlling the activity of the glucokinase enzyme [6].

SLC22A5 (carnitine transporter) - mutations in this gene, which encodes a carnitine transporter, can disrupt the beta-oxidation of fatty acids, leading to dyslipidemia [7].

LPL (lipoprotein lipase) - this gene encodes a key enzyme involved in the breakdown of triglycerides. Defective variants of *LPL* are the cause of hereditary hyperlipidemia type I [8].

FLCN (folliculin) - this gene is associated with energy metabolism and lipid regulation and may play a role in the development of metabolic syndrome [9].

Data analysis and classification of genetic variants

Sequenced samples were subjected to further bioinformatic analysis aimed at identifying genetic variants in genes associated with susceptibility to cardiovascular disease. Sequence data processing involved the use of SureCall (version 2.0.7.0), ANNOVAR, GATK, BWA, Bowtie, Bowtie 2, and VarScan software packages. International genomic databases, including ExAC, SIFT, ESP, GenBank, NCBI, EP 6500, 1000 Genomes, MutationTaster, SNPedia, Ensemble, and ClinVar, were utilized for variant annotation and filtering. Interpretation of the clinical significance of identified variants was performed according to the ACMG/AMP criteria (2015) using the InterVar platform (<https://wintervar.wglab.org/>) [10]. Based on this interpretation, variants were classified into one of five categories: pathogenic (P), likely pathogenic (LP),

variant of uncertain significance (VUS), likely benign (LB), or benign (B) [11]. Normality of data distribution was checked using the Kolmogorov-Smirnov and the Shapiro-Wilk test. For the comparison of more than two groups, One-way ANOVA and Kruskal-Wallis tests were performed.

Patients were evaluated comprehensively, considering both biochemical indicators of lipid profile and genetic variants associated with hyperlipidemia.

Results

During the sequencing of the whole exome, genetic variants associated with disorders of triglyceride metabolism were identified in patients with varying degrees of cardiovascular risk: 19 cases in the low-risk group, 43 cases in the high-risk group, and 82 cases in the very high-risk group. A comparative analysis of the biochemical parameters of triglycerides between these groups is presented in Table 1.

Table 1.

Comparative characteristics of biochemical parameters in patients with different levels of cardiovascular risk.

Variables	Low risk (n=19)	High risk (n=43)	Very high risk (n=82)	P-value
Age	44.6±9.6	52.3±7.9	56.3±6.1	0.000001
Body mass index (kg/m ²)	30.7±4.7	31.5±5.3	30.8±5.5	ns
Total cholesterol (mg/dL)	207.8±30.3	228.8±35.2	217.9±51.2	0.0467*
LDL-C (mg/dL)	139.3±30.5	156.3±27.5	149.2±43.6	ns
HDL-C (mg/dL)	50.1±9.9	47.8±10.7	44.6±10.5	0.0411*
Non-HDL-C (mg/dL)	157.7±30.4	181±33.6	173.4±47.9	ns
Glucose (mg/dL)	101.1±8.3	118.3±45.3	135.4±60.5	0.0004*
Apolipoprotein A (g/L)	1.4±0.3	1.3±0.3	1.1±0.3	<0.0001
Apolipoprotein B (g/L)	1.1±0.2	1.2±0.2	1.2±0.3	ns
Triglycerides (mg/dL)	206.5±73.1	256.8±214.1	241.9±96.7	ns
Lipoprotein (a) (mg/dL)	47.3±61.3	26.9±32.3	27±38.9	ns
Creatinine (mg/dL)	0.8±0.2	0.9±0.2	0.9±0.2	ns
C- reactive protein (mg/L)	0.3±0.4	0.3±0.2	0.7±3	ns
Homocysteine (μmol/L)	10.3±2.1	11.2±2.8	10.8±2.9	ns

Analysis of the lipid profile and markers of atherosclerosis depending on the degree of cardiovascular risk (low, high and very high) revealed several statistically significant differences. Total cholesterol was significantly higher in the high-risk group (228.8±35.2 mg/dl) compared with the low-risk group (207.8±30.3 mg/dl, $p=0.0467$). LDL (LDL-C) and non-lipoprotein cholesterol (non-HDL-C) levels did not differ statistically significantly between the groups ($p>0.05$), but there was a tendency to increase them in the high- and very high-risk groups. The level of high-density lipoprotein cholesterol (HDL-C) decreased with increasing cardiovascular risk and was significantly lower in the very high-risk group (44.6±10.5 mg/dl) compared with the low-risk group (50.1±9.9 mg/dl, $p=0.0411$). Triglyceride concentrations increased in the high-risk (256.8±214.1 mg/dl) and very high-risk (241.9±96.7 mg/dl) groups compared with the low-risk (206.5±73.1 mg/dl) groups, but the differences did not reach statistical significance ($p>0.05$). There was also a significant decrease in the level of apolipoprotein A ($p<0.0001$) with increased risk, which may indicate a decrease in the atheroprotective activity of high-density lipoproteins in these groups.

The analysis of genotype frequencies in the study cohort revealed statistically significant differences in a number of genes. In particular, the GCKR variant (c.G1004A) was exclusively represented in the low-risk group, where all participants had the GG genotype, and was completely absent in patients with high and very high risk. For another variant of GCKR (c.G307A), the GG genotype was dominant (94.7–100%), whereas the heterozygous GA variant was found only in low (5.3%) and very high (2.4%) risk groups. A similar pattern was observed for the genes SLC22A5 (c.G1451T,

c.G364T, c.C1400G), *FLCN* (c.G918A), *LPL* (c.G484A) and *LDLR* (c.C419T): homozygotes prevailed in all groups (up to 100%), and heterozygotes were detected in isolated cases or very rarely (about 1%). The APOE polymorphism (c.T388C) demonstrated a more pronounced distribution: the TT genotype was dominant in all groups (57.9–67.4%), the TC genotype was found in 28–36.8% of patients, and the CC genotype was rare (0–5.3%). For the APOE polymorphism (c.C526T), the CC genotype was found in the vast majority of patients (86–96.3%), while CT heterozygotes accounted for up to 14%. The *MYO15A* polymorphism (c.G5925A) was also characterized by a predominance of the GG genotype, and the GA variant was found in only one patient classified as a very high-risk group.

The table shows an analysis of the relationship between APOE (c.T388C) genotypes and treatment response rates according to various genetic models (codominant, dominant, recessive, overdominant, and log-additive). The average response ranges from 1.36 to 1.6, depending on the genotype. However, in all models, the differences between the groups did not reach statistical significance. The highest response was observed in carriers of the C/C genotype (1.6 ± 0.4), however, due to the small number of the group ($n=5$), the confidence interval was wide, and the difference with other genotypes turned out to be statistically insignificant (for example, $p=0.66$ in the codominant model). In all models, p -values > 0.05 , including: Codominant model: $p = 0.66$ Dominant model: $p = 0.55$ Recessive model: $p = 0.61$ Overdominant model: $p = 0.41$ Log-additive model: $p = 0.73$. Also, the AIC and BIC indicators do not show an improvement in the model when APOE (c.T388C) is included, which additionally indicates the absence of a significant association.

Table 2.

Distribution of lipid-associated gene genotypes among patients with varying degrees of cardiovascular risk.

Genes	Low risk (n=19)	High risk (n=43)	Very high risk (n=82)
GCKR (c.G1004A)			
GG (%)	19 (100 %)	0 (0 %)	0 (0 %)
GA (%)	0 (0 %)	0 (0 %)	0 (0 %)
AA (%)	0 (0 %)	0 (0 %)	0 (0 %)
GCKR (c.G307A)			
GG (%)	18 (94.7 %)	43 (100 %)	80 (97.6 %)
GA (%)	1 (5.3 %)	0 (0 %)	2 (2.4 %)
AA (%)	0 (0 %)	0 (0 %)	0 (0 %)
SLC22A5 (c.G1451T)			
GG (%)	0 (0 %)	42 (97.7 %)	82 (100 %)
GT (%)	0 (0 %)	1 (5.3 %)	0 (0 %)
TT (%)	0 (0 %)	0 (0 %)	0 (0 %)
SLC22A5 (c.G364T)			
GG (%)	0 (0 %)	0 (0 %)	82 (100 %)
GT (%)	0 (0 %)	0 (0 %)	0 (0 %)
TT (%)	0 (0 %)	0 (0 %)	0 (0 %)
SLC22A5 (c.C1400G)			
CC (%)	0 (0 %)	0 (0 %)	81 (98.8 %)
CG (%)	0 (0 %)	0 (0 %)	1 (1.2 %)
GG (%)	0 (0 %)	0 (0 %)	0 (0 %)
FLCN (c.G918A)			
GG (%)	0 (0 %)	0 (0 %)	81 (98.8 %)
GA (%)	0 (0 %)	0 (0 %)	1 (1.2 %)
AA (%)	0 (0 %)	0 (0 %)	0 (0 %)
LPL (c.G484A)			
GG (%)	0 (0 %)	0 (0 %)	81 (98.8 %)
GA (%)	0 (0 %)	0 (0 %)	1 (1.2 %)
AA (%)	0 (0 %)	0 (0 %)	0 (0 %)
APOE (c.T388C)			
TT (%)	11 (57.9 %)	29 (67.4 %)	55 (67.1 %)
TC (%)	7 (36.8 %)	14 (32.6 %)	23 (28 %)
CC (%)	1 (5.3 %)	0 (0 %)	4 (4.9 %)
APOE (c.C526T)			
CC (%)	17 (89.5 %)	37 (86 %)	79 (96.3 %)
CT (%)	2 (10.5 %)	6 (14 %)	3 (3.7 %)
TT (%)	0 (0 %)	0 (0 %)	0 (0 %)
LDLR (c.C419T)			
CC (%)	0 (0 %)	0 (0 %)	81 (98.8 %)
CT (%)	0 (0 %)	0 (0 %)	1 (1.2 %)
TT (%)	0 (0 %)	0 (0 %)	0 (0 %)
MYO15A (c.G5925A)			
GG (%)	0 (0 %)	43 (100 %)	81 (98.8 %)
GA (%)	0 (0 %)	0 (0 %)	1 (1.2 %)
AA (%)	0 (0 %)	0 (0 %)	0 (0 %)

Table 3.

Analysis of the association of APOE (c.T388C) polymorphism with treatment response in various genetic models (n=144)

APOE (c.T388C) association with response Status (n=144, crude analysis)							
Model	Genotype	n	Response mean (s.e.)	Difference (95% CI)	P-value	AIC	BIC
Codominant	T/T	95	1.46 (0.07)	0	0.66	318.8	330.7
	T/C	44	1.36 (0.11)	-0.10 (-0.36 - 0.16)			
	C/C	5	1.6 (0.4)	0.14 (-0.51 - 0.78)			
Dominant	T/T	95	1.46 (0.07)	0	0.55	317.3	326.2
	T/C-C/C	49	1.39 (0.11)	-0.08 (-0.32 - 0.17)			
Recessive	T/T-T/C	139	1.43 (0.06)	0	0.61	317.4	326.3
	C/C	5	1.6 (0.4)	0.17 (-0.47 - 0.81)			
Overdominant	T/T-C/C	100	1.47 (0.07)	0	0.41	317	325.9
	T/C	4	1.36 (0.11)	-0.11 (-0.36 - 0.15)			
Log-additive	---	---	---	-0.04 (-0.25 - 0.18)	0.73	317.6	3265

Conclusion: According to the results of the analysis, there was no statistically significant relationship between the APOE (c.T388C) polymorphism and the level of response to treatment in any of the tested genetic models. The data suggests that APOE (c.T388C) probably has no significant effect on this phenotype in this sample. For a more accurate estimate, an extended analysis is needed, taking into account covariates and increasing the sample size.

Discussions.

This study is the first to analyze the genetic variants involved in the regulation of lipid metabolism in a Kazakh cohort of patients with hypertriglyceridemia and atherosclerosis. The results obtained convincingly demonstrate that triglyceride metabolism disorders are one of the fundamental factors determining increased cardiovascular risk. Despite the absence of statistically significant differences in triglyceride levels between risk groups, there was a marked tendency for their increase in high- and very high-risk groups. This phenomenon correlates with data from international studies highlighting the role of hypertriglyceridemia in synergy with elevated LDL cholesterol levels in accelerating the atherosclerotic process through the induction of inflammation and endothelial dysfunction. The observed decrease in HDL cholesterol and apolipoprotein A levels in high-risk patients indicates a compromise of the atheroprotective potential of high-density lipoproteins, which is a pathognomonic sign of dyslipidemia in atherosclerosis. This highlights the importance of an integrated approach to assessing the lipid profile in the context of risk stratification. Genetic analysis of the APOE polymorphism (p. T388C) did not reveal significant differences between risk groups, which may indicate a limited contribution of this particular variant to the formation of cardiovascular risk in the studied sample. However, the potential effect of other APOE variants, as well as polymorphisms in the GCKR, LPL, and SLC22A5 genes, which, according to literature data, have a significant effect on triglyceride metabolism, remains the subject of further research. It should be noted that the limited sample size (n=144 patients) could affect the statistical power of the study. Large-scale studies involving diverse ethnic groups and the use of advanced multifactorial analysis methods are needed to more accurately validate the associations between genetic variants and the risk of atherosclerosis in the Kazakh population. Thus, this study confirms the critical role of hypertriglyceridemia as a predictor of increased cardiovascular risk. The study of the genetic determinants of lipid metabolism opens up new horizons for the development of highly accurate risk stratification methods and the creation of personalized strategies for the prevention and treatment of atherosclerosis, which is important for public health in Kazakhstan.

Conclusions.

In a study of Kazakhstani patients with atherosclerosis and elevated triglyceride levels, genetic features related to the regulation of fat metabolism were found. High triglyceride levels are known to be associated with an increased risk of cardiovascular disease. This confirms the importance of this indicator as an independent factor affecting heart health. In high-risk patients, there was a decrease in "high" HDL cholesterol and apolipoprotein A,

which indicates a weakening of the protective mechanisms preventing the development of atherosclerosis. The genetic variant APOE (C. T388C) was equally common in all risk groups, so its association with the risk of cardiovascular diseases in this sample was not established. The data obtained emphasize the need for further research aimed at identifying specific genetic variants characteristic of the population of Kazakhstan that affect lipid metabolism and the risk of atherosclerosis.

Conflict of interest: The authors declare that they have no conflicts of interest.

Contribution of the authors: Each of the authors made an equal contribution.

Funding: This research has been funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (AP23490249, AR19677442, BR24993023, BR21881970, BR24992841, BR27199879) and Nazarbayev University under the Collaborative Research Program (Grant № 211123CRP1608, Ainur Akilzhanova).

Literature:

1. Jacqueline S. Dron Robert A. Hegele. Genetics of Hypertriglyceridemia // Front. Endocrinol., 24 July 2020, Sec. Clinical Diabetes, Volume 11 - 2020 | <https://doi.org/10.3389/fendo.2020.00455>
2. Alves M., Laranjeira F., Correia-da-Silva G. Understanding Hypertriglyceridemia: Integrating Genetic Insights. Genes 2024, 15, 190. <https://doi.org/10.3390/genes15020190>
3. Ana M. Bea, Asier Larrea-Sebal, Victoria Marco-Benedi, Kepa B. Uribe, Unai Galicia-Garcia, Itziar Lamiquiz-Moneo, Martín Laclaustra, Belén Moreno-Franco, Pablo Fernandez-Corredoira, Salvador Olmos, Fernando Civeira, César Martín and Ana Cenarro. Contribution of APOE Genetic Variants to Dyslipidemia // Arteriosclerosis, Thrombosis, and Vascular Biology, volume 43, number 6, 1066-1077, 2023. Doi: <https://doi.org/10.1161/ATVBAHA.123.318977>
4. Isabel De Castro-Orós, Ana Cenarro, María Teresa Tejedor, Lucía Baila-Rueda, Rocío Mateo-Gallego, Itziar Lamiquiz-Moneo, Miguel Pocoví, Fernando Civeira. Common Genetic Variants Contribute to Primary Hypertriglyceridemia Without Differences Between Familial Combined Hyperlipidemia and Isolated Hypertriglyceridemia // Circulation: Cardiovascular Genetics, volume 7, number 6, pages 814-821, 2024. <https://doi.org/10.1161/CIRCGENETICS.114.00052>
5. Mach F., Baigent C., Catapano A.L., Koskinas K.C., Casula M., Badimon L., et al. 2019 ESC/EAS Guidelines for the Management of dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk. European Heart Journal. 2019 Aug 31;41(1). DOI: <https://doi.org/10.1093/eurheartj/ehz455>
6. K. Horvatovich, Bokor S, Polgar N, P. Kisfali, F. Hadarits, L. Jaromi, et al. Functional glucokinase regulator gene variants have inverse effects on triglyceride and glucose levels, and decrease the risk of obesity in children. Diabetes & Metabolism. 2011 Apr 22;37(5):432–9. DOI: <https://doi.org/10.1016/j.diabet.2011.02.003>
7. Longo N. et al. Primary carnitine deficiency. GeneReviews®. 2006.
8. Brunzell J.D., Per-Henrik Iverius, Scheibel MS, Fujimoto WY, Hayden MR, McLeod R, et al. Primary

Lipoprotein Lipase Deficiency. Springer eBooks. 1986 Jan 1;227–39. DOI: https://doi.org/10.1007/978-1-4684-1262-8_20

9. Hisashi Hasumi, Baba M., Hasumi Y., Huang Y., Oh H., Hughes R.M., et al. Regulation of Mitochondrial Oxidative Metabolism by Tumor Suppressor FLCN. *Journal of the National Cancer Institute*. 2012 Nov 20;104(22):1750–64. DOI: <https://doi.org/10.1093/jnci/djs418>

10. Richards S., Aziz N., Bale S., Bick D., Das S., Gastier-Foster J., et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular

Pathology. *Genetics in medicine: official journal of the American College of Medical Genetics*. 2015;17(5):405–24. DOI: <https://doi.org/10.1038/gim.2015.30>

11. Priori S.G., Wilde A.A., Horie M., Cho Y., Behr E.R., Berul C., Blom N., Brugada J., Chiang C.E., Huikuri H., Kannankeril P., Krahn A., Leenhardt A., Moss A., Schwartz P.J., Shimizu W., Tomaselli G., Tracy C. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013 Dec;10(12):1932–63. DOI: 10.1016/j.hrthm.2013.05.014

Author Information

Makhabbat S. Bekbossynova – Doctor of Medical Sciences, Deputy Chairman of the Management Board, cardiologist, “University Medical Center” Corporate Fund, Astana, Kazakhstan, Turan avenue, 38, cardiacsurgeryres@gmail.com, <https://orcid.org/0000-0003-2834-617X> ; 8 (7172) 70 31 00

Zhanel Zh. Mirmanova - Assistant Researcher, Laboratory of Genomic and Personalized Medicine, Center for Life Sciences, National Laboratory Astana, Astana, Kazakhstan, <https://orcid.org/0000-0002-0284-3891>

Tomiris K. Shakhmarova - Assistant Researcher, Laboratory of Genomic and Personalized Medicine, Center for Life Sciences, National Laboratory Astana, Astana, Kazakhstan, <https://orcid.org/0009-0008-6884-3908>

Ayaulym E. Chamoieva - Junior Researcher, Laboratory of Genomic and Personalized Medicine, Center for Life Sciences, National Laboratory Astana, Astana, Kazakhstan, <https://orcid.org/0000-0003-0877-3537>

Madina R. Zhalbinova - Junior Researcher, Laboratory of Genomic and Personalized Medicine, Center for Life Sciences, National Laboratory Astana, Astana, Kazakhstan, <https://orcid.org/0000-0001-9704-8913>

Nazerke N. Satvaldina - Junior Researcher, Laboratory of Genomic and Personalized Medicine, Center for Life Sciences, National Laboratory Astana, Astana, Kazakhstan, <https://orcid.org/0000-0002-0611-4485>

Dauren A. Yerezhepov - Leading Researcher, Laboratory of Genomic and Personalized Medicine, Center for Life Sciences, National Laboratory Astana, Astana, Kazakhstan, <https://orcid.org/0000-0002-4161-1348>

Saule E. Rakhimova – Leading Researcher, Laboratory of Genomic and Personalized Medicine, Center for Life Sciences, National Laboratory Astana, Astana, Kazakhstan, <https://orcid.org/0000-0002-8245-2400>

Ulykbek E. Kairov – Head of the Laboratory of bioinformatics and systems biology, Center for Life Sciences, National Laboratory Astana, Astana, Kazakhstan, <https://orcid.org/0000-0001-8511-8064>

Asset Zh. Daniyarov ², Junior Researcher, Laboratory of bioinformatics and systems biology, Center for Life Sciences, National Laboratory Astana, Astana, Kazakhstan, <https://orcid.org/0000-0003-3886-718X>

Saltanat A. Andossova - candidate of medical sciences, Chief of Cardiology #1 Department, “University Medical Center” Corporate Fund, Astana, Kazakhstan, Turan avenue, 38, <https://orcid.org/0000-0001-7259-183X>

Aliya I. Sailybaeva - Chief of Research Department, “University Medical Center” Corporate Fund, Astana, Kazakhstan, Turan avenue, 38, s.aliya@umc.org.kz, <https://orcid.org/0000-0002-1489-3837> ; +7 701 795 17 76

Sadyk R. Khamitov¹, - Manager of Research Department, “University Medical Center” Corporate Fund, Astana, Kazakhstan, Turan avenue, 38, <https://orcid.org/0000-0001-6296-0507>

*Corresponding author:

Ainur R. Akilzhanova – Doctor of Medical Sciences, PhD, M.D., Professor, Head of Laboratory of Genomic and Personalized Medicine, Acting director, Center for Life Sciences, National Laboratory Astana, Astana, Kazakhstan, <https://orcid.org/0000-0001-6161-8355>

Post address: Kabanbay batyr avenue 53, Astana, 010000, Republic of Kazakhstan;

E-mail: akilzhanova@nu.edu.kz

Phone: +7 777 658 4089 +7(7172)70-6501