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THE EFFECT OF POLYMORPHISMS IN THE BCL2, BID AND BAX GENES ON THE DEVELOPMENT OF SENSORINEURAL HEARING LOSS

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The problem of etiopathogenesis and treatment of sensorineural hearing loss remains unresolved in Ukraine and worldwide. Perceptive disorders can be congenital or acquired. Congenital cases are quite common, occurring in 1 out of 1000 newborns, and are the most common congenital defect in developed societies [1]. Prior to the implementation of early detection strategies for hearing impairments in children, deafness or significant hearing loss was typically diagnosed around the age of 2-3 years, exceeding the age of active language and speech development [2]. Hereditary hearing loss accounts for approximately 50% of all hearing impairments [3]. It can be classified into nonsyndromic cases, which constitute about 70% of all cases and are limited to the inner ear, and syndromic cases, which are part of overall body anomalies.

Among the nonsyndromic forms of hearing loss, the autosomal recessive type of inheritance (DFNB) is the most common, accounting for 55% of cases, followed by autosomal dominant (DFNA) in 37%, X-linked (DFN) in 4%, and the remaining 1% attributed to other causes (including Y-linked). Numerous genes that influence various aspects of the structure and function of the inner ear have been studied [1, 4]. Among the syndromic forms, the most well-known are Alport syndrome [5], brachio-oto-renal syndrome [6], CHARGE syndrome [7], Jervell and Lange-Nielsen syndrome [8], Norrie disease [9], and others.

In recent decades, there has been an increasing number of scientific studies dedicated to the role of gene polymorphism in the pathogenesis of sensorineural hearing disorders. Several pathways can be identified in the pathogenesis, including microvascular [10-13], inflammation, oxidative stress [14-18], and changes in potassium channels [19-23]. One of the areas of polymorphism research focuses on studying the role of apoptosis in the pathogenesis of perceptive hearing impairment.

Under normal function of the body, tissues, and cells, there is a balance between cell generation and their destruction.

Apoptosis is a controlled cell death process that is an integral part of its life cycle. During apoptosis, the cell's genome is disrupted, and the cell undergoes fragmentation into smaller parts, which are subsequently eliminated through phagocytosis [24].

Under the presence of mutations in genes that affect various stages of the apoptotic cascade, the regulation of this process can be disrupted, accelerated or decelerated. The role of apoptosis in the death of cochlear hair cells, as a cause of sensorineural disorders, is still not fully understood and has therefore been a subject of interest over the past two decades. Apoptosis can be divided into three stages: initiation or encountering signals, the stage of perception, analysis, and transmission of signal molecules, and the activation stage of caspases [25, 26].

The initiation phase is triggered by external (extracellular) and internal (intracellular) stress factors.

There are proteins that stimulate apoptosis (pro-apoptotic) and inhibit it (anti-apoptotic). There needs to be a delicate balance between these proteins within the cell. The anti-apoptotic proteins include Bcl-2, Bcl-xL,

Bcl-W, Mcl-1, A1, and Bcl-B. The pro-apoptotic groups include Bid, Bim, Bad, Noxa, Puma, as well as the group with multiple domains – Bax, Bak, and Bok [27, 28].

Studying the polymorphism of the Bcl-2, Bax, and Bid genes and their impact on the occurrence and development of perception hearing disorders through apoptosis could serve as a basis for genetic diagnostics and gene therapy of sensorineural hearing loss in the future.

To assess the effect of polymorphisms in the Bcl-2 rs2279115, Bax rs4645878, and Bid rs8190315 genes on the development of sensorineural hearing loss in patients working under conditions of sound exposure.

Methods and Materials

A case-control study was conducted at the Kyiv Clinical Hospital of Railway Transport No. 2. The study included 41 patients with perception hearing disorders (with and without noise) in the main group. The control group consisted of 48 individuals without signs of hearing impairment. The inclusion criteria for the study were age ranging from 18 to 50 years and a work experience of over 3 years in conditions of increased sound exposure. The exclusion criteria were diabetes or impaired glucose tolerance, disorders of the endocrine and connective tissue systems, dyslipidemia, arterial hypertension, cerebral circulation disorders, and psychiatric illnesses, neoplasms. Such restrictions made it possible to rule out with high probability the presence of an association between the polymorphism of the studied genes and the pathology of connective and glandular tissues, and therefore to compare the obtained results with the peculiarities of the response of the nervous tissue to the causative factor (production noise). Informed consent was obtained from all patients, and the study protocol was approved by the ethics committee.

For a comprehensive assessment of the patients' auditory function, a complete audiological examination was performed, in a soundproof chamber with a background noise level not exceeding 30 dB.

The patients were distributed according to age: Group 1 – patients up to 35 years old, Group 2 – patients between 35 and 45 years old, Group 3 – patients between 45 and 50 years old. They were also categorized based on work experience: Group 1 – up to 10 years, Group 2 – between 10 and 20 years, Group 3 – over 20 years. Additionally, the degree of hearing loss was classified as follows: Mild – hearing loss ranging from 20 to 39 dB, Moderate – hearing loss ranging from 40 to 69 dB, Severe – hearing loss ranging from 70 to 89 dB, Profound or deafness – hearing loss exceeding 90 dB.

The analysis of the impact of polymorphisms in the Bcl-2, Bax, and Bid genes on the development of sensorineural hearing loss was conducted using the PCR method on samples of venous blood from the patients. Molecular and genetic studies were performed in the laboratory of the Research Institute of Experimental and Clinical Medicine of O.O. Bogomolets National Medical University according to standard methods. Peripheral blood samples were collected in sterile closed system tubes with EDTA, with a volume of 2.5 ml. The sterile tubes with the collected material were stored at -20ºC (for no longer than 1 month). Genomic DNA isolation from peripheral blood leukocytes of patients was performed using a commercial kit for nucleic acid (RNA/DNA) extraction from clinical material, "Biocore® Nucleo-M" (Ukraine, based on Thermo Scientific, USA), according to the manufacturer's instructions. For the determination of the Bcl-2 gene polymorphism, PCR was conducted using TaqMan® Assays (USA) for rs2279115, for the Bax gene – rs4645878, and for the Bid gene – rs8190315, provided by Thermo Scientific (USA).

The Bcl-2 gene (Apoptosis regulator Bcl-2) encodes a 26266 d protein consisting of 239 amino acids. It is localized on the short arm of chromosome 18. The primer used to detect the *BCL2* (rs: 2279115) polymorphism was CTCCCCAGGAGAGAGACAGGGGAGA **[G/T]**GGGACGATGAAGGAGCCGGGGAC GG.

The Bid gene (BH3 interacting domain death agonist) encodes a 21 995 d protein consisting of 195 amino acids. It is localized on the short arm of chromosome 22. The primer used to detect the Bid (rs: 8190315) polymorphism was TTTGTGATGCAC-TCATCCCTGAGGC**[C/T]**GGAACCGTTGT TGACCTGAGGGGAA.

The Bax gene (Bcl2 associated X, apoptosis regulator) encodes a 21 184 d protein consisting of 192 amino acids. It is localized on the short arm of chromosome 19. The primer used to detect the Bax (rs: 4645878) polymorphism was AGGCATTAGAGCTGCATTGGACGG**[A/G]**CGGCTGTTGGACGGCGCCACTGCTG.

The alleles present in the sample were identified by measuring fluorescence on the FAM and VIC channels of the study.

Statistical analysis of the data was performed using IBM SPSS Statistics Base v.22 software. Non-parametric tests were used to analyze the statistical differences between the test and control values. A critical level of significance was set at 0.05. Bonferroni correction was applied to each p-value of any SNP. For an additional assessment of the probability of the obtained results, the odds ratio (OR) with a 95% confidence interval was calculated. An online calculator (www.gigacalculator.com) was used for this purpose.

Research Results

In this case-control study, 41 patients with perception disorders and 48 control patients who worked under the same conditions of increased sound exposure but without the development of auditory pathology were included. Detailed information on the distribution of patients in the control group and the study group is presented in Table 1.

Table 1

The distribution of patients in the main and control groups

Indicators	Groups		Significance, ρ
	Study (n=41)	Control (n=48)	
Age (Me (Q_I÷Q_{III}))	47 (43÷49)	45 (38÷48)	ρ>0.05
Work experience (Me (Q_I÷Q_{III}))	14 (8÷19)	14 (11÷18)	ρ>0.05

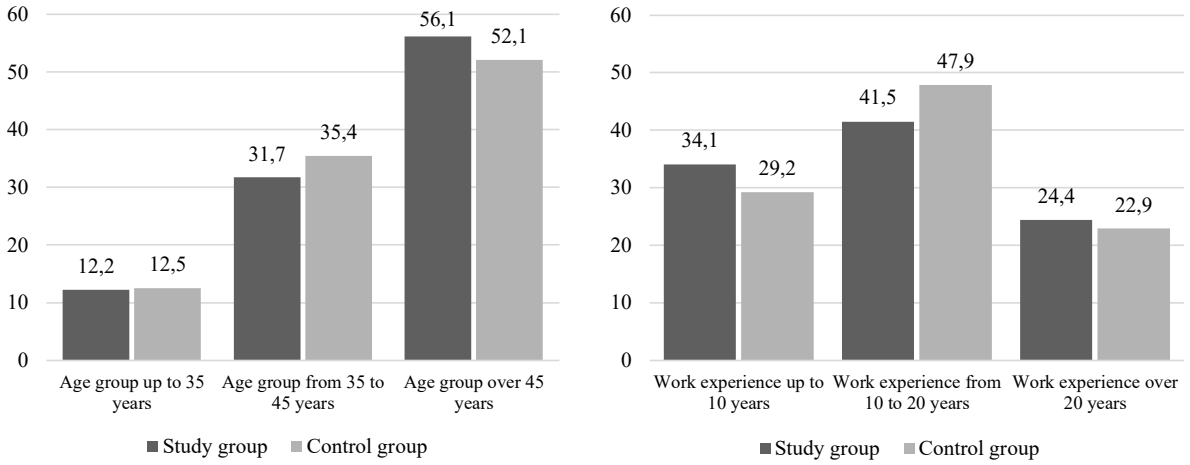

Figure 1. Distribution of patients into age and experience subgroups, %.

Therefore, there were no statistically significant differences in age and work experience between patients in both research groups (ρ>0.05). The distribution of patients into subgroups based on age and work experience is shown in Figure 1. As shown in Figures 1 and 2, there were no significant differences observed in the age and experience subgroups between patients in both groups. In the results of the polymerase chain reaction (PCR) for

SNP determination, all patients were classified into heterozygous and homozygous genotypes as follows:

- Bcl-2 – C/C, C/A, A/A.
- Bid – C/C, C/T, T/T.
- Bax – A/A, A/G, G/G.

The prevalence of genotypes and allele frequencies of the Bcl-2, Bid, and Bax genes between the groups are shown in Figure 2 and presented in Table 2.

Based on the data in the table, a significant association was found between the Bcl-2 gene polymorphism and the risk of developing perception disorders in individuals working in noise ($\rho<0.05$). The C allele was statistically significantly more prevalent in patients in the main research group compared to individuals without sensorineural hearing loss. However, no significant association was found between the Bid and Bax gene polymorphisms ($\rho>0.05$). The ratio of the A and G alleles in the assessment of the Bax gene polymorphism differed between the research groups: the A allele was more common in the main group of patients, while the G allele was more common in the control group of patients. However, the difference did not reach statistical significance ($\rho>0.05$). The results were obtained with Bonferroni correction for each ρ-value of any SNP.

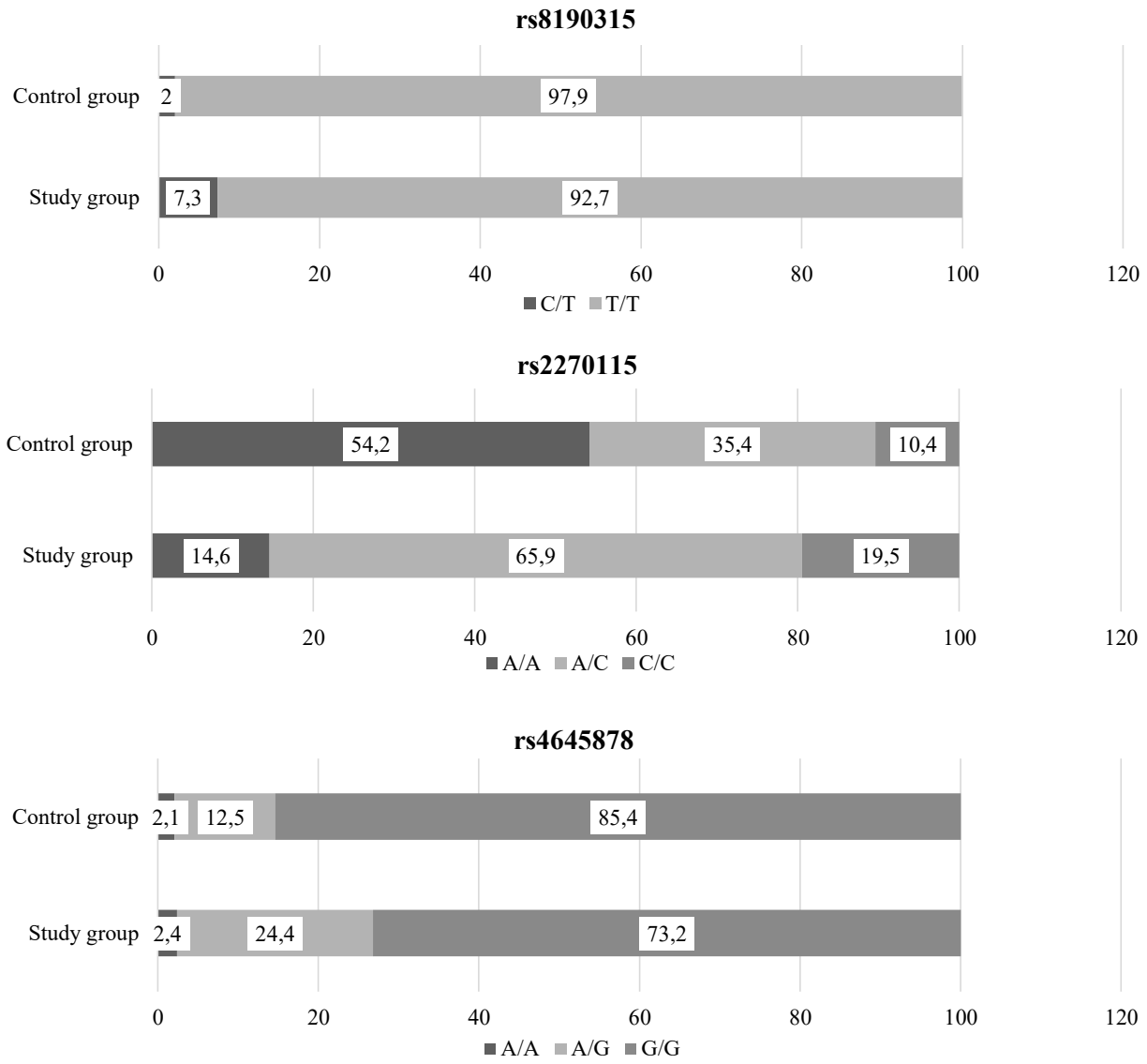

Figure 2. The prevalence of genotypes and allele frequencies of the Bcl-2, Bid, and Bax genes between the groups.

Table 2

The prevalence of genotypes and allele frequencies between the groups

Genotype		Groups		Odds Ratio	Significance, ρ
		study group, (n=41), abs (%)	control group, (n=48), abs (%)		
Bcl-2, C/A (rs2279115)	C/C	8 (19.5)	5 (10.4)	2.085 (0.624-6.963)	ρ >0.05
	C/A	27 (65.9)	17 (35.4)	3.517 (1.465-8.441)	ρ<0.05*
	A/A	6 (14.6)	26 (54.2)	0.145 (0.051-0.409)	ρ<0.05*
Allele	C	43 (52.4)	27 (28.1)	2.818 (1.514-5.244)	ρ<0.05*
	A	39 (47.6)	69 (71.9)	0.355 (0.191-0.66)	ρ<0.05*
Bid, C/T (rs8190315)	C/C	0 (0)	0 (0)	-	ρ >0.05
	C/T	3 (7.3)	1 (2)	3.71(0.371-37.128)	ρ >0.05
	T/T	38 (92.7)	47 (97.9)	0.27 (0.027-2.697)	ρ >0.05
Allele	C	3 (3.7)	1 (1)	3.556 (0.363-34.845)	ρ >0.05
	T	79 (96.3)	95 (99)	0.277 (0.028-2.718)	ρ >0.05
Bax. A/G (rs4645878)	A/A	1 (2.4)	1 (2.1)	1.175 (0.071-19.394)	ρ >0.05
	A/G	10 (24.4)	6 (12.5)	2.258 (0.742-6.875)	ρ >0.05
	G/G	30 (73.2)	41 (85.4)	0.466 (0.162-1.324)	ρ >0.05
Allele	A	12 (14.6)	8 (8.3)	1.886 (0.731-4.867)	ρ >0.05
	G	70 (85.4)	88 (91.2)	0,53 (0,205-1,369)	ρ >0.05

Comment: *- statistically significantly result.

Table 3

The combined distribution of Bcl-2 and Bax genotypes in the study and control groups

Genotype combination	Groups		Odds Ratio	Significance, ρ
	study group (n=41), abs (%)	control group (n=41), abs (%)		
GG/GT and AG/GG	34 (82.9%)	21 (43.7%)	6.245 (2.312-16.865)	ρ<0.05*
GG/GT and AA	1 (2.45%)	1 (2.1%)	1.175 (0.071-19.394)	ρ>0.05
TT and AG/GG	6 (14.65%)	26 (54.2%)	0.145 (0.051-0.409)	ρ<0.05
TT and AA	0	0	-	-

Comment: * – statistically significantly result.

Based on the combination of C and A alleles in the Bcl-2 gene and A and G alleles in the Bax gene, the research cohorts were further divided into four subgroups. The data for these subgroups are presented in Table 3.

It was found that the combination of the GG/GT and AG/GG genotypes significantly increases the risk of developing perception disorders. Meanwhile, the combination of the TT genotype and AG/GG is more common

among workers without perception disorders ($p<0.05$). In order to identify the factors associated with the risk of developing perception disorders in individuals working under conditions of increased sound load, a method of constructing and analyzing logistic regression models was used. The results of the multifactorial analysis are shown in Table 4.

Table 4

Coefficients of the five-factor model for predicting the development of perception hearing disorders in individuals working under conditions of increased sound load

Risk factors	Model coefficient value, b±m	The level of significance for the coefficient difference less than 0, r.	HR (95% CI)
Const	-6.01±5.21	0.249	-
Age	-0.06±0.04	0.121	0.94 (0.86-1.02)
Work experience	0.05±0.04	0.181	1.05 (0.98-1.14)
The polymorphism of the Bcl-2 gene (rs2279115)	1.21±0.38	0.001*	3.37 (1.60-7.09)
The polymorphism of the Bid gene (rs8190315)	1.51±1.50	0.316	4.52 (0.24-86.1)
The polymorphism of the Bax gene (rs4645878)	0.37±0.53	0.490	1.44 (0.51-4.10)

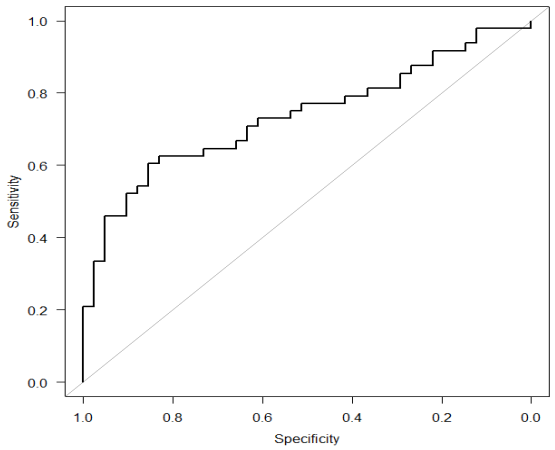

Figure 3. ROC curve of the logistic regression model, the relationship between the polymorphism of the Bcl-2 gene (rs2279115), and the risk of developing perception disorders in individuals working under conditions of increased sound load.

The analysis was conducted based on the examination results of 89 railway workers, 41 of whom were diagnosed with sensorineural hearing loss. The Stepwise method (stepwise variable selection) was used to select a minimal set of predictor variables. As a result, the main predictor variable identified was the polymorphism of the Bcl-2 gene (rs2279115). Based on the data, a logistic regression model was constructed with an AUC of 0.74 (95% CI 0.63-0.84), which is statistically significant and exceeds 0.5 ($p<0.05$) – see Figure 3.

Conclusions

In this case-control study, we conducted an examination of 89 workers in railway transportation under the age of 50 without any established comorbidities that could influence the development of perception disorders (such as diabetes, arterial hypertension, dyslipidemia, etc.). The aim was to determine the impact of apoptosis gene polymorphisms on the occurrence of sensorineural hearing loss. The investigation of the SNP of the Bcl-2 gene (rs2279115) revealed that the C/A genotype significantly increases the risk of developing perception disorders compared to the C/C and A/A genotypes ($\rho<0.05$). The difference in the genotypes of the Bid gene (rs8190315) and Bax gene (rs4645878) between patients in both groups did not reach statistical significance ($\rho>0.05$). The construction and analysis of a multifactorial logistic regression model (age, tenure, polymorphisms of the Bcl-2 (rs2279115), Bid (rs8190315), and Bax (rs4645878) genes)

confirmed the statistically significant influence of the Bcl-2 apoptosis gene polymorphism (rs2279115). We did not find any impact of genetic variability in the Bid (rs8190315) and Bax (rs4645878) genes on the risk of developing perception disorders.

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Conflict of interests. There is no conflict of interest regarding the publication of this article.

Ethical standards. The study has been approved by the ethics committee of the Bogomolets National Medical University, Ukraine (the approval number: 144, date: 29.03.2021). Prior to the studying, the written informed consent from each individual were obtained, according to the guidelines of the ethics committee.

References

1. Egilmez OK, Kalcioglu MT. Genetics of non-syndromic congenital hearing loss. Scientifica (Cairo). 2016;2016:7576064. doi: 10.1155/2016/7576064.
2. Centers for Disease Control and Prevention (CDC). Infants tested for hearing loss: United States, 1999-2001. MMWR Morb Mortal Wkly Rep. 2003 Oct 17;52(41):981-4.
3. ACMG. Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. Genetic Evaluation of Congenital Hearing Loss Expert Panel. ACMG statement. Genet Med. 2002 May-Jun;4(3):162-71. doi: 10.1097/00125817-200205000-00011.
4. Smith RJ, Bale JFJr, White KR. Sensorineural hearing loss in children. Lancet. 2005 Mar;365 (9462):879-90. doi: 10.1016/S0140-6736(05) 71047-3.
5. Mochizuki T, Lemmink HH, Mariyama M, Antignac C, Gubler MC, Pirson Y, et al. Identification of mutations in the alpha 3(IV) and alpha 4(IV) collagen genes in autosomal recessive Alport syndrome. Nat Genet. 1994 Sep;8(1):77-81. doi: 10.1038/ng0994-77.
6. Hoskins BE, Cramer CH, Silvius D, Zou D, Raymond RM, Orten DJ, et al. Transcription factor SIX5 is mutated in patients with branchio-otorenal syndrome. Am J Hum Genet. 2007 Apr;80 (4):800-4. doi: 10.1086/513322.
7. Lalani SR, Safiullah AM, Molinari LM, Fernbach SD, Martin DM, Belmont JW. SEMA3E mutation in a patient with CHARGE syndrome. J Med Genet. 2004 Jul;41(7):e94. doi: 10.1136/jmg.2003.017640.
8. Neyroud N, Tesson F, Denjoy I, Leibovici M, Donger C, Barhanin J, et al. A novel mutation in the potassium channel gene KVLQT1 causes the Jervell and Lange-Nielsen cardioauditory syndrome. Nat Genet. 1997 Feb;15(2):186-9. doi: 10.1038/ng0297-186.
9. Berger W, van de Pol D, Warburg M, Gal A, Bleeker-Wagemakers L, de Silva H, Meindl A, et al. Mutations in the candidate gene for Norrie disease. Hum Mol Genet. 1992 Oct;1(7):461-5. doi: 10.1093/hmg/1.7.461.
10. Uchida Y, Teranishi M, Nishio N, Sugiura S, Hiramatsu M, Suzuki H, et al. Endothelin-1 gene polymorphism in sudden sensorineural hearing loss. Laryngoscope. 2013 Nov;123(11):E59-65. doi: 10.1002/lary.24298.
11. Castiglione A, Ciorba A, Aimoni C, Orioli E, Zeri G, et al. Sudden sensorineural hearing loss and polymorphisms in iron homeostasis genes: new insights from a case-control study. Biomed Res Int. 2015;2015:834736. doi: 10.1155/2015/834736.
12. Kitoh R, Nishio SY, Ogawa K, Okamoto M, Kitamura K, Gyo K, et al. SOD1 gene polymorphisms in sudden sensorineural hearing loss. Acta Otolaryngol. 2016;136(5):465-9. doi: 10.3109/00016489.2015.1116047.
13. Yazdani N, Hamidi AK, Soroush N, Jalili N, Vahidi A, Ahrabi NZ, et al. eNOS gene Glu298Asp variant confer risk in sudden sensorineural hearing loss. Acta Otolaryngol. 2018 Oct;138(10):904-908. doi: 10.1080/00016489. 2018.1497806.
14. Manche SK, Jangala M, Putta P, Koralla RM, Akka J. Association of oxidative stress gene polymorphisms with presbycusis. Gene. 2016 Nov 30;593(2):277-83. doi: 10.1016/j.gene.2016.08.029.
15. Shu J, Si Y, Yin S, He M. Association between the V Leiden G1691A mutation and sudden sensorineural hearing loss in Italian population: a meta-analysis. Eur Arch Otorhinolaryngol. 2016 Sep; 273(9):2467-72. doi: 10.1007/s00405-015-3844-x.
16. Koide Y, Teranishi M, Sugiura S, Uchida Y, Nishio N, Kato K, et al. Association between uncoupling protein 2 gene Ala55 val polymorphism and sudden sensorineural hearing loss. J Int Adv Otol. 2018 Aug;14(2):166-169. doi: 10.5152/iao.2018.5442.

17. Tian G, Zhang S, Yang J. Coexistence of IL-6 -572C/G and ICAM-1 K469E polymorphisms among patients with sudden sensorineural hearing loss. Tohoku J Exp Med. 2018;245(1):7-12. doi: 10.1620/tjem.245.7.
18. Hamidi AK, Yazdani N, Seyedjavadi KH, Ahrabi NZ, Tajdini A, Aghazadeh K, Amoli MM. MTHFR AND ApoE genetic variants association with sudden sensorineural hearing loss. Am J Otolaryngol. 2019 Mar-Apr;40(2):260-264. doi: 10.1016/j.amjoto.2018.10.015.
19. Sand PG, Luettich A, Kleinjung T, Hajak G, Langguth B. An Examination of KCNE1 Mutations and Common Variants in Chronic Tinnitus. Genes (Basel). 2010 Apr 28;1(1):23-37. doi: 10.3390/genes1010023.
20. Yu P, Jiao J, Gu G, Chen G, Zhang H, Zhou W, et al. [Relationship between GRM7 gene polymorphisms and the susceptbility to noise-induced hearing loss]. Wei Sheng Yan Jiu. 2018 Mar;47(2): 218-227. [Article in Chinese].
21. Xie S, Li J, Wang W, Chen X. Association of glutamate metabotropic receptor polymorphisms and sensorineural hearing loss in adults of different age groups. Braz J Otorhinolaryngol. 2019 Sep-Oct;85(5):560-564. doi: 10.1016/j.bjorl.2018.04.007.
22. Loukzadeh Z, Sani HE, Sheikhha MH, Ratki FM. Association of GST gene polymorphism and noise-induced hearing loss: GST gene polymorphism and NIHL. AIMS Public Health. 2019;6(4):546-553. doi: 10.3934/publichealth.2019.4.546.
23. Zhou WH, Gu GZ, Wu H, Li YH, Chen GS, Zhang HL, Yu SF, Zheng YX. [Prediction of KCNQ4gene polymorphism varies with CNE or noise exposure duration on the Risk of NIHL-Cox model analysis based on cohort study]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2020 Feb 20;38(2):111-116. doi: 10.3760/cma.j.issn.1001-9391.2020.02.007. [Article in Chinese].
24. Fadok VA, Chimini G. The phagocytosis of apoptotic cells. Semin Immunol. 2001 Dec;13(6):365-72. doi: 10.1006/smim.2001.0333.
25. Moreira MEC, Barcinski MA. Apoptotic cell and phagocyte interplay: recognition and consequences in different cell systems. An Acad Bras Cienc. 2004 Mar;76(1):93-115. doi: 10.1590/s0001-37652004000100009.
26. Fink SL, Cookson BT. Apoptosis, Pyroptosis, and Necrosis: Mechanistic Description of Dead and Dying Eukariotic Cells. Infect Immun. 2005 Apr; 73(4):1907-16. doi: 10.1128/IAI.73.4.1907-1916.2005.
27. Danial NN. BCL-2 family proteins: critical checkpoints of apoptotic cell death. Clin Cancer Res. 2007 Dec 15;13(24):7254-63. doi: 10.1158/1078-0432.CCR-07-1598.
28. Du H, Wolf J, Schafer B, Moldoveanu T, Chipuk JE, Kuwana T. BH3 domains other than Bim and Bid can directly activate Bax/Bak. J Biol Chem. 2011 Jan 7;286(1):491-501. doi: 10.1074/jbc.M110.167148.

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ВПЛИВ ПОЛІМОРФІЗМУ ГЕНІВ BCL2, BID І BAX НА РОЗВИТОК СЕНСОНЕВРАЛЬНОЇ ПРИГЛУХУВАТОСТІ

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А н о т а ц і я

Вступ: В останні десятиліття одним із напрямів дослідження поліморфізму є вивчення ролі апоптозу в патогенезі перцептивних порушень слуху. Вивчення поліморфізму антиапоптотичних і проапоптотичних генів, їх впливу на виникнення та розвиток розладів слуху через апоптоз може стати основою генетичної діагностики та генної терапії сенсоневральної приглухуватості в майбутньому.

Мета: Оцінити вплив поліморфізму генів Bcl-2, Bax і Bid на розвиток сенсоневральної приглухуватості.

Дизайн дослідження: Випадок-контроль.

Матеріали та методи: Обстежено 41 пацієнта з порушенням сприйняття слуху в основній групі, контрольну групу склали 48 осіб без ознак порушення слуху. Досліджено такі генетичні варіанти: поліморфізм Bcl2 (rs2279115); Гени Bid (rs8190315) і Bax (rs4645878).

Статистичний аналіз даних: для аналізу статистичних відмінностей між тестовими та контрольними значеннями використовували непараметричні тести. Критичний рівень значущості був встановлений на рівні 0,05. Поправка Бонферроні була застосована до кожного p-значення будь-якого SNP. Для додаткової оцінки вірогідності отриманих результатів, розраховувався показник співвідношення шансів (OR – Odds Ratio) з 95% довірчим інтервалом. З цією метою використовувався онлайн-калькулятор (www.gigacalculator.com).

Результати: Виявлено суттєвий зв'язок між поліморфізмом гена Bcl-2 і ризиком розвитку розладів сприйняття в осіб, які працюють в умовах шуму ($\rho<0,05$): гомозиготний генотип C/C і гетерозиготний генотип C/A підвищують ризик розвитку сенсоневрального слуху. втрата. Алель C була статистично значуще більш поширеною у пацієнтів основної дослідницької групи. Між поліморфізмом генів Bid і Bax не виявлено істотного зв'язку ($\rho>0,05$). Встановлено, що поєднання генотипів CC/CA (ген Bcl2) і AG/GG (ген Bax) значно підвищує ризик розвитку розладів сприйняття.

Висновки: Наше дослідження вказує на те, що алель C гена Bcl2 статистично значуще пов'язана з підвищеним ризиком розвитку сенсоневральної втрати слуху. Ці знахідки свідчать про необхідність проведення нових досліджень у галузі поліморфізмів та їх ролі в розвитку захворювань внутрішнього вуха.

Ключові слова: сенсоневральна приглухуватість, перцептивні порушення, поліморфізми, генотип, гени, апоптоз.

THE EFFECT OF POLYMORPHISMS IN THE BCL2, BID AND BAX GENES ON THE DEVELOPMENT OF SENSORINEURAL HEARING LOSS

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A b s t r a c t

Background: In recent decades, one of the areas of polymorphism research focuses on studying the role of apoptosis in the pathogenesis of perceptive hearing impairment. Studying the polymorphism of the anti-apoptotic and pro-apoptotic genes, and their impact on the occurrence and development of perception hearing disorders through apoptosis could serve as a basis for genetic diagnostics and gene therapy of sensorineural hearing loss in the future.

Objectives: To assess the effect of polymorphisms in the Bcl-2, Bax, and Bid genes on the development of sensorineural hearing loss.

Study Design: Case-control study.

Materials and Methods: The study included 41 patients with perception hearing disorders in the main group and the control group consisted of 48 individuals without signs of hearing impairment. The following genetic variants were investigated: the polymorphism Bcl2 (rs2279115); Bid (rs8190315) and Bax (rs4645878) genes. Statistical analysis of the data: non-parametric tests were used to analyze the statistical differences between the test and control values. A critical level of significance was set at 0.05. Bonferroni correction was applied to each p-value of any SNP. For an additional assessment of the probability of the obtained results, the odds ratio (OR) with a 95% confidence interval was calculated. An online calculator (www.gigacalculator.com) was used for this purpose.

Results: A significant association was found between the Bcl-2 gene polymorphism and the risk of developing perception disorders in individuals working in noise ($\rho<0.05$): the homozygous genotype C/C and heterozygous genotype C/A increase the risk of development of sensorineural hearing loss. C allele was statistically significantly more prevalent in patients in the main research group. No significant association was found between the Bid and Bax gene polymorphisms ($\rho>0.05$). It was found that the combination of the CC/CA (Bcl2 gene) and AG/GG (Bax gene) genotypes significantly increases the risk of developing perception disorders.

Conclusions: Our study indicates that the C allele of the Bcl2 gene was statistically significantly associated with increased risk of developing sensorineural hearing loss. These findings suggest new research should be conducted in the field of polymorphisms and their role in the development of diseases of the inner ear.

Keywords: perception disorders, polymorphisms, genotype, genes, apoptosis, sensorineural hearing loss.