Original Article

Functional *BCL-2* rs2279115 Noncoding variant associated with noise-induced hearing loss in Chinese workers: a case-control study

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Background: Noise-induced hearing loss (NIHL) is one of the most common form of severe sensorineural hearing impairment. Both environmental and genetic factors contribute to the occurrence and severity of NIHL.

Methods: A total of 2,607 workers exposed to occupational noise from two factories in China were recruited into the study. General information was collected and measurements of pure-tone audiometry and ambient noise were made. Finally, rs2279115, rs3860, and rs8660 in *BCL-2*, *FAM136A*, and *L3HYPDH*, respectively, were genotyped in 482 cases and 482 controls who met the screening criteria. The target single nucleotide polymorphisms (SNPs) in *BCL-2*, *FAM136A*, and *L3HYPDH* genes were genotyped by Taqman genotyping technology. Age, sex, and the duration of noise-exposed years were corrected by logistic regression model and the SHEsis was used to analyze haplotypes. Multifactor dimensionality reduction (MDR) analysis was applied to detect potential interactions among the SNPs.

Results: The genotype frequency of BCL-2 rs2279115 was significantly increased in the NIHL case group compared to the control group in different genetic models (codominant, dominant, and recessive models). Also, the CGA haplotype (rs2279115-rs3806-rs8660) was associated with an increased risk for NIHL. Interaction analysis indicated that BCL-2 rs2279115, FAM136A rs3806, and L3HYPDH rs8660 had statistically significant interactions with increased NIHL risk.

Conclusions: BCL-2 rs2279115 may be a potential genetic biomarker for NIHL susceptibility.

Keywords: *BCL-2*; noise induced hearing loss (NIHL); single nucleotide polymorphism (SNP)

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Introduction

Noise-induced hearing loss (NIHL) is one of the most common form of severe sensorineural hearing impairment (1). At present, more than 10 million employees work in environments with excessive noise levels in China and millions of them experience varying degrees of hearing impairment (2). Both environmental and genetic factors contribute to the occurrence and severity of NIHL (3). Our previous studies illustrated that *Notch*, *SIK3*, *KCNE1*, and *ATP2B2* genes were associated with NIHL in Chinese workers (4-8).

The *BCL-2* gene encodes an integral outer mitochondrial

membrane protein that blocks the apoptotic death of some cells such as lymphocytes. Studies have provided evidence that *BCL-2* and the Bcl-2 pathway play crucial roles in both age-related hearing loss and NIHL. Huang *et al*. transfected an miR-34a mimic or miR-34a inhibitor into primary auditory cortex neurons and found a link between age-related apoptosis in auditory cortex neurons and miR-34a/Bcl-2 signaling (9). The p53 and Bcl-2 immunoreactivity was found by Xu *et al*. to elevate in aging hair cells, showing early signs of apoptotic changes in the nuclei, and Bcl-2 expression was increased in hair cells displaying early signs of necrosis (10). Yamashita *et al*. uncovered an important role of Bcl-2 family proteins in the prevention of sensory cell death following TTS (temporary threshold shift) levels of noise, and PTS (permanent threshold shift) exposure provoked the expression of Bak-associated cell death (11). Some studies have indicated that, sensorineural hearing neuron apoptosis and damage can be induced by noise exposure (12,13). *FAM136A* also encodes a mitochondrially localized protein. The *FAM136A* gene is expressed in rat neurosensorial epithelium of the crista ampullaris and a mutation in this gene has been associated with familial Meniere's disease, a chronic disorder of the inner ear (14). *L3HYPDH* encodes a dehydratase that may function to degrade dietary proteins that contain trans-3-hydroxy-L-proline as well as collagen IV and other proteins. Alport syndrome (a progressive hereditary renal disease) characterized by sensorineural hearing loss and ocular abnormalities has been known as a genetic disorder (15). It may be arising from the mutations in the genes encoding alpha-3, alpha-4, and alpha-5 proteins of collagen IV or collagen IV alpha345 network (16).

No associations between mutations of these three genes and NIHL have been reported. Some studies have showed that mutations of genes can cause changes in relevant gene expression (17). Considering the vital functions of BCL-2, FAM136A, and L3HYPDH in hearing loss, we proposed that polymorphisms in the *BCL-2*, *FAM136A*, and *L3HYPDH* genes may be associated with genetic susceptibility to NIHL. Therefore, a case-control study was conducted to reveal the associations between functional single nucleotide polymorphisms (SNPs) in *BCL*-2, *FAM136A*, and *L3HYPDH* with the genetic susceptibility to NIHL in noise-exposed Chinese workers. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jphe-20-123).

Methods

Study subjects

We conducted a case-control study to explore the associations between three functional SNPs in *BCL-2*, *FAM136A*, and *L3HYPDH* and NIHL susceptibility. In our research, a total of 2607 workers exposed to occupational noise from two factories in the Jiangsu province of China were recruited in October 2018. Chinese occupational NIHL diagnostic criteria (GBZ49-2014) were applied to diagnose NIHL. First, all workers exposed to noise levels exceeding 85dB (A) were selected. The case and control groups were defined as follows. In the case group, the average binaural high-frequency (3,000, 4,000, and 6,000 Hz) hearing threshold was >25 dB (A), or it was ≤25 dB (A) and the worse ear's speech frequency (500, 1,000, and 2,000 Hz) hearing threshold was >25 dB (A). The control group was defined as workers with an average binaural high-frequency hearing threshold of ≤25 dB (A) and the worse ear's speech frequency hearing threshold was ≤25 dB (A). The subjects with missing data, ototoxic drug administration, or without blood collection were excluded. Finally, 482 cases and 482 controls with matched sex, age, smoking, drinking and noise working time were included in this study. All subjects in the two factories who met the screening criteria were included in this study. All data (questionnaire, pure-tone audiometry, measurement of ambient noise, and temperature) in this research were collected by trained investigators according to relevant guidelines and regulations. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The informed consent of all participants was obtained and the current research was approved by the Ethics Committee of Jiangsu Provincial Center for Disease Control and Prevention (2014029).

Questionnaire investigation

The questionnaire included the following parts: general demographic characteristics (e.g., gender, age, and nationality), history of diseases that may affect hearing (e.g., primary ear disease and history of ototoxic drug use), and living habits (e.g., history of smoking and drinking). In this study, smoking status was divided into two levels, smoking and no smoking. Similarly, drinking status was divided into two groups, drinking and no drinking. If a worker smoked a cigarette or drank 50 grams of alcohol (spirits and beer)

a day for more than one year, they were assigned to the smoking or drinking group, respectively. Otherwise, they were assigned to the no drinking group and no smoking groups.

Pure-tone audiometry

Before the pure tone audiometry test, the subjects were instructed to avoid exposure to noise (>85 dB) for at least 12 hours. Then, 500, 1,000, 2,000, 3,000, 4,000, and 6,000 Hz pure tone air threshold tests were performed by an otorhinolaryngologist in the sound attenuation room. According to the Chinese Diagnostic Criteria of Occupational Noise-induced Hearing Loss (GBZ49-2014), the binaural hearing threshold was measured by a 5 dB (A) step-up method.

Measurement of ambient noise

According to GBZ/T 189.8-2007 "Measurement of physical factors in the workplace - Part 8: Noise", a noise dosimeter is used to measure the noise exposure level of the workplace at each post. Individual sound pressure noise meters (Noise-Pro, Quest, Oconomowoc, WI, USA) were applied to measure the noise exposure levels for three consecutive days at ten a.m., three p.m., and five p.m.

SNP selection

Firstly, SNPs were selected based on the 1000 Genome Project data (https://www.genome.gov/27528684/1000-genomes-project), the NCBI (National Center of Biotechnology Information) dbSNP database (https://www.ncbi.nlm.nih.gov/), and a previous literature review. Our criteria for identifying SNPs included a minor allele frequency (MAF) in the Han Chinese population (CHB) of >10%. Then, the SNPs located in the gene functional regions such as missense, promoter binding, 3′UTR, and 5′UTR or previously reported to be related to human diseases were considered. In the end, rs2279115, rs3860, and rs8660 in *BCL-2*, *FAM136A*, and *L3HYPDH*, respectively, were found to be reported before and included.

DNA extraction and SNP genotyping

QIAcube HT and QIAamp 96 DNA QIAcube HT Kits (Qiagen, Dusseldorf, Germany) were used to extract the DNA from about 200 ul blood samples in ethylenediaminetetraacetic acid (EDTA) at –20 ℃. In this study, the target SNPs in *BCL-2*, *FAM136A*, and *L3HYPDH* genes were genotyped by Taqman genotyping technology using an ABI 7900HT (Applied Biosystems, Massachusetts, USA). PCR primers and TaqMan probes were designed for different SNP sites on chromosome for real-time PCR amplification. The 5'- and 3'-ends of the probe were labeled with a reporter fluorescent group and a quenched fluorescent group, respectively. When PCR products were present in the solution, the probe annealed with the template to produce a substrate suitable for the activity of exonuclease. The fluorescent molecules connected with the 5'-end of the probe were cut off from the probe to destroy the pret between the two fluorescent molecules and emit fluorescence SDS v2.4 software (Applied Biosystems, Massachusetts, USA) was used to analyze the genotyping results.

Statistical analysis

All data were analyzed by SAS 9.4 software. Measurement data such as age, duration of noise-exposed years, and high-frequency hearing threshold (dB) are expressed as the mean ± SD, and the differences between the two groups were analyzed by two-sided *t*-test. The classified variables are expressed as percentages, and the χ^2 test was used to analyze differences between the groups. The goodness-of-fit χ^2 test was used to evaluate whether the SNPs in the control group conformed to Hardy-Weinberg equilibrium (HWE). Age, sex, and the duration of noise-exposed years were corrected by logistic regression model to reduce bias, and the odds ratio (OR) and 95% confidence interval (CI) were estimated. The SHEsis, a web-based platform for haplotype construction and analyses, was used to analyze haplotypes. Multifactor dimensionality reduction (MDR) analysis was applied to detect potential interactions among the SNPs. Three different genetic models (codominant model, dominant model, and recessive model) were used for sensitive analysis to find the effect of model alteration on the results. A P value of <0.05 indicated statistical significance. Missing data were not included in analysis.

Results

Demographic characteristics of the study subjects and the Hardy-Weinberg test

In this study, a total of 2,607 workers exposed to noise were potentially eligible and examined according to the inclusion

Table 1 Demographic characteristics of study subjects

Variables	Cases (n=482)		Controls (n=482)		P
	n	%	n	%	
Age (years)					
Mean ± SD	46.44±6.83		46.40±6.78		0.917[a]
≤35	37	7.68	38	7.88	0.952[b]
35–45	113	23.44	109	22.61	
>45	332	68.88	335	69.50	
Sex					
Male	443	91.91	441	91.49	0.815[b]
Female	39	8.09	41	8.51	
Tobacco use					
No	96	38.55	100	40.16	0.714[b]
Yes	153	61.45	149	59.84	
Alcohol consumption					
No	99	39.76	95	38.15	0.713[b]
Yes	150	60.24	154	61.85	
Duration of noise exposed work (years)					
Mean ± SD	24.86± 9.19		24.81±9.17		0.933[a]
≤20	130	26.97	131	27.18	0.942[b]
>20	352	73.03	351	72.82	
High frequency hearing threshold (dB)					
Mean ± SD	37.48±11.78		18.21±5.40		<0.001[a]

[a], students' *t*-test; [b], two-sided χ^2 test.

and exclusion criteria. Finally, a total of 964 workers (482 cases and 482 controls matched for sex, age, smoking and drinking history, and noise exposure years) were included and analyzed in this study. As shown in *Table 1*, no significant differences in age, sex, tobacco use, alcohol consumption, or the number of noise-exposed years were found between the case and control groups (P>0.05). The average binaural high-frequency hearing threshold in the case group was significantly higher [37.48±11.78 dB (A)] than that in the control group [18.21±5.40 dB (A)] (P<0.001). *Table 2* shows the general information of rs2279115, rs3860, and rs8660 and the Hardy-Weinberg test results. The MAF of SNPs rs2279115, rs3860, and rs8660 was ≥10%. Rs2279115 and rs8660 conformed to HWE (P>0.05). Of the participants, 466 had data missing on tobacco use and alcohol consumption.

Analysis of SNPs and NIHL risk

The logistic regression analysis of the genotype frequency of BCL-2 rs2279115 in the NIHL case and control groups adjusted for age, gender, and the number of noise-exposed years showed statistical significance in the four different genetic models (codominant model, dominant model, and recessive model) (P=0.0106, 0.0074, and 0.0255, respectively) (*Table 3*). In the codominant model, workers with the rs2279115 CC and AC genotypes had an increased NIHL risk with an OR of 1.310. The OR in the dominant model was 1.622 for AC/CC and 1.341 for CC in the recessive model (logistic regression adjusted for age, gender, and noise exposure years). The distributions of *FAM136A* rs3806 and *L3HYPDH* rs8660 were not significantly different between the two groups.

Table 2 General information of selected SNPs and Hardy-Weinberg test

Gene	SNP	Alleles	Chromosome	Functional consequence	MAF		P for HWE
					Control	Database	
BCL-2	rs2279115	A/C	18:63319604	Noncoding region	0.409	0.433	0.289
FAM136A	rs3806	A/G	13:102678368	3'UTR	0.405	0.463	0.010
L3HYPDH	rs8660	A/G	14:59473009	missense	0.104	0.098	0.706

[a], data from NCBI dbSNP; [b], P value of Hardy-Weinberg test. SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

Table 3 Distribution of three polymorphisms and the associations with NIHL

Genetic models	Genotypes	Cases		Controls		P[a]	Adjusted OR
		n=482	%	n=482	%		(95% CI)[b]
rs2279115							
Codominant	AA	59	12.24	89	18.46	0.0106	1.00 (Ref.)
	AC	212	43.98	216	44.81		1.310 (1.092–1.570)
	CC	211	43.78	177	36.72		
Dominant	AA	59	12.24	89	18.46	0.0074	1.00 (Ref.)
	AC/CC	423	87.76	393	81.54		1.622 (1.135–2.319)
Recessive	AA/AC	271	56.22	305	63.28	0.0255	1.00 (Ref.)
	CC	211	43.78	177	36.72		1.341 (1.035–1.737)
rs3806							
Codominant	AA	74	15.35	86	17.84	0.4205	1.00 (Ref.)
	AG	213	44.19	218	45.23		0.888 (0.743–1.062)
	GG	195	40.46	178	36.93		
Dominant	AA/AG	287	59.54	304	63.07	0.2609	1.00 (Ref.)
	GG	195	40.46	178	36.93		0.863 (0.665–1.119)
Recessive	AA	74	15.35	86	17.84	0.2989	1.00 (Ref.)
	GG/AG	408	84.65	396	82.16		0.837 (0.595–1.177)
rs8660							
Codominant	AA	393	81.54	393	81.54	0.8111	1.00 (Ref.)
	AG	75	15.56	78	16.18		0.970 (0.740–1.272)
	GG	14	2.90	11	2.28		
Dominant	AA/AG	468	97.10	471	97.72	0.5432	1.00 (Ref.)
	GG	14	2.90	11	2.28		0.784 (0.352–1.746)
Recessive	AA	393	81.54	393	81.54	1.0000	1.00 (Ref.)
	GG/AG	89	18.46	89	18.46		0.997 (0.720–1.384)

[a], two-sided χ^2 test; [b], adjusted for age, gender, noise exposure year in logistic regression model. NIHL, noise-induced hearing loss.

Table 4 Stratified analysis of noise exposure year in four genetic models of rs2279115

Model	Group	Genotype	Noise exposure year	
			≤20	>20
Dominant	Case	AA	18	41
		AC/CC	112	311
	Control	AA	18	71
		AC/CC	113	280
	P[a]		0.9802	0.0019
	Adjusted OR (95% CI)[b]		0.984 (0.485–1.995)	1.921 (1.266–2.916)
Codominant	Case	AA	18	41
		AC	63	149
		CC	49	162
	Control	AA	18	71
		AC	67	149
		CC	46	131
	P[a]		0.8985	0.0035
	Adjusted OR (95% CI)[b]		1.054 (0.733–1.515)	1.408 (1.141–1.737)
Recessive	Case	AA/AC	81	190
		CC	49	162
	Control	AA/AC	85	220
		CC	46	131
	P[a]		0.6652	0.0193
	Adjusted OR (95% CI)[b]		1.116 (0.673–1.850)	1.431 (1.059–1.934)

[a], two-sided χ^2 test; [b], adjusted for age, sex in logistic regression model.

Stratification analysis

Table 4 shows that individuals exposed to noise for over 20 years and carrying the rs2279115 AC/CC genotype (adjusted OR =1.408, 95% CI: 1.141–1.737) in the dominant model, the rs2279115 CC genotype (adjusted OR =1.431, 95% CI: 1.059–1.934) in the recessive model, and rs2279115 AC+CC (adjusted OR =1.921, 95% CI: 1.266–2.916) in the codominant model had an increased risk for NIHL.

Haplotype analysis results

Table 5 showed the frequencies of the inferred haplotypes among the cases and controls and their association with the risk of NIHL. The alleles of the haplotypes were arrayed as rs2279115-rs3806-rs8660. Haplotypes AAA and CGA showed decreased and increased risks for NIHL with ORs of 0.80 and 1.26, respectively, compared to the groups with mixed haplotypes.

Gene and environment interaction analysis

MDR v3.0.2 software was used to detect the potential interactions of *BCL-2* rs2279115, *FAM136A* rs3806, and *L3HYPDH* rs8660. *Table 6* and *Figure 1* shows that *BCL-2* rs2279115, *FAM136A* rs3806, and *L3HYPDH* rs8660 had a statistically significant interaction with increased NIHL risk (P=0.0083, OR =1.41, 95% CI: 1.09–1.81).

Discussion

In the current study, the genotype frequency of *BCL-2*

Table 5 Frequencies of inferred haplotypes among the cases and controls and their association with risk of NIHL

Haplotypes[a]	Case (n=964)		Control (n=964)		P[b]	Adjusted OR	Global P
	n	%	n	%		(95% CI)[c]	
AAA	249.43	25.9	303.48	31.5	0.03	0.80 (0.65–0.98)	0.05
AAG	70.08	7.3	79.44	8.2	0.58	0.91 (0.65–1.27)	
CGA	574.99	59.6	547.34	56.8	0.02	1.26 (1.04–1.52)	
Others[d]	69.5	7.2	33.74	3.5		1.00 (Ref.)	

[a], the alleles of haplotypes were arrayed as rs2279115-rs3806-rs8660; [b], two-sided χ^2 test; [c], generated by permutation test with 1,000 times of simulation; [d], haplotypes with a frequency <0.05 were pooled into the others group. NIHL, noise-induced hearing loss.

Table 6 Analysis of the interaction of the 3 SNPs by MDR

Model	Training balanced accuracy	Testing balanced accuracy	Cross-validation consistency	P	OR (95% CI)
rs2279115	0.5358	0.5218	10/10	0.0255	1.34 (1.04–1.74)
rs2279115*rs3806	0.5392	0.5104	6/10	0.0178	1.37 (1.06–1.77)
rs2279115*rs3806*rs8660	0.5441	0.5104	10/10	0.0083	1.41 (1.09–1.81)

SNP, single nucleotide polymorphism; MDR, multifactor dimensionality reduction.

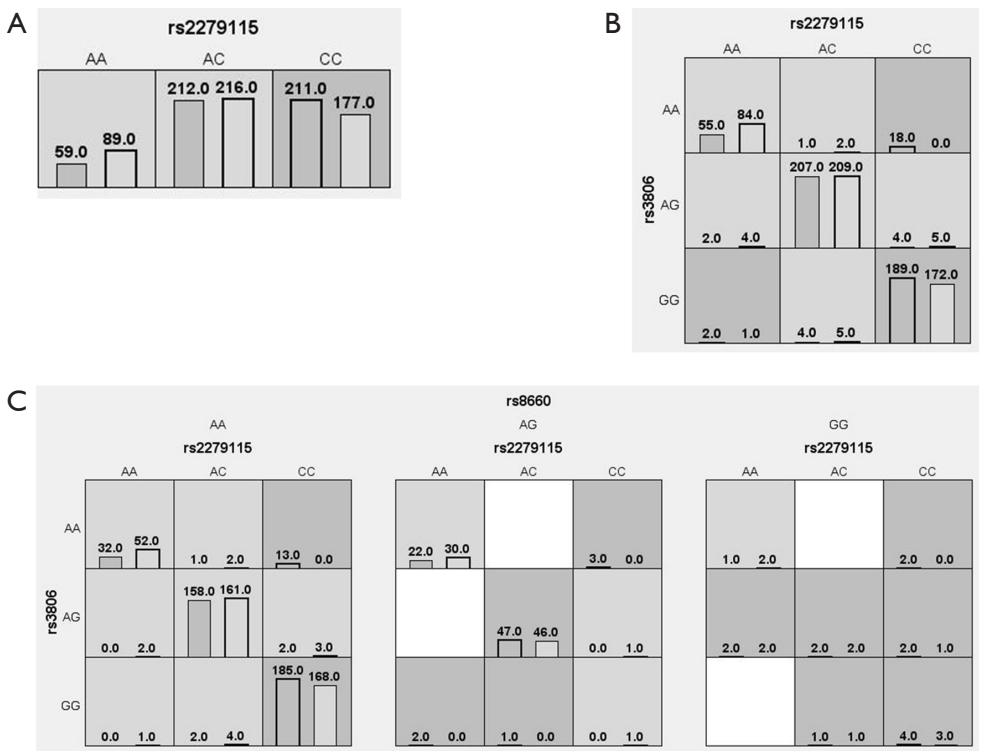

Figure 1 The model of the MDR analysis. Each multifactor cell bars' implications and background color are as follows. Left bars mean the sum of scores in the case. Right bars mean the sum of scores in control. High-risk cells are expressed by black shadow if the ratio of the number of cases to the number of controls exceeds the preset value. Low-risk cells are expressed by light shadow if not more than the threshold. Empty cells are expressed by no shadow which means no cases and controls. MDR, multifactor dimensionality reduction.

rs2279115 was statistically significant in the NIHL case group compared to the control group in the three different genetic models (codominant model, dominant model, and recessive model). Also, haplotype CGA (rs2279115-rs3806-rs8660) was associated with an increased risk for NIHL. Interaction analysis indicated that *BCL-2* rs2279115, *FAM136A* rs3806, and *L3HYPDH* rs8660 had statistically significant interactions with increased NIHL risk. Our results provide evidence that *BCL-2* polymorphism was associated with NIHL risk in Chinese workers.

The *BCL-2* gene has been associated with numerous diseases (18-20). Ahmed *et al*. evaluated the association of *BCL-2* gene polymorphism (rs2279115) and hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) susceptibility in 270 individuals and uncovered an association with a genetic polymorphism in *BCL-2* (rs2279115) with susceptibility to HCV-related hepatocellular carcinoma (21). The association between the *BCL-2*-938C>A (rs2279115) genotype and prostate cancer outcome was studied by Renner *et al*. The study reported that the homozygous *BCL-2*-938 CC genotype was associated with overall survival in prostate cancer patients (22).

No associations between NIHL or hearing loss and *BCL-2* gene polymorphism have been reported. However, some molecular studies have provided evidence that *BCL-2* and the Bcl-2 pathway play crucial roles in both age-related hearing loss and NIHL. Huang *et al*. found a link between age-related apoptosis in auditory cortex neurons and miR-34a/Bcl-2 signaling (9). The expression of immunoreactive p53 and Bcl-2 was increased in aging hair cells showing early signs of apoptotic changes in the nuclei and Bcl-2 expression was increased in hair cells displaying early signs of necrosis (10). Yamashita *et al*. reported an important role of the Bcl-2 family proteins in the prevention of sensory cell death following TTS noise levels, and PTS exposure provoked the expression of Bak-associated cell death (11). *BCL-2* rs2279115 is a functional genetic variant located in the inhibitory P2 promoter region. Also, the *BCL-2* rs2279115A allele may have an interaction with TP53, which will eventually lead to decreases in Bcl-2 expression levels (23).

BCL-2 rs2279115 was also found to be associated with noised-induced hearing loss. A possible reason may be the function of rs2279115 to inhibit the P2 promoter and subsequently alter Bcl-2 expression levels. Bcl-2 has been shown to induce sensory cell death in animals. There were several limitations to this case-control study. First, all NIHL cases were recruited from two factories in this retrospective study, which may lead to selection bias. Then, this is a retrospective case-control study. The evidence of association of BCL-2 polymorphism and NIHL is relative weak. As a result, our findings need to be validated in a prospective study in the future. Second, a larger population of multi-centric study can be conducted to confirm this risk SNP of BCL-2 gene. Third, future animal or cell experimental research will clarify the underlying mechanism of the association between BCL-2 SNP and risk of NIHL. In the end, *BCL-2* rs2279115 may be a potential genetic biomarker for NIHL susceptibility.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/jphe-20-123

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jphe-20-123). Dr. BZ serves as an Editors-in-Chief of *Journal of Public Health and Emergency* from Jan. 2017 to Dec. 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The informed consent of all participants was obtained and the current research was approved by the Ethics Committee of Jiangsu Provincial Center for Disease Control and Prevention (2014029).

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