Small ubiquitin-like modifier 1 gene associated with noise-induced hearing loss in Chinese workers

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Background: Noise-induced hearing loss (NIHL) is harmful to the health quality of noise exposed workers in developed and industrialized countries. The occurrence of NIHL is the result of the interactions between genetic and environmental factors. We aim to study the relationship between rs6709162 genotype located in small ubiquitin-like modifier 1 (*SUMO-1*) gene and susceptibility to NIHL.

Methods: Workers exposed to noise were divided into case group or control group for retrospective study. The two groups were matched by gender, age, smoking, drinking, noise exposure time and intensity. 2 mL of fasting peripheral blood was taken from the two groups, and DNA was extracted. According to the Millennium Genome Project and literature review, rs6709162 of *SUMO-1* gene was selected. TaqMan probe method was taken to detect rs6709162 genotypes.

Results: The distribution of the different genotypes of the *SUMO-1* gene rs6709162 between the case group and the control group was statistically significant (P=0.001). Individuals exposed to high levels of noise (>92 dB) and carrying the rs6709162T allele have an increased risk of NIHL (P=0.004). Environmental factors such as smoking and high temperature interact with rs6709162 (P=0.0001).

Conclusions: rs6709162 may serve as a factor for the susceptibility to NIHL and can be used for the early prevention and diagnosis of NIHL in Chinese Han noise-exposed workers.

Keywords: Noise-induced hearing loss (NIHL); *SUMO-1* gene; single nucleotide polymorphism (SNP)

Introduction

NIHL is an important category of hearing loss, which is primarily caused by continuous or intermittent noise expose for a long time (1), and usually develops slowly within a few years (2). In the world, the hearing loss of adults caused by occupational noise accounts for 16% (3). At present, more than 10 million employees in China work in environments with excessive noise levels, and millions of them suffer from hearing impairment to varying degrees (4). Noise is not the only cause of NIHL. Environmental factors such as smoking, drinking, exposure to organic solvents are also risk factors for NIHL (5,6). Genetic are also factors of consequence in the occurrence and development of NIHL. Single nucleotide polymorphisms (SNPs), as one of the most common human heritable variants, refers to the polymorphism of DNA sequence caused by single nucleotide variation at the genomic level. The studies of Ding and Xu found that the SNPs of *OGG1*, *APEX1*, *XRCC1* and *PCDH15* genes is related to human NIHL

susceptibility (7,8). To comprehend the pathogenesis of NIHL, more genetic epidemiology studies still need to explore the genes related to NIHL susceptibility.

SUMO (small ubiquitin-related modifier) can enhance the stability of proteins or regulate the location and distribution of proteins in cells, as well as affect the transcriptional activity of proteins. The small ubiquitin-like modifier 1 (SUMO-1) is reported to be a critical member of the ubiquitin-related protein family. Through binding to intracellular target proteins, SUMO-1 is an essential component of the post-translational modification system, which participates in numerous of cellular biological processes, covering nuclear transport, transcriptional regulation, cell apoptosis, and protein stability. Many studies have found that the imbalance of SUMOylation or deSUMOylation processes of protein is related to the occurrence of many diseases and even cancers (9-11). For example, SUMO-1 siRNA down-regulated H4 SUMOylation, Keep the endometrial cancer cells from proliferation and induces apoptosis (12). Prostaglandin E2 (PGE2) enhances the proliferation and invasion of endometrial cancer cells by increasing SUMO-1, through EP4 receptors (13). Ginkgolic Acid is a SUMO-1 inhibitor, which can inhibit the progression of oral squamous cell carcinoma by reducing the SUMOylation of SMAD4 (14). And silencing *SUMO-1* gene can reduce the proliferation of gastric cancer cells (15). However, there are none report about the relationship between *SUMO-1* gene polymorphism and NIHL susceptibility. Therefore, we propose the hypothesis that the polymorphism of *SUMO-1* gene may be related to the pathogenesis and susceptibility to the NIHL. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jphe-20-114).

Methods

Patient selection

A retrospective case/control study was conducted to find the relationship between *SUMO-1* SNP and NIHL susceptibility. In this current research, 2,689 workers who were exposed to occupational mechanical noise in one plant in Jiangsu province, east China were gathered as objects of study in 2015. Chinese occupational NIHL diagnostic criteria (GBZ49-2014) were then used to identify subjects with hearing loss or not. Occupational noise exposure in this research is defined as exceeding 85 dB (A) within 8 hours of a working day. Case definition and control

definition were assigned as follows, case group: average binaural high-frequencies in 3,000, 4,000, and 6,000 Hz hearing thresholds were >25 dB (25 dB not included), or they were ≤25 dB but with the worse ear's speech frequencies in 500, 1,000, and 2,000 Hz hearing threshold were >25 dB (25 dB not included). In the control group, the average binaural high-frequencies hearing threshold were ≤25 dB with the worse ear's speech frequencies hearing thresholds were ≤25 dB. According to the exclusion criteria (a. subjects with missing data, b. subjects without blood collection, c. subjects with ototoxic drug administration were excluded). Finally, 586 cases and 639 controls were included in this study, matching sex, age, smoking, drinking, noise working time and noise exposure intensity. Study size: all subjects accord with screening criteria were included in this study. All data (questionnaire, pure-tone audiometry, measurement of ambient noise, temperature) in current research were collected by trained investigators following relevant pipelines and regulations. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study obtained the informed consent of all participants and was approved by the Ethics Committee of Jiangsu Center for Disease Control and Prevention [2014029].

Questionnaire investigation

The questionnaire content mainly includes: the general demographic characteristics (such as gender, age and education level), the histories of diseases affecting hearing (head trauma, history of use of ototoxic drugs, etc.), living habits (history of smoking and drinking). Smoking status in this study was split into three groups: smoking group, ever smoking group and never smoking group. Drinking status was also split into three groups: drinking group, ever drinking group and never drinking group. If a person smokes a cigarette or more or drinks fifty grams of alcohol or more (spirits and beer) in a day for more than a year, he or she was assigned into a smoking or drinking group. If a participant has quit smoking or drinking for more than a year, he or she was assigned to ever smoking group or ever drinking group.

Pure-tone audiometry

Subjects should avoid exposure to noise (>85 dB) for at least twelve hours before accepting pure tone audiometry. Then 500, 1,000, 2,000, 3,000, 4,000, and 6,000 Hz pure tone air threshold tests were performed by otorhinolaryngologist

in the sound attenuation room. In accordance with the Chinese Diagnostic criteria of Occupational noise-induced hearing loss (NIHL), the binaural hearing threshold was measured by 5 dB (A) step-up method.

Measurement of ambient noise

Based on the Chinese national standard for workplace noise, a noise dosimeter is used to measure the noise exposure intensity of the workplace at each post. Individual noise meters (Noise-Pro, Quest, Oconomowoc, WI, USA) were utilized in the workplace to measure noise exposure intensities for everyone for three consecutive days at ten a.m., three p.m., and five p.m.

Measurement of ambient temperature

Three measuring points were selected: dry bulb thermometer, natural wet bulb thermometer and black bulb thermometer. Three kinds of temperature are measured respectively, and the WBGT index is calculated by the following formula. Three times a day, take the average. When WBGT ≥25 ℃, or WBGT-outdoor WBGT ≥2 ℃, it is high temperature operation. Outdoor: WBGT = wet bulb temperature (℃) ×0.7 + black bulb temperature (℃) ×0.2 + dry bulb temperature (℃) ×0.1. Indoor: WBGT = wet bulb temperature (℃) ×0.7 + black bulb temperature (℃) ×0.3.

SNP selection

To be consistent with the purpose of the study, we focus the candidate SNPs related to the *SUMO1* gene. Firstly, selected SNPs is based on the information of the Thousand Genome Project, dbSNP database and the previous literature reviews. Our criteria for identifying SNPs included: first, the minor allele frequency (MAF) in the Chinese Han population (CHB) was over 0.1. Then the linkage disequilibrium (LD) r^2 was over 0.8. The SNPs locating in the gene functional regions (missense region, 3´UTR region, or 5´UTR region) or previously being reported were selected. At last, we found that rs6709162 was satisfactory, and can be used in follow-up experiments.

SNP genotyping

In this study, the target SNP was genotyped by Taqman genotyping technologies using ABI 7900HT (Applied Biosystems, Massachusetts, USA). SDS software (Applied Biosystems, v2.4) was used to analyze the results of genotyping.

Statistical analysis

All data were analyzed by SPSS 24.0 software (IBM, NYC, USA). Missing data was excluded. The measurement data such as age, duration of noise-exposed (years), noise exposure levels (dB) and high-frequency hearing threshold (dB) were expressed as mean ± SD, and the differences were analyzed by *t*-test. The classified variables were expressed by percentage, and the comparison was made by bilateral χ^2 test. The goodness-of-fit χ^2 test was performed to evaluate whether the SNP of the control group conformed to Hardy-Weinberg equilibrium. Gender, age, smoking status and drinking status were corrected to reduce bias by logistic regression model, and the odds ratio (OR) and its 95% confidence interval (CI) were estimated. The multifactor dimensionality reduction (MDR) analysis was performed to identify the possible interactions between SNP and occupational environmental exposure. Four different genetic models (codominant model, dominant model, recessive model, and allelic model) were used for sensitive analysis to find the effect of model alteration on the results. The value of P less than 0.05 was considered to be statistically significant.

Results

Demographic characteristics of the participants and Hardy-Weinberg test

In this study, 2,689 workers exposed to noise were potentially eligible and examined for eligibility. According to the exclusion criteria, (I) subjects with missing data, (II) subjects without blood collection, (III) subjects with ototoxic drug administration were excluded. Finally, a total of 1,225 workers (586 cases and 639 controls matching gender, age, smoking status, drinking status, noise working time and noise exposure intensity) were confirmed eligible, included and analyzed in the study. *Table 1* showed that, there were no significant differences in general characteristics, year and intensity of noise-expose between the two groups (P>0.05). The average high-frequency hearing threshold of the NIHL case group was significantly higher (35.75±9.78 dB) than that of the control group (14.06±4.15 dB) (P<0.001). *Table 2* showed the database information of the rs6709162 and the result of Hardy-Weinberg test. No subjects had missing data.

Table 1 Demographic characteristics of the study subjects

Variables	Cases (n=586)		Controls (n=639)		P
	n	%	n	%	
Age (years)					0.815[a]
Mean ± SD	40.43±6.31		40.36±6.21		0.808[b]
≤35	142	24.2	163	25.5	
35–45	327	55.8	345	54.0	
>45	117	20.0	131	20.5	
Sex					0.611[b]
Male	542	92.5	586	91.7	
Female	44	7.5	53	8.3	
Tobacco use					0.411[b]
Now	337	57.5	349	54.6	
Ever	12	2.0	19	3.0	
Never	237	40.4	271	42.4	
Alcohol consumption					0.960[b]
Now	239	40.8	257	40.2	
Ever	10	1.7	12	1.9	
Never	337	57.5	370	57.9	
Duration of noise-exposure (years)					0.303[a]
Mean ± SD	18.54±7.60		18.08±7.38		0.535[b]
≤16	262	44.7	297	46.5	
>16	324	55.3	342	53.5	
Levels of noise exposure (dB)					0.919[a]
Mean ± SD	87.22±7.63		87.17±7.53		0.985[b]
≤85	262	44.7	284	44.4	
85–92	114	19.5	123	19.2	
>92	210	35.8	232	36.3	
High frequency hearing threshold (dB)					<0.001[a]
Mean ± SD	35.75±9.78		14.06±4.15		<0.001[b]
≤26	61	10.4	639	100.0	
>26	525	89.6	0.0	0.0	

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

Analysis of SNPs and NIHL risk

The logistic analysis in *Table 3* showed results adjusting for gender, age, alcohol use, and tobacco use. The genotype frequencies of rs6709162 in the two groups was statistically significant different in codominant model, dominant model, recessive model, and allelic model (P<0.001, P=0.041, P<0.001, P=0.001, respectively). Workers with the rs6709162TT genotype had a relatively increased NIHL

Table 2 Database information of rs6709162 and result of Hardy-Weinberg test

SNP	Gene	Alleles	Chromosome	Functional Consequence	MAF		P for HWE
					Control	Database	
rs6709162	*SUMO-1*	C/T	2:202233836	Intron variant	0.337	0.341	0.802

[a], data from NCBI dbSNP; [b], P value of Hardy-Weinberg test.

Table 3 Distributions of rs6709162 and the associations with NIHL

Genetic model	Genotype	Cases		Controls		P[a]	Adjusted P[b]	Adjusted OR (95% CI)[b]
		n=586	%	n=639	%			
Codominant	CC	220	37.5	276	43.2	0.001	<0.001	1.00 (Ref.)
	CT	264	45.1	296	46.3			1.13 (0.88–1.43)
	TT	102	17.4	67	10.5			1.92 (1.35–2.75)
Dominant	CC	366	62.5	276	43.2	0.048	0.041	1.00 (Ref.)
	CT/TT	220	37.5	363	56.8			1.27 (1.01–1.60)
Recessive	CC/CT	484	82.6	572	89.5	<0.001	<0.001	1.00 (Ref.)
	TT	102	17.4	67	10.5			1.81 (1.30–2.52)
Alleles	C	704	60.1	848	66.4	0.001	0.001	1.00 (Ref.)
	T	468	39.9	430	33.6			1.32 (1.12–1.55)

[a], two-sided χ^2 test; [b], adjusted for age, gender, alcohol use and tobacco use in logistic regression model.

risk with the OR value of 1.92 (95% CI, 1.35–2.75) in the codominant model. The NIHL risk of workers with the TT genotype was relatively larger with an OR value of 1.81 (1.30–2.52) in the recessive model. And the NIHL risk of workers of the T allele increased in the allele model with an OR value of 1.32 (95% CI, 1.12–1.55).

Stratification analysis

In the *Table 4*, for individuals exposed to noise levels above 92 dB (A), carrying rs6709162 TT genotype (adjusted OR =2.83, 95% CI, 1.53–5.25) in the codominant model, rs6709162 CT+TT genotype (with adjusted OR =1.47, 95% CI, 1.00–2.16) in the dominant model, rs6709162 TT genotype (with adjusted OR =2.56, 95% CI, 1.44–4.56) in the recessive model and rs6709162 T (with adjusted OR =1.84, 95% CI, 1.17–2.03) in allelic model show an increased risk for NIHL.

Analysis of gene and environment interactions

MDR software was performed to detect the interaction of

rs6709162 with environmental factors. *Table 5* and *Figure 1* showed that, rs6709162 and smoking had a statistical interaction with P=0.0021 (OR =1.44, 95% CI, 1.14–1.81). rs6709162, smoking and physical (high temperature) also had a statistical interaction (P=0.0001, OR =1.59, 95% CI, 1.26–2.01).

Discussion

NIHL has been known to be the interaction result of genetic and environmental factors, and clinical association studies have confirmed that NIHL has genetic predisposition (16,17). In this study, the relationship between *SUMO-1* gene and NIHL susceptibility was discussed for the first time. It was found that exposure to high levels of noise (>92 dB) and carrying rs6709162T alleles will increase the risk of NIHL. Environmental factors such as smoking and high temperature interact with rs6709162. Related studies show that NIHL is linked to physical (high temperature) (18) environmental factors and living habits (smoking) (8), which are consistent with the results of this study.

Table 4 Stratified analysis results of rs6709162 in genetic models

Genetic model	Group	Genotype	Expose level of noise (dB)		
			≤85	85–92	>92
Codominant	Case	CC	104	40	76
		CT	117	53	94
		TT	41	21	40
	Control	CC	116	54	20
		CT	135	55	106
		TT	33	14	106
	P[a]		0.383	0.203	0.004
	Adjusted P[b]		0.340	0.302	0.003
	Adjusted OR (95% CI)[b]		1.44 (0.84–2.47)	1.90 (0.84–4.28)	2.83 (1.53–5.25)
Dominant	Case	CC	104	40	76
		CT/TT	158	74	134
	Control	CC	116	54	106
		CT/TT	168	69	126
	P[a]		0.794	0.185	0.053
	Adjusted P[b]		0.698	0.277	0.049
	Adjusted OR (95% CI)[b]		1.07 (0.76–1.51)	1.35 (0.79–2.31)	1.47 (1.00–2.16)
Recessive	Case	CC/CT	221	93	170
		TT	41	21	40
	Control	CC/CT	251	109	212
		TT	33	14	20
	P[a]		0.143	0.163	0.001
	Adjusted P[b]		0.211	0.145	0.002
	Adjusted OR (95% CI)[b]		1.45 (0.88–2.40)	1.70 (0.80–3.61)	2.56 (1.44–4.56)
Alleles	Case	C	325	133	246
		T	199	95	174
	Control	C	367	163	318
		T	201	83	146
	P[a]		0.375	0.075	0.002
	Adjusted P[b]		0.313	0.138	0.002
	Adjusted OR (95% CI)[b]		1.14 (0.89–1.46)	1.33 (0.91–1.95)	1.84 (1.17–2.03)

[a], two-sided χ^2 test; [b], adjusted for age, gender, alcohol use and tobacco use in a logistic regression model.
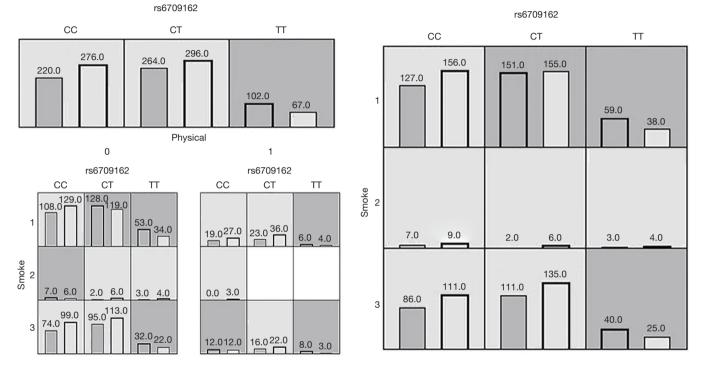
Studies have shown that SUMO-1 belongs to the SUMO family, which can compete with ubiquitin for receptor binding sites of some substrate proteins, inhibit ubiquitin degradation of p53 protein and other substrates, and enhance the stability and transcriptional activity of wild-type p53 and other tumor suppressor genes. Long-term exposure

Table 5 Results of MDR analysis of the interactions between the SNP and environmental factors

Model	Training balanced accuracy	Testing balanced accuracy	Cross-validation consistency	P	OR (95% CI)
rs6709162	0.5346	0.5346	10/10	0.0005	1.80 (1.29–2.51)
rs6709162, smoke	0.5435	0.5206	6/10	0.0021	1.44 (1.14–1.81)
rs6709162, smoke, physical	0.555	0.5168	5/10	0.0001	1.59 (1.26–2.01)

Figure 1 The best fit model of the MDR analysis. The implications of bars and background color were as follows. Left bar represented sum of scores in case group and right bar represented sum of scores of control group. High-risk cells were expressed by black shadow while the ratio of cases to controls exceeded the preset value, as low-risk cells by light shadow if not exceeded the threshold. The empty cells by no shadow means no cases and controls (physical represented high temperature 0: no, 1: yes; smoke 1: now, 2: ever, 3: never).

to impulse noise can activate phosphorylated p53 and cause apoptosis of outer hair cells and Sertoli cells (19-21).

rs6709162 is located in the non-coding intron region of *SUMO-1* gene. It was previously thought that only exons would be translated into proteins, while introns would be cut off during pre-mRNA processing into mature mRNA without biological function. However, with the in-depth study of gene regulatory transcription, it is found that intron is an important component of the genome, which plays a crucial role in maintaining the specific structure of chromosomes, ensuring the particular function of genes, regulating gene expression and so on (22). In post-

transcriptional processing, intron regions have more mutations than exon regions. Some studies have showed that intron mutations of insulin-like growth factor 2 (IGF2), ESR (estrogen receptor), FSH β, Nodal, CPT-Iα, β-actin, β-keratin and immunoglobulin can cause changes in gene expression. Intron gene polymorphism has also been shown to be associated with numerous diseases such as aortic dissection (23), diabetes (24), and schizophrenia (25) in the studies of Ekmekci, Mazaheri and Železníková. A deletion in 19q13.32 region including *SAE1* gene, which codes a SUMO-1 activating enzyme subunit, was reported by Leal on a patient with severe mental retardation, deafness,

megacolon tetralogy of Fallot, cleft lip and palate, and other dysmorphic features. This case report indicates that, genome deletion in *SUMO-1* region may associated with hearing loss (26).

We speculate that rs6709162 site mutation may increase the expression of *SUMO-1* gene, overexpression of *SUMO-1* gene and long-term exposure to high levels of noise activates p53 in hair cells and Sertoli cells of the cochlea, resulting in structural damages to hair cells and Sertoli cells, thus increasing the risk of NIHL. However, due to the lack of environmental noise exposure information such as traffic noise and music noise, measurement bias may exit.

There were several limitations to this case-control study. First, this is a retrospective case-control study, the evidence is relative weak, our findings can be validated in a prospective cohort study in the future. Second, we can conduct a multi-center study or GWAS study in a larger population to confirm this risk SNP of *SUMO-1* gene. Third, future experimental research will clarify the underlying mechanism of the association between SNP and risk of NIHL.

Because of the concealment and irreversibility of NIHL, it is impossible to cure the hearing loss caused by noise. Primary prevention of NIHL is the key to reduce the incidence. On the one hand, factories should properly deduce the noise intensity and the duration of noise exposure of workers; on the other hand, they should find new ideas for noise-induced hearing prevention (27). At present, the application of noise deafness susceptibility genes in clinical diagnosis, prevention and treatment of NIHL has not been realized (28). However, with the continuous recognition and study of the susceptible genes of noise-induced deafness, it is believed that one day the susceptible individuals can be screened out before they are exposed to high noise. For workers with susceptibility genes, we should inform and guide them to develop good living habits, pay attention to personal protection in work places, and advise them to stay away from the noise in the living environment. And regular occupational health examination, once found that there is high-frequency hearing loss have been transferred from the noise job in time. The compensation of NIHL workers shall have the same rights as other employees. Therefore, studying the relationship between genes and susceptibility to NIHL and screening people susceptible to NIHL are of great significance on the terms of the prevention of NIHL and improving the living standards of NIHL workers.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jphe-20-114

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jphe-20-114

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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). This study obtained the informed consent of all participants and was approved by the Ethics Committee of Jiangsu Center for Disease Control and Prevention [2014029].

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