Macedonian pharmaceutical bulletin, **71** (1) 11 - 17 (2025)
ISSN: 1857-8969
DOI: 10.33320/maced.pharm.bull.2025.71.01.002
Original scientific paper

Analysis of the *AKR1D1*36* (rs1872930) genetic variant in the Kosovo population: allele frequency and genotype distribution

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Received: January 2025; Accepted: February 2025

Abstract

Aldo-keto reductases (AKRs), particularly family member D1 (AKR1D1), play a crucial role in steroid hormone metabolism and bile acid biosynthesis. Following the identification of the *AKR1D1*36 C>T (rs1872930)* variant as a predictive marker for the activity of multiple cytochrome P450 enzymes within the metabolic network, studies have been conducted that potentially associate it with therapy response. However, its prevalence and association with cardiovascular disease (CVD) remain understudied, particularly in European populations, including Kosovo. This study aimed to investigate the frequency of the *AKR1D1*36* variant in a cohort of 384 unrelated individuals of Albanian ethnicity from Kosovo, comprising 150 CVD patients and 234 healthy controls. No significant differences in allele or genotype distributions were observed between the cardiovascular disease (CVD) patients and healthy controls ($p > 0.05$), indicating no independent association between the *AKR1D1*36* variant and CVD. The overall frequency of the *AKR1D1*36* allele in the total study population was 21.74%, which is consistent with the frequency reported for European population. The distribution of *AKR1D1*36* genotypes in the study population was 5.73% for **36/*36*, 32.03% for **1/*36*, and 62.4% for **1/*1*. These findings provide the first insight into *AKR1D1*36* prevalence in Kosovo, contributing to the understanding of genetic diversity in underrepresented European groups. While no direct link to CVD was observed, these findings highlight the need for further research into *AKR1D1*36* variation, particularly in the context of pharmacogenetics and disease susceptibility.

Key words: AKR1D1*36, cardiovascular disease, Kosovo, genetic polymorphism, pharmacogenetics, Caucasian population

Introduction

Aldo-keto reductases (AKRs) are a family of NADPH-dependent enzymes that catalyze the reduction of carbonyl groups in endogenous and exogenous compounds, playing an integral role in metabolic homeostasis. Among these, AKR1D1 is integral to the stereospecific reduction of Δ4-3-ketosteroids, key process in bile acid biosynthesis and the regulation of steroid hormone bioavailability and activity (Barski et al., 2008; Penning., 2015, 2019). This enzyme facilitates the conversion of cholesterol to the

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primary bile acids, chenodeoxycholic acid and cholic acid. In addition to their role in lipid solubilization and absorption, bile acids function as signaling molecules that regulate key metabolic pathways via nuclear hormone receptors, including the pregnane X receptor (PXR) and the constitutive androstane receptor (CAR). These receptors modulate the expression of cytochrome P450 (CYP450) enzymes, which are pivotal in the metabolism of drugs, lipids, and steroid hormones (Chen and Penning, 2014; Rižner and Penning, 2014). Dysregulation of AKR1D1 expression has been implicated in a range of metabolic and pathological conditions, including bile acid synthesis disorders (cholestasis and bile acid malabsorption), non-alcoholic fatty liver disease (NAFLD), congenital adrenal hyperplasia (CAH) and hormone-dependent cancers (Mindnich et al., 2011; Nikolaou et al., 2019; Zhu et al., 2021). The enzyme's role in metabolizing reactive lipid peroxidation products also suggests its involvement in the pathogenesis of inflammatory diseases, neurodegenerative conditions, diabetes and cardiovascular diseases (Appanna et al., 2021; Cacabelos, 2020; Valanejad et al., 2018; Williams et al., 2016).

Beyond its role in disease susceptibility, AKR1D1 has gained attention for its potential in pharmacogenetics and personalized medicine. A study by Chaudry et al. (2013) identified *AKR1D1* as a novel candidate gene regulating *CYP450* co-expression. Specifically, genetic variation within the gene encoding for this enzyme, notably the *AKR1D1*36 C>T (rs1872930)* polymorphism, was associated with increased mRNA expression of *AKR1D1.* Furthermore, this variant was found to correlate with enhanced expression and activity of several *CYP450* enzymes, including *CYP2B6, CYP2C19, CYP2C8,* and *CYP3A4.* The authors proposed that the *AKR1D1**36 genetic variant could be a predictive marker for the activity of multiple P450 enzymes within the metabolic network (Chaudhry et al., 2013; Tracy et al., 2016).

Recent research has highlighted the significance of the AKR1D1**36 (rs1872930)* variant in drug metabolism. This genetic variation has been independently associated with clopidogrel treatment outcomes (Kapedanovska Nestorovska et al., 2019a). Furthermore, when considered alongside the CYP2C9*2 genotype, the AKR1D1*36 allele provided a more accurate prediction of ibuprofen pharmacokinetics compared to CYP2C9*2 alone (Kapedanovska Nestorovska et al., 2019b), underscoring the combined genetic influence on drug metabolism. The *AKR1D1*36* variant has a reported global minor allele frequency (MAF) of 22.2%, with significant population-specific variations. The MAF is observed to be 12% in African populations, 21.4% in European populations, 23.7% in Asian populations and 34% American populations, highlighting the ethnic diversity in allele distribution (Phan et al., 2020). Despite its potential clinical importance, data on this genetic variant in European populations with distinct geographic and ethnic characteristics are sparse, and its frequency in the Kosovo population is unreported. Investigating this variant in Kosovo is particularly relevant due to the limited representation of this region in genomic studies, which hinders the application of pharmacogenomics and precision medicine in local clinical practice.

This study aims to address these gaps by determining the frequency of the *AKR1D1*36 (rs1872930)* variant in a cohort from Kosovo and evaluating its association with cardiovascular disease. The findings will contribute to a better understanding of population-specific genetic diversity and its implications for cardiovascular risk and personalized medicine in under-researched populations.

Material and methods

Study population

The study population comprised 384 unrelated individuals of Albanian ethnicity from Kosovo (Table 1). Of these, 150 individuals (40%; mean age 67.95 ± 10.65; 90 men and 60 women) were patients recruited from the Cardiology Clinic of the University Clinical Center of Kosovo between May 2023 and January 2024. These patients were indicated for clopidogrel treatment due to diagnosed cardiovascular conditions, including percutaneous coronary intervention (PCI) with or without stenting, acute coronary syndrome (ACS), myocardial infarction (MI), coronary artery disease (CAD), coronary artery bypass graft (CABG), peripheral arterial disease (PAD), cerebrovascular disease (CVA), with a history of multiple atherothrombotic risk factors, such as Type 1 or Type 2 diabetes, hypercholesterolemia, or hypertension. The remaining 234 subjects (60%; mean age 36.01 ± 12.70; 116 women and 118 men) were healthy participants from the historical genetic control group derived from previous research conducted at the Center for Biomolecular Pharmaceutical Analysis, Faculty of Pharmacy, UKIM, Skopje, Republic of Macedonia.

Demographic and clinical data for the patients were manually collected from their medical records. Individual informed consent was obtained from all subjects on the condition of full anonymity. The study complied with the Declaration of Helsinki and the protocol, and it was approved by the Committee Ethics of Alma Mater Europaea Campus College "REZONANCA" (Protocol No: AD-762/23) and Chamber of Pharmacists of Kosova (No.105).

Genotyping procedures

Genomic DNA was extracted from 3 mL of whole blood collected in EDTA blood tubes, utilizing the NX-48S Genomic DNA Kit according to the manufacturer's protocol (Genolution Inc., Seoul, Republic of Korea). The extraction process was performed at the Prolab Laboratory Diagnostics Center in Prishtina, Kosovo. Conversely, DNA samples from the historical control group were previously

isolated at the Center for Biomolecular and Pharmaceutical Analysis, Faculty of Pharmacy, Ss Cyril and Methodius University in Skopje, N. Macedonia, using a QIAGEN DNA extraction kit (QIAGEN AS, Oslo, Norway). All DNA samples were stored at –20 °C until genotyping analysis. Genotyping for the *AKR1D1*36 C>T (rs1872930)* variant was conducted for both groups at the Center for Biomolecular and Pharmaceutical Analysis, Faculty of Pharmacy, Ss Cyril and Methodius University in Skopje, N. Macedonia. DNA concentrations were measured spectrophotometrically using NanoDrop®, with sample purity evaluated through the 260/280 nm absorbance ratio. DNA integrity was assessed by 0.8% agarose gel electrophoresis with ethidium bromide staining. Identification of the *AKR1D1*36 C>T (rs1872930)* variant alleles was performed using real-time polymerase chain reaction (RT-PCR) on the MxPro 3005P system (Stratagene, La Jolla, CA, USA). TaqMan SNP and drug metabolism genotyping assays were employed in accordance with the manufacturer's instructions (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

Observed and expected allele and genotype frequencies were compared using the Hardy-Weinberg equilibrium (HWE), and deviations from HWE were assessed using the Chi-squared test. Fisher's exact test was employed to evaluate differences in allele frequencies and genotype distributions between the two subject groups (patients and healthy genetic controls). Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated to estimate the strength of associations. Statistical significance was defined as $p \leq 0.05$. Within the patient group, stratified analyses were performed to assess the effect of *AKR1D1*36* genotypes while accounting for potential confounders or effect modifiers (e.g., age, gender, diabetes mellitus, history of myocardial infarction, and PCI stenting). All statistical analyses were conducted using MedCalc version 14.12.0.

Results and discussion

The distribution of the *AKR1D1*36* allelic variant and genotypes in both the patient and healthy control groups is summarized in Table 2. The *AKR1D1*36* allele was observed at a frequency of 23.67% in the patient group and 20.51% in the control group. Genotype distributions conformed to Hardy-Weinberg equilibrium in both groups ($\chi^2 = 0.52$, $p = 0.47$ for the patient group; $\chi^2 = 0.78$, $p = 0.38$ for the control group). The proportions of individuals with the **36/*36*, **1/*36*, and **1/*1* genotypes in the patient group were 6.67%, 34.0%, and 59.33%, respectively, compared to 5.13%, 30.77%, and 64.10% in the control group. Statistical analysis revealed no significant differences in allele frequencies or genotype distributions between the two groups across the allelic, codominant, and dominant models of analysis (all $p > 0.05$).

Table 3 summarizes the demographic and clinical characteristics of the patient group, stratified by *AKR1D1*36* status. Among the 150 patients, 67.30% had hypertension, 43.30% had diabetes mellitus, and 4.0% had dyslipidemia. Furthermore, 36.30% of the patients exhibited more than one comorbidity. Statistical analysis revealed no significant differences in the distribution of the AKR1D1 polymorphism across all statistical models (allelic, codominant, and dominant) when comparing the clinical and demographic subgroups of patients (all $p > 0.05$).

Table 1. Demographic and clinical characteristics of patients and healthy controls

Demographic and clinical characteristic		Patients (N=150) n *(freq.)*	Controls (N=234) n *(freq.)*
Age (mean ± SD)	*Years*	67.95 ± 10.65	36.01 ± 12.70
	range	34 - 88	20 - 65
Gender	*Male*	90 *(0.60)*	118 *(0.50)*
	Female	60 *(0.40)*	116 *(0.50)*
Number of cardiovascular risk factors	*One*	97 *(0.65)*	
	More than one	53 *(0.35)*	
Diabetes mellitus	*With*	65 *(0.43)*	
	Without	85 *(0.57)*	
Hypertension	*With*	101 *(0.67)*	
	Without	49 *(0.33)*	
Dyslipidemia	*With*	6 *(0.04)*	
	Without	144 *(0.96)*	

Table 2. Distribution of AKR1D1*36 allelic variant and genotypes in patient and healthy control groups

*AKR1D1*36* genetic variant	Patients n *(freq.)*		Controls n *(freq.)*		OR	95% CI	p -Value
Genotype							
*1/*1	89	*(0.59)*	150	*(0.64)*		reference	
*1/*36	51	*(0.34)*	72	*(0.30)*	1.11	0.85 - 1.45	0.43
*36/*36	10	*(0.67)*	12	*(0.51)*	1.22	0.75 - 1.98	0.45
*1/*36 and*36/*36	61	*(0.41)*	84	*(0.36)*	1.13	0.89 - 1.45	0.35
Allele							
*1	229	*(0.76)*	372	*(0.79)*		reference	
*36	71	*(0.23)*	96	*(0.21)*	1.12	0.91 -1.37	0.30

Table 3. Distribution of AKR1D1*36 allele and genotypes by demographic and clinical characteristics in the patient population

Demographic and clinical characteristics		*AKR1D1*36* variant									
		Genotype, *n (freq.)*						Allele, *n (freq.)*			
		*1/*1		*1/*36		*36/*36		*1		*36	
Gender	*Male*	52	*(0.58)*	31	*(0.34)*	7	*(0.08)*	135	*(0.75)*	45	*(0.25)*
	Female	37	*(0.62)*	20	*(0.33)*	3	*(0.05)*	94	*(0.78)*	26	*(0.22)*
Number of Cardiovascular risk factors	*One*	53	*(0.55)*	38	*(0.39)*	6	*(0.06)*	144	*(0.74)*	50	*(0.26)*
	More than one	36	*(0.68)*	13	*(0.25)*	4	*(0.07)*	85	*(0.80)*	21	*(0.20)*
Diabetes mellitus	*With*	43	*(0.66)*	16	*(0.25)*	6	*(0.09)*	102	*(0.78)*	28	*(0.22)*
	Without	46	*(0.54)*	35	*(0.41)*	4	*(0.05)*	127	*(0.11)*	43	*(0.04)*
Hypertension	*With*	65	*(0.64)*	29	*(0.29)*	7	*(0.07)*	159	*(0.79)*	43	*(0.21)*
	Without	24	*(0.49)*	22	*(0.45)*	3	*(0.06)*	70	*(0.71)*	28	*(0.29)*
Dyslipidemia	*With*	4	*(0.67)*	2	*(0.33)*	0	*(0.00)*	10	*(0.83)*	2	*(0.17)*
	Without	85	*(0.59)*	49	*(0.34)*	10	*(0.07)*	219	*(0.76)*	69	*(0.24)*

Table 4. Genotype distribution and allelic frequency of the AKR1D1*36 (rs1872930) variant in the total study population from Kosovo (N = 384)

*AKR1D1*36* variant	n	Frequency	
		observed	*expected*
Genotype			
*1/*1	239	*0.623*	*0.613*
*1/*36	123	*0.320*	*0.340*
*36/*36	22	*0.057*	*0.047*
Allele			
*1	601	*0.783*	
*36	167	*0.217*	

Given that no significant differences were observed between the patient and healthy control groups, as shown in Table 2, their data were merged for subsequent analysis. The overall frequency of the *AKR1D1*36* variant allele in the total study population, comprising 384 subjects, was estimated at 21.74%. The *AKR1D1*36* genotype distribution in the combined group was in accordance with Hardy-Weinberg equilibrium (χ^2 = 1.33, p = 0.25). The frequencies of the *AKR1D1*36* genotypes were 5.73% for **36/*36*, 32.03% for **1/*36*, and 62.4% for **1/*1* (Table 4).

In this study, we evaluated the association between the *AKR1D1*36 (rs1872930)* genetic variant and cardiovascular disease (CVD) risk in a population from

Kosovo. Our results revealed no significant association between the *AKR1D1*36* allele or genotype frequencies and CVD, suggesting that this variant may not contribute directly to cardiovascular disease susceptibility in this population. Despite the lack of a significant association with cardiovascular disease (CVD), our study revealed a noteworthy frequency of the *AKR1D1*36* variant in the Kosovo population. The overall frequency of the AKR1D1*36 allele in our Kosovo population (21.74%) aligns with global and European averages (21.7% and 21.4%, respectively) (Phan et al., 2020), but shows variability when compared to other European populations. Notably, there is a geographical gradient observed, with higher frequencies found in southern European populations (e.g., N. Macedonia and Spain; both 25%) and lower frequencies in northern European populations (Denmark - 12%, Finland - 16.4%, Estonia - 16.9%, the Netherlands - 18%, Sweden- 19.8%, and the United Kingdom - 20.8%) (Kapedanovska Nestorovska et al., 2018; National Center for Biotechnology Information, 2024). This gradient suggests potential geographic and ethnic factors influencing the prevalence of the *AKR1D1*36* variant across Europe. However, due to the limited available data on this variant in diverse European populations, further research is needed to better understand the regional and ethnic variation in its frequency and its potential implications for health and disease susceptibility.

The frequency data from this study provides a valuable reference point for future research into the genetic makeup of the Kosovo population and its implications for health outcomes. Given the importance of defining genetic variation in under-researched populations, this study contributes to the growing body of knowledge on the prevalence of genetic variants in different ethnic groups. Future studies with larger sample sizes, expanded genetic analyses, and consideration of lifestyle and environmental factors are warranted to further investigate the potential role of AKR1D1 in complex diseases, including cardiovascular conditions.

This study has several limitations that should be acknowledged. The relatively small sample size may have limited the statistical power to detect subtle associations between the *AKR1D1*36* variant and *CVD.* Expanding the cohort in future research would enhance the robustness of the findings. Moreover, while this provides valuable insights into a largely under-researched population, the findings may not be directly extrapolated to other ethnic groups within the region or to broader European Caucasian populations, which may exhibit distinct genetic variations. Additionally, the study did not incorporate functional assays or in-depth phenotypic analyses to elucidate the biological mechanisms underlying the potential role of *AKR1D1*36* in CVD risk. Furthermore, the influence of potential confounding factors, such as environmental exposures, lifestyle variables, and interactions with other genetic variants, was not comprehensively addressed, which may have influenced the findings regarding its correlation with the CVD. Addressing these limitations in future studies will be critical to fully understand the implications of *AKR1D1* polymorphisms in disease susceptibility and therapeutic responses.

Conclusion

This study represents the first investigation of the *AKR1D1*36 (rs1872930)* variant in the Kosovo population and its potential association with cardiovascular disease (CVD). Our findings indicate that the prevalence of the *AKR1D1**36 allele in this population closely mirrors frequencies reported in other Caucasian populations. However, the lack of a significant association between this variant and CVD in our cohort suggests that *AKR1D1*36* does not independently contribute to cardiovascular risk. These findings lay the groundwork for future research to explore the broader implications of *AKR1D1* genetic variation, particularly in the field of pharmacogenetics, where its potential influence on drug metabolism, treatment outcomes, and susceptibility to other complex diseases warrants further investigation.

Acknowledgments

The authors extend their gratitude to the patients who participated in this study. We also acknowledge the invaluable support of the researchers from the Cardiology Clinic of the University Clinical Center of Kosovo for their assistance in patient identification and data acquisition. Additionally, we are thankful to the team at the Center for Biomolecular Pharmaceutical Analyzes (CBPA), Faculty of Pharmacy, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia, for their expertise and assistance with the genotyping procedures.

References

Appanna, N., Gibson, H., Gangitano, E., Dempster, N.J., Morris, K., George, S., Arvaniti, A., Gathercole, L.L., Keevil, B., Penning, T.M., Storbeck, K.H., Tomlinson, J.W, Nikolaou N., 2021. Differential activity and expression of human 5β-reductase (AKR1D1) splice variants. J. Mol. Endocrinol. 66(3), 181-194. doi: 10.1530/JME-20-0160.

Barski, O.A., Tipparaju, S.M. & Bhatnagar, A., 2008. The Aldo-Keto Reductase Superfamily and its Role in Drug Metabolism and Detoxification. Drug Metab. Rev. 40(4), 553-624. doi:10.1080/03602530802431439.

Cacabelos, R., 2020. Pharmacogenomics of Cognitive Dysfunction and Neuropsychiatric Disorders in Dementia. Int. J. Mol. Sci. 21(9), 3059. doi: 10.3390/ijms21093059.

Chaudhry, A.S., Thirumaran, R.K., Yasuda, K., Yang, X., Fan, Y., Strom, S.C. and Schuetz, E.G., 2013. Genetic Variation in Aldo-Keto Reductase 1D1 (AKR1D1) Affects the Expression and Activity of Multiple Cytochrome P450s. Drug Metab. Dispos. 41(8), 1538-1547.

doi:10.1124/dmd.113.051672

Chen, M. & Penning, T.M., 2014. 5β-Reduced steroids and human Δ(4)-3-ketosteroid 5β-reductase (AKR1D1). Steroids 83, 17-26. doi: 10.1016/j.steroids.2014.01.013.

Kapedanovska-Nestorovska, A., Dimovski, A.J., Sterjev, Z., Matevska Geskovska, N., Suturkova, L., Ugurov, P., Mitrev, Z. & Rosalia, R., 2019a. The AKR1D1*36 (rs1872930) Allelic Variant Is Independently Associated With Clopidogrel Treatment Outcome. Pharmacogenomics Pers. Med. 12, 287-295. doi:10.2147/PGPM.S222212

Kapedanovska-Nestorovska, A., Jakjovski, K., Naumovska, Z., Sterjev, Z., Geskovska, N.M., Mladenovska, K., Suturkova, L. & Dimovski, A., 2019b. AKR1D1*36 C>T (rs1872930) allelic variant is associated with variability of the CYP2C9 genotype predicted pharmacokinetics of ibuprofen enantiomers - a pilot study in healthy volunteers. Acta Pharm. 69(3), 399-412. doi: 10.2478/acph-2019-0032

Kapedanovska-Nestorovska, A., Naumovska, Z., Jakovski, K., Sterjev, Z., Matevska Geskovska, N., Dimovski, A. & Shuturkova, L., 2018. Allele frequency and genotype distribution of aldo keto reductase 1D1 (AKR1D1) rs1872930 genetic variant in a Macedonian population. Maced. Pharm. Bull. 64(01), 57-62. doi:10.33320/maced.pharm.bull.2018.64.01.005

Mindnich, R., Drury, J.E. & Penning, T.M., 2011. The effect of disease associated point mutations on 5β-reductase (AKR1D1) enzyme function. Chem. Biol/ Interact. 191(1-3), 250-4. doi: 10.1016/j.cbi.2010.12.020

Nikolaou, N., Gathercole, L.L., Marchand, L., Althari, S., Dempster, N.J., Green, C.J., van de Bunt, M., McNeil, C., Arvaniti, A., Hughes, B.A., Sgromo, B., Gillies, R.S., Marschall, H.U., Penning, T.M., Ryan, J., Arlt, W., Hodson, L. & Tomlinson, J.W., 2019. AKR1D1 is a novel regulator of metabolic phenotype in human hepatocytes and is dysregulated in non-alcoholic fatty liver disease. Metabolism 99, 67-80. doi: 10.1016/j.metabol.2019.153947.

National Center for Biotechnology Information (NCBI), 2024. "SNP rs1872930 [AKR1D1*36]." [online] Available at: https://www.ncbi.nlm.nih.gov/snp/rs1872930#variant_details [Accessed December 15, 2024].

Penning, T.M., 2015.The aldo-keto reductases (AKRs): Overview. Chem. Biol. Interact. 234, 236-46. doi: 10.1016/j.cbi.2014.09.024.

Penning, T.M., Wangtrakuldee, P. & Auchus, R.J., 2019. Structural and Functional Biology of Aldo-Keto Reductase Steroid-Transforming Enzymes. Endocr. Rev. 40(2), 447-475. doi: 10.1210/er.2018-00089.

Phan, L., Jin, Y., Zhang, H., Qiang, E., Shekhtman, D., Shao, D., Revoe, R., Villamarin, E., Ivanchenko, M., Kimura, Z.Y., Wang, L., Hao, N., Sharopova, M., Bihan, A., Sturcke, A., Lee, M., Popova, N., Wu, W., Bastiani, C., Ward, M., Holmes, J.B., Lyoshin, V., Kaur, K., Moyer, E., Feolo, M. & Kattman, B.L., 2020. ALFA: Allele Frequency Aggregator. National Center for Biotechnology Information, U.S. National Library of Medicine. [online] Available at: https://www.ncbi.nlm.nih.gov/snp/docs/gsr/alfa/ [Accessed 15 December 2024]

Rižner, T.L. & Penning, T.M., 2014. Role of aldo-keto reductase family 1 (AKR1) enzymes in human steroid metabolism. Steroids 79, 49-63. doi: 10.1016/j.steroids.2013.10.012.

Tracy, T.S., Chaudhry, A.S., Prasad, B., Thummel, K.E., Schuetz, E.G., Zhong, X.B., Tien, Y.C., Jeong, H., Pan, X., Shireman, L.M., Tay-Sontheimer, J. & Lin, Y.S., 2016. Interindividual Variability in Cytochrome P450-Mediated Drug Metabolism. Drug Metab. Dispos. 44(3), 343-51. doi: 10.1124/dmd.115.067900.

Valanejad, L., Ghareeb, M., Shiffka, S., Nadolny, C., Chen, Y., Guo, L., Verma, R., You, S., Akhlaghi, F. & Deng, R., 2018. Dysregulation of Δ4-3-oxosteroid 5β-reductase in diabetic patients: Implications and mechanisms. Mol. Cell. Endocrinol. 470, 127-141. doi: 10.1016/j.mce.2017.10.005.

Williams, S.R., Hsu, F.C., Keene, K.L., Chen, W.M., Nelson, S., Southerland, A.M., Madden, E.B., Coull, B., Gogarten, S.M., Furie, K.L., Dzhivhuho, G., Rowles, J.L., Mehndiratta, P., Malik, R., Dupuis, J., Lin, H., Seshadri, S., Rich, S.S., Sale, M.M. & Worrall, B.B., 2016. The Genomics and Randomized Trials Network GARNET Collaborative Research Group. Shared genetic susceptibility of vascular-related biomarkers with ischemic and recurrent stroke. Neurology. 86(4), 351-9. doi: 10.1212/WNL.0000000000002319.

Zhu, P., Feng, R., Lu, X., Liai, Y., Du, Z., Zhai, W. & Chen, K., 2021. Diagnostic and prognostic values of AKR1C3 and AKR1D1 in hepatocellular carcinoma. Aging (Albany NY). 13(3), 4138-4156. doi: 10.18632/aging.202380.

Резиме

Анализа на AKR1D1*36 (rs1872930) генетската варијанта во Косовска популација: алелна фреквенција и генотипска дистрибуција

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Клучни зборови: *AKR1D1*36*, кардиоваскуларни заболувања, Косово, генетски полиморфизам, фармакогенетика, Европска популација

Ензимите од суперфамилијата на Алдо-кето редуктази (Aldo-keto reductases -AKRs), особено членот на подфамилијата D1 (AKR1D1), имаат значајна улога во метаболизмот на стероидните хормони и биосинтезата на жолчните киселини. Последователно, на идентификацијата на AKR1D1*36 C>T (rs1872930) алелната варијанта во генот кој ја кодира синтезата на овој ензим како предиктивен маркер за активноста на цитохром P450 ензими (Cytochrome P450- CYP450), спроведени се студии чии резултати упатуваат на потенцијална поврзаност на овој еднонуклеотиден полиморфизам (single nucleotid polymorphism-SNP) со одговорот на терапијата со клопидогрел. Сепак, фрекфенцијата на неговата застапеност и потенцијалната поврзаност со ризикот за појава на кардиоваскуларни заболувања (КВЗ) индицирани за третман со клопидогрел остануваат недоволно истражени, особено кај европските популации, вклучително и популацијата во Косово.

Оваа студија има за цел да ја процени фреквенцијата на AKR1D1*36 варијантата и да ја евалуира нејзината потенцијална поврзансот со ризикот за појава на КВЗ во популација на вкупно 384 испитаници (150 пациенти со КВЗ и 234 здрави доброволци) од албанска етничка припадност од Косово. Согласно добиените резултати, не беа забележани значајни разлики во алелната и генотипската дистрибуција на AKR1D1*36 помеѓу пациентите и здравите контролни испитаници ($p > 0,05$), што укажува на отсуство на независна асоцијација помеѓу AKR1D1*36 варијантата и појавата на КВЗ индицирани за терапија со клопидогрел. Севкупната фреквенција на AKR1D1*36 алелот во испитувана популација изнесува 21,74%, што е во согласност со фреквенцијата пријавена за европската популација. Дистрибуцијата на одделните AKR1D1*36 генотипови -*36/*36 1/*36 и *1/*1 изнесува 5,73; 32,03 и 62,4% соодветно.

Иако не беше забележана директна поврзаност со КВЗ, резултатите обезбедуваат прв увид во распространетоста на AKR1D1*36 во Косово и придонесуваат за унапредување на разбирањето на генетската разновидност во недоволно истражените европски групи како Косовската популација и ја истакнуваат потребата од понатамошни истражувања за варијациите на AKR1D1*36, особено во контекст на фармакогенетиката и подложноста на појава на заболувања.