Available Online at http://www.journalajst.com

ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN: 0976-3376

Asian Journal of Science and Technology
Vol. 12, Issue, 11, pp. 11918-11923, November, 2021

RESEARCH ARTICLE

FIBROBLAST GROWTH FACTOR1POLYMORPHISM WITHIN 3'-UNTRANSLATED REGIONS IS ASSOCIATED WITH NOISE-INDUCED HEARING LOSS

Yuquan Chen, Erbao Bao, Yuqiang Lin, Wenzhong Jiang and Yimin Liu*

Guangzhou Occupational Disease Prevention and Treatment Hospital (Guangzhou Twelfth People's Hospital), Guangzhou 510620, China

ARTICLE INFO

Article History:
Received 17th August, 2021
Received in revised form
15th September, 2021
Accepted 20th October, 2021
Published online 28th November, 2021

Key words:
Noise; Noise-Induced Hearing Loss; Polymorphism; 3'-Untranslated Regions; Fibroblast Growth Factor 1.

Corresponding author:** **Yimin Liu

ABSTRACT

Introduction: It has been presented that noise-induced hearing loss is a complex disease that is a combination of genetic and environmental factors. There are consistent results concerning the association between variation in the fibroblast growth factor 1 genetic polymorphisms and susceptibility to noise-induced hearing loss. **Objectives:** This study was carried out to clarify the association between fibroblast growth factor1 gene polymorphism within 3'-untranslated regions and noise-induced hearing loss among noise-exposed workers. **Methods:** A case-control study of 174 pairs of Chinese carmaking male workers was carried out to investigate the relationship between fibroblast growth factor1 polymorphisms and noise-induced hearing loss susceptibility. The fibroblast growth factor1 polymorphism of all individuals was evaluated by multiplex polymerase chain reaction. Three polymorphism sites (AA/ CC/AC) of FGF1 3'-untranslated regions were genotyped by using the polymerase chain reaction technique. Questionnaires and laboratory data were collected and analyzed with independent *t*-test, Wilcoxon test, Pearson correlation analysis, and multiple linear regression models. **Results:** The gene rs17099022, rs17099029, rs34000, rs17217583, rs33999, rs2278688, rs34001, and rs34002 loci genotypes in 174 hearing loss persons and 174 healthy controls were found and performed to analyze. There were significant variances of genotype frequencies of rs17099022 existed obviously between the cases and controls (P =0.038). Analysis results revealed that the T allele of rs17099022 (95% CI = 0.320-0.987, odds ratio (OR) = 0.562, P = 0.038) was a protective factor, individuals who were exposed to noise ≤ 95 dB with the rs17099022 CC genotype (95% CI = 0.249-0.903, OR = 0.474, P =0.023) have a higher susceptibility to NIHL while compared to TC genotype. **Conclusions:** Our research confirmed that fibroblast growth factor1 rs17099022 gene polymorphism in the 3'-untranslated regions may be a susceptible biomarker for noise-induced hearing loss patients. rs17099022 T and TC genotype could be a protective factor for hearing loss.

Citation: Yuquan Chen, Erbao Bao, Yuqiang Lin, Wenzhong Jiang and Yimin Liu, 2021. "Fibroblast growth factor1polymorphism within 3'-untranslated regions is associated with noise-induced hearing loss", *Asian Journal of Science and Technology*, 12, (11), 11918-11923.

INTRODUCTION

Noise-induced hearing loss (NIHL) is one of the most common occupational disease experienced around the world in occupational environments[1] and the second most common type of sensorineural hearing impairment with the genetic incidence after presbyacusis[2]. More than 600 million workers are exposed to noise worldwide, and the permanent irreversible hearing loss of about 10 million people in the United States is due to by noise[3]. In China, NIHL has been the second most frequent occupational disease after pneumoconiosis. It not only has an effect on the quality of life of employees but also leads to a huge economic burden on society[4]. NIHL has become a major public health problem with industrialization. There is great variability in susceptibility to hearing loss; some subjects present different level of NIHL after exposure to the same level of noise, so has been initiated that NIHL is a complex disease that is affected by the interaction of genetic and environmental factors[5].Sliwinska-Kowalska created an animal model and proved that gene-knockout mice have expressed more susceptibility to noise than their wild-type littermates and confirmed that genetic polymorphisms contribute to the occurrence of NIHL. Sliwinska-Kowalska[2] created ananimal model and proved that gene-knockout mice have expressed more susceptibility to noise than their wild-type littermates and confirmed that genetic polymorphisms promote the occurrence of NIHL. Little knows about the involvement of genetic factors that influence NIHL in humans. Recent studies have found a variety of susceptible genes that may be linked with NIHL, such as potassium channel genes (KCNQ4, KCNQ1), catalase, PCDH15, CDH23, HOTAIR70, SOD and other genes[6-8]. Fibroblast growth factor 1 (FGF1), a member of FGF superfamily, involved in embryonic

development, angiogenesis, wound healing, and neuron survival, which is one of the basic fibroblast growth factors to be discovered and studied[9]. It has been demonstrated to play an important role in various physiological and pathological processes such as optic nerve atrophy, neurological deafness, and visceral ischemia-reperfusion injury[10].FGF1 is expressed in cochlear hair cells, spiral ganglia, and cochlear precursors. It reaches maturity levels in the early stages of embryos. When it is stimulated by excessive noise or cochlea damage, FGF1 expression increases[11]. FGF1 plays a major role in maintaining the stability of hair cells and changes in cochlear function. Single Nucleotide Polymorphisms (SNPs) are the most common genetic mutation. SNPs refer to the changes of single nucleotides in germline DNA caused by mutations and variations present a minimum of 1% of a given population[12]. After inferring that the human genome has at least 3 million SNPs, a single nucleotide polymorphism may occur in every 1,000 base sequences, which constitute more than 90% of the mutation in the human genome[13].

There are limited results about the association between variation in FGF1 genes and susceptibility to NIHL. Studies on the association between SNPs of the FGF1 gene and the risk of NIHL have been declared in China[14]. Such studies have focused on the FGF1 SNP rs17217562; However, are there more SNP loci in the FGF1 gene related to NIHL susceptibility? A case-control study was designed and conformed to analyze the potential link between FGF1 SNPs (rs17099022, rs17099029, rs34000, rs17217583, rs33999, rs2278688, rs34001, and rs34002)and genetic susceptibility to NIHL is discussed in this article.

MATERIALS AND METHODS

Ethics statement: This study was authorized by the Medical Ethics Committee of The Occupational Prevention and Treatment Hospital of Guangzhou (The Twelfth People's Hospital of Guangzhou). And all the studies were carried out in accordance with correlative standards and rules. Informed consent was acquired from all study subjects. All data were only available to the investigators[15].

Subjects: In the current study, a total of 3241 workers who participated in the annual health checkup at Guangzhou Prevention and Treatment Hospital of Occupational diseases were selected as subjects. All persons met the inclusion criteria was as follows: ①exposed to hazardous noise (≥ 85 dB)[16]; ②the exposure period of noise was not less than 1year; ③no history of a disease or current illness that might affect their hearing, nor of the long-term use of ototoxic drugs; ④no hearing system disease; ⑤earplugs or earmuffs were used daily or at least 4 days a week; ⑥no fever or other diseases occurred within 1 month before the pure-tone audiometry. Butwhich could influence hearing thresholds, such as a family history of deafness, otitis media, congenital or familial hearing loss, and ototoxic drug consumption, diabetes mellitus, hypertension, head trauma, head surgery, conductive hearing loss in pure-tone audiometry were excluded from the study[17].Age, duration of employment in a current job, smoking status, alcohol consumption, medical history, and commonly used medicines was investigated by a questionnaire for each subject.

Pure-tone audiometry (PTA) and NIHL Evaluation: Pure-tone tests were executed for the subjects to identify the degree of hearing impairment. According to diagnostic criteria for occupational noise-induced deafness in China (GBZ 49-2014), the air conduction hearing thresholds at 0.5, 1.0, 2.0, 3.0, 4.0 and 6.0kHz were monitored using an audiometer (GSI, USA)[18]. All subjects were divided into two groups according to the result of audiometry who continued to be exposed to at least 85 dB noise approximately 8 hours per day. Persons with bilateral threshold deviations of more than 25 dB at high and low frequencies were classified as the hearing loss groups. Oppositely, individuals with bilateral threshold deviations of less than 25 dB at high and low frequencies were classified as the normal hearing groups[19]. Then we found 2732 with normal hearing while 509 belonged to the hearing loss groups. We matched control groups based on age, the exposure period of noise and degrees of noise exposure. The matching conditions include the equivalent noise position, the age difference is within 3 years, and the noise receiving service age is within 1 year. At last, 174 NIHL cases and 174 controls from the individuals met our requirement and then be selected.

DNA Extraction: Five milliliters of venous blood samples were collected in EDTA-containing anticoagulant tubes at the workplace and placed immediately container, then transported on dry ice to the laboratory for DNA extraction and genotyping[17].DNA extraction from blood was performed using a commercial kit under the guidance of the manufacturers' instructions. The abstracted DNA was stored up at -80°C for future use[19].

SNP Selection and Genotyping: Candidate SNPs in the FGF1 genes were selected based on the HapMap database. (http://hapmap. ncbi.nlm.nih.gov), dBSNP (http://www.ncbi.nlm.nih.gov/SNP), and 1000 Genomes (http://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/). SNP function prediction software was also adopted such as Variant Effect Predictor (http://asia.ensembl.org/info/docs/tools/vep/index.html) and SNP Function Prediction (http://snpinfo.niehs.nih.gov/snpinfo/snpfunc.htm). Inclusion criteria were as follows: (1) minor allele frequency (MAF) of the Chinese Han population (CHB) ≥0.10; (2) located in 3′-untranslated region (UTR); (3) linkage disequilibrium value of $r2 > 0.80$[20,21]. We distinguished eight SNPs (rs17099022, rs17099029, rs34000, rs17217583, rs33999, rs2278688, rs34001 and rs34002) in FGF1 were selected according to these criteria. Genotyping of the SNPs was carried out using the polymerase chain reaction- ligase detection reactions (PCR-LDR) method, which was finished by Huada Gene Biotechnology (Shenzhen) Co., Ltd.

Statistical analysis: The questionnaire was double-entered by Epidata3.1 software and checked for consistency. Questionnaires with inconsistent data were corrected in time. Data were analyzed by SPSS version 23.0 (SPSS, Inc., Chicago, IL). Independent Student's t-test and Mann-Whitney test were used to compare continuous variables between groups. One-Sample Kolmogorov-Smirnov test was applied to test the normality of studying variables. The frequency of polymorphism was compared between groups by chi-square test and Fisher's exact test and odds ratios with corresponding 95% confidence intervals (95% *CI*) was calculated with the Mantel-Haenszel method. *P*-value≤ 0.05 was considered statistically significant[17].

RESULTS

Demographic Characteristics of Studying Individuals: A total of 3,241male subjects that comprised 2,732 normal hearing persons and 509 individuals with audiograms suggestive NIHL, with an abnormal hearing rate of 15.7%. The median age was 22.35±3.01 years (18-41 years).After strict matching according to the conditions, a total of 384 subjects were included in the study according to 1: 1, there were 174 as a case group and 174 as a control participated in this study. Table 1 presents the demographic and personal characteristics of the study subjects. There were no significant differences in the distribution of general characteristics, body mass index(BMI), years of noise exposure, and noise intensity exposure between the NIHL groups and control groups (P> 0.05). The results of the hearing loss rate of different demographic characteristics between the two groups are showed in Table 2, and we found no statistical significance in marital status, work shift system, smoking status, drinking and wearing headphones (P>0.05).

Association between FGF1 SNPs and Risks of NIHL: The relationship between FGF1 and the NIHL risk was analyzed by multivariate analysis. Our study screened the SNP loci in each functional area of FGF-1 gene through bioinformatics database, and finally obtained 8 loci existing in the 3'-UTR regions (rs17099022, rs17099029, rs34000, rs17217583, rs33999, rs2278688, rs34001, and rs34002), with a small error that all detection rate of each site reached were more than 97%. The results of eight chosen SNPs and Hardy-Weinberg tests are shown in Table 3, andχ^2tests indicated every chosen SNP was in Hardy-Weinberg equilibrium (P> 0.05) except rs17099029(P< 0.05) and rs2278688 (P< 0.05). The genotype and allele distribution of rs17099022, rs34000, rs17217583, rs33999, rs34001 and rs34002 under recessive, dominant, codominant, and allelic models was shown in Table 4. It showed significant variances of genotype frequencies of rs17099022 existed obviously between the cases and controls under the codominant model (P = 0.027). The rs17099022 showed a statistically significant difference in the two groups (P< 0.05), and associations were only found between rs17099022 and the risk of NIHL. For rs17099022, T genotype was related with a decreased NIHL risk (OR = 0.562, 95% CI = 0.320-0.987) when compared with the C genotype. It means that carrying the T allele in rs17099022 is a protective factor of NIHL. But CC Genotype is a risk factor for NIHL (OR = 1.901, 95% CI = 1.059-3.413). The risk of NIHL with CC genotype in rs17099022 is 1.901 time to genotype TC.

DISCUSSION

Exposure to hazardous noise is one of the most widespread occupational risks[22]. This study was based on a sample of 3241 carmaking male workers who participated in an occupational health examination. Owing to the prevalence of welding and stamping in the automobile manufacturing process, noise is the most important and the most serious occupational disease hazard factor in automobile manufacturing enterprises[23].Noise exposure at work is accountable for an estimated 16% of disabling hearing loss in adults worldwide[24]. Paying attention to the health damage of noise to the professional population has become an urgent public health problem to be solved in the automobile manufacturing industry.

The human FGF1 gene is located on chromosome 5q31 and consists of 154 amino acids. It is commonly used clinically to accelerate wound healing, treat optic atrophy, neurological deafness, visceral ischemia-reperfusion injury, regulate tumorigenesis and fat formation[25].The basis of FGF1's role in oxidative damage and apoptosis of cochlear hair cells may be related to its reduction in the generation and release of oxygen free radicals, the promotion of the activation of reductase systems, and the regulation of the expression of apoptosis-related genes[26]. It appears that many factors play a significant role in NIHL including environmental and genetic factors. The purpose of this study was to evaluate the genetic variability of FGF1 associated with susceptibility to NIHL[27].Researchers have postulated that as much as 50% of the variability in NIHL susceptibility may be because of genetic[28]. SNP is an ordinary phenomenon in the human genome and there are 15 million SNPs in all humans. Although the SNPs distribute in humans widely, SNPs do not distribute homogeneously and most SNPs are in noncoding areas of the genome[29]. SNPs located in the 3'-UTR region play an important role in regulating the stability of mRNAs, mediating mRNA localization, assisting in identifying special codons, and controlling the level of mRNA translation[30,31]. At present, because of the rapid development of molecular biology techniques, the study of polymorphisms of NIHL and population susceptibility genes, especially the relationship with SNP has become a research hotspot[32]. There are many SNPs in the 3′-UTR region of some genes related to the pathogenesis of various human diseases, mainly due to the presence of miRNA binding sites, a large number of SNP sites are related to miRNA, among which polymorphisms in the seed sequence region of the target gene 3′-UTR bound to miRNA are related to the susceptibility of many diseases including NIHL[33]. We found eight SNPs (rs17099022, rs17099029, rs34000, rs17217583, rs33999, rs2278688, rs34001 and rs34002) are located in the 3′-UTR[34]. But only rs17099022 proved to be relevant to NIHL. rs17099022 may also influence the expression of FGF1 by controlling mRNA translation levels.

According to the literature review, studies on the correlation between FGF and NIHL are hardly found in the English literature. In this study, we adopted TaqMan genotyping to analyze the eight selected FGF1 SNPs (rs17099022, rs17099029, rs34000, rs17217583, rs33999, rs2278688, rs34001, and rs34002) in 174 NIHL cases and 174 controls, and found statistically significant associations between the rs17099022 and NIHL hazard. Demographic characteristic calculations for the population ensured homogeneity between the two groups. We also found that the rs17099022 T genotype of FGF1 (OR = 0.562, 95% CI = 0.320-0.987) was significantly relative with a lower NIHL risk in which the result is a powerful evidence for our hypothesis that FGF1 polymorphisms could decrease the NIHL susceptibility in the Chinese employees. It means that rs17099022 carrying the T allele is a protective factor for NIHL, CC genotype is a risk factor for NIHL, and the risk of NIHL with CC genotype is 1.901 time to TC genotype. FGF1 gene polymorphism is linked to the risk of NIHL (OR = 1.901, 95% CI = 1.059-3.413). There are even many shortcomings in this study. First of all, although it adopted a 1:1 matched case-control design, the sample size was small, and some positive results that could only have been disclosed by large samples may not have been able to found. Second, all of the workers exposed to the noise were from the same workplace that limits to a car factory,

Table 1.Characteristics of the study participants (Mean±SD)

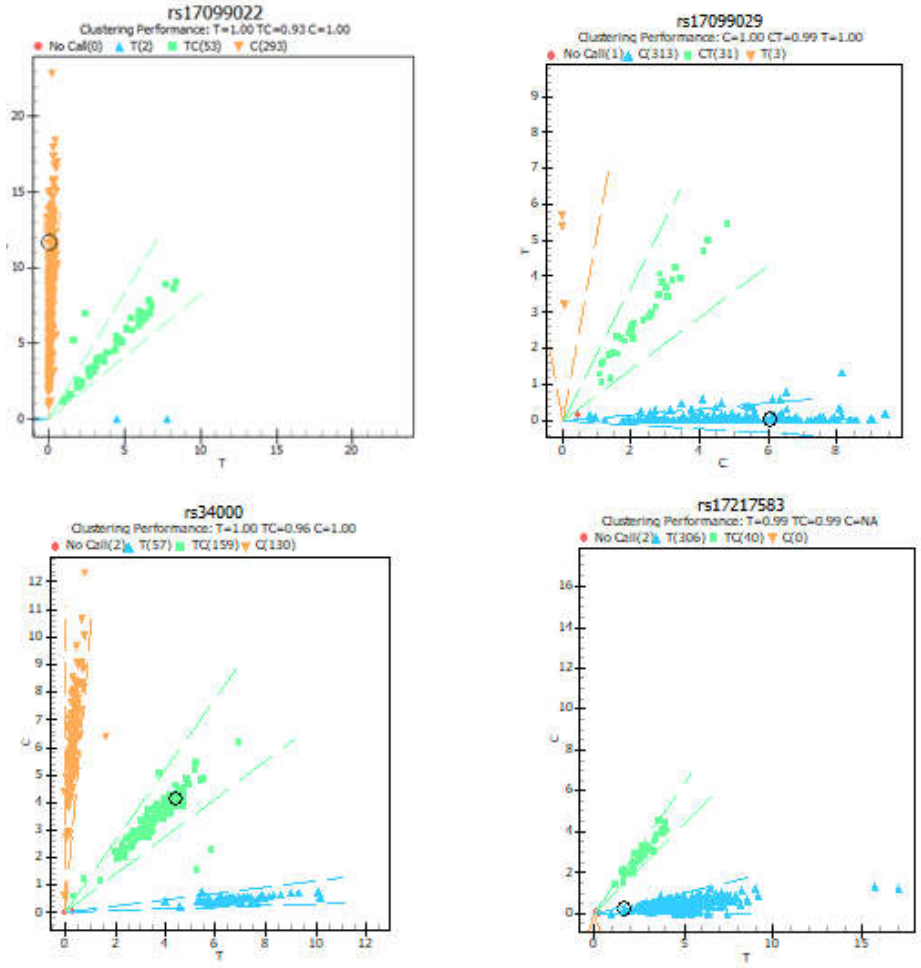
	Case group (n = 174)	Control group (n = 174)	*t*-test	*P*
Age(years)	22.54±3.29	21.95±2.55	1.875	0.062
Empolyment (years)	3.65±2.53	3.67±2.27	0.119	0.906
Noise exposure (TWA) dB	85.95±2.85	85.69±2.18	0.835	0.652
BMI	21.52±3.45	21.28±3.29	0.655	0.776

BMI= Body Mass Index. There were no significant differences in the distribution of general characteristics, BMI, years of noise exposure, and noise intensity exposure between the NIHL groups and control groups.

Table 2.Comparison of hearing loss rates between two groups of patients with different demographic characteristics

	Case group (n = 174)		Control group (n = 174)		χ^2	*P*
	N	%	N	%		
Marital status					0.341	0.560
married	30	8.6	26	7.5		
unmarried	144	41.4	148	42.5		
Work shift						
single shift	1	0.3	2	0.6	3.204	0.106
two shifts	171	49.1	172	49.4		
three shifts	2	0.6	--	--		
Wear protective						
occasionally or not	47	13.5	49	14.1	6.240	0.101
often	127	36.5	125	25.9		
Smoking or not					2.960	0.228
yes	37	10.6	30	8.6		
no	137	39.4	144	41.4		
Drinking or not					0.206	0.902
yes	42	12.1	40	11.5		
no	132	37.9	124	38.5		

There were no statistical significance in marital status, work shift system, smoking status, drinking and wearing headphones (P>0.05)



Continue …..

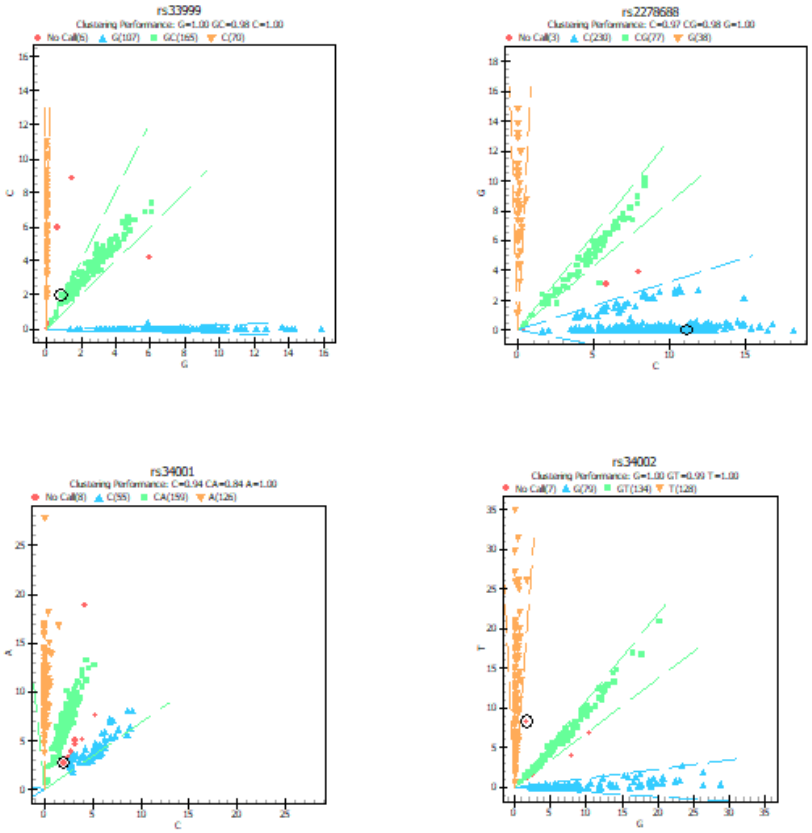


Fig. 1. Eight FGF1 SNPs were chosen to genotype in the 348 noise-exposed employees, a cluster graph of eight FGF1 SNPs sites.

which may have led to selection bias. Thus, consequent targets are performing more massive sample size researches, cohort studies, and functional experiments in the future[35].

Conclusion

We detected that the genetic variability of rs17099022 gene polymorphism in the 3'-UTR effect on susceptibility to noise-induced hearing loss in the carmaking worker of China. Further studies should include workers with different noise exposure patterns. A combination of genes variation with other risk factors should also be analyzed.

Authors' Contributions

Yuquan Chen wrote the paper. Yuqiang Lin and Wenzhong Jiang collected the specimens and statistically analyzed the data. Yimin Liu designed the research and wrote the paper. All authors read and approved the final manuscript. Yuquan Chen and Yimin Liu contributed equally to this work.

Acknowledgments

Thanks to other colleagues in our department, for their assistance in this study.

Funding: Guangzhou Health and Family Planning Technology Project （20191A011044.

Conflict of interest: Declarations of interest: none.

List of Abbreviations

NIHL = Noise-induced hearing loss
BMI = Body mass index
3'-UTR = 3'Unstranslated Region
95%CI = 95% confidence interval
OR = Odds radio
PCR = Polymerase chain reaction
DNA = Deoxyribo Nucleic Acid
MAF =Minor allele frequency
CHB =Chinese Han population
PCR-LDR =Polymerase chain reaction- ligase detection reactions

REFERENCES

1. KV G. Audiological findings in individuals exposed to organic solvents: case studies. *Noise health.* 2008;10:74-82.
2. M S-K, M P. Contribution of genetic factors to noise-induced hearing loss: a human studies review. *Mutation research.* 2013;752:61-65.
3. J A, H K, R S, B N. Predicting hearing thresholds in occupational noise-induced hearing loss by auditory steady state responses. *Ear hearing Research.* 2014;35:330-338.
4. SH S, J S. Emerging therapeutic interventions against noise-induced hearing loss. *Expert opinion on investigational drugs.* 2017;26:85-96.
5. A K, L VL, G VC. Genetic studies on noise-induced hearing loss: a review. *Ear hearing Research.* 2009;30:151-159.
6. Muscella A, Calabriso N, Vetrugno C, Fanizzi FP, Pascali SAD, Marsigliante S. The signalling axis mediating neuronal apoptosis in response to [Pt(O,O′-acac)(γ-acac)(DMS)]. *sciencedirect.* 2011;81:1271-1285.

7. U P, L X-Q, J V, M S, C M, A M C, *et al*. Rescue of Hearing, Auditory Hair Cells, and Neurons by CEP-1347/KT7515, an Inhibitor of c-Jun N-Terminal Kinase Activation. *Journal of Neuroscience.* 2000;20:43-50.
8. Ylikoski J, Xing-Qun L, Virkkala J, Pirvola U. Blockade of c-Jun N-terminal kinase pathway attenuates gentamicin-induced cochlear and vestibular hair cell death. *Hear Res.* 2002;163:0-81.
9. Y Z, J H, W H, S Y, F H, J D, *et al*. Non-Mitogenic Fibroblast Growth Factor 1 Enhanced Angiogenesis Following Ischemic Stroke by Regulating the Sphingosine-1-Phosphate 1 Pathway. *Front Pharmacol.* 2020:59.
10. Fransen E, Topsakal V, Hendrickx J-J, Laer LV, Huyghe JR, Eyken EV, *et al*. Occupational Noise, Smoking, and a High Body Mass Index are Risk Factors for Age-related Hearing Impairment and Moderate Alcohol Consumption is Protective: A European Population-based Multicenter Study. *J Assoc Res Otolaryngol.* 2008;9:264-276.
11. Schreckenberg D, Griefahn B, Meis MJN. The associations between noise sensitivity, reported physical and mental health, perceived environmental quality, and noise annoyance. *Noise Health.* 2010;12:7.
12. H Y, J G, E D, H Z, L H, B Z. Salt-Inducible Kinase 3 Haplotypes Associated with Noise-Induced Hearing Loss in Chinese Workers. *Audiology neuro-otology.* 2020:1-9.
13. Kim S, Misra A. SNP Genotyping: Technologies and Biomedical Applications. *Annual Review of Biomedical Engineering.* 2007;9:289-320.
14. Guo Y, Zhao Y, Li Y, Feng Y, Xue C, Liu Y. Correlation between hearing-related gene polymorphism and susceptibility of noise-induced hearing loss. *Chin Occup Med.* 2017;44:253-260.
15. Wang Y, Chen Y, Mao L, Zhao G, Hong G, Li M, *et al*. Effects of hemoperfusion and continuous renal replacement therapy on patient survival following paraquat poisoning. *Plos One.* 2017;12:1-13.
16. Carlsson PI, Laer LV, Borg E, Bondeson ML, Thys M, Fransen E, *et al*. The influence of genetic variation in oxidative stress genes on human noise susceptibility. *Hearing Research.* 2005;202:0-96.
17. Z L, HE S, MH S, FM R. Association of GST gene polymorphism and noise-induced hearing loss: GST gene polymorphism and NIHL. *AIMS public health.* 2019;6:546-553.
18. F Z, A S, S M, Z T, J L, Z W, *et al*. Relationship between occupational noise exposure and hypertension: A cross-sectional study in steel factories. *American journal of industrial medicine.* 2019;62:961-968.
19. Zhang S, Ding E, Yin H, Zhang H, Zhu B. Research and Discussion on the Relationships between Noise-Induced Hearing Loss and ATP2B2 Gene Polymorphism. *International Journal of Genomics.* 2019;2019:1-8.
20. SS Y, JE C, WK L, YY C, S K, MJ K, *et al*. Polymorphisms in the CASPASE genes and survival in patients with early-stage non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27:5823-5829.
21. Q L, LM M, B A, P H, I M, T Z, *et al*. Genetic variation in caspase genes and risk of non-Hodgkin lymphoma: a pooled analysis of 3 population-based case-control studies. *Blood.* 2009;114:264-267.
22. CL T, EA M. Occupational noise exposure: A review of its effects, epidemiology, and impact with recommendations for reducing its burden. *The Journal of the Acoustical Society of America.* 2019;146:3879.
23. Yang J, Zhang J, Wang X, Wang C, Duan Z. Identification of functional tag single nucleotide polmorphisms within the entire CAT gene and their clinical relevance in patients with noise-induced hearing loss. *International Journal of Clinical Experimental Pathology.* 2015;8:2852-2863.
24. DI N, RY N, M C-B, M F. The global burden of occupational noise-induced hearing loss. *American journal of industrial medicine.* 2005;48:446-458.
25. EZ S, RS H, head, surgery n. Noise-induced hearing loss: an occupational medicine perspective. *Current Opinion in Otolaryngology & Head & Neck Surgery.* 2014;22:388-393.
26. Fetoni AR, De Bartolo P, Eramo SLM, Rolesi R, Paciello F, Bergamini C, *et al*. Noise-Induced Hearing Loss (NIHL) as a Target of Oxidative Stress-Mediated Damage: Cochlear and Cortical Responses after an Increase in Antioxidant Defense. *Journal of Neuroscience.* 2013;33:4011-4023.
27. PM R, J PW, B HM, PG A, C P, M S. Antioxidant status and hearing function in noise-exposed workers. *Hearing research.* 2002;173:164-171.
28. Sliwinska-Kowalska M, Pawelczyk M. Contribution of genetic factors to noise-induced hearing loss: A human studies review. *Mutation Research/reviews in Mutation Research.* 2013;752:61-65.
29. R J, J D, A W, JC S, R J, C X. Genome-wide evaluation of the public SNP databases. *Pharmacogenomics.* 2003;4:779-789.
30. Vella, M. C. The C. elegans microRNA let-7 binds to imperfect let-7 complementary sites from the lin-41 3\"UTR. *Genes Development.* 2004;18:132-137.
31. DE A, AL DLE, S F, AV G. Role of RNA structures present at the 3'UTR of dengue virus on translation, RNA synthesis, and viral replication. *Virology.* 2005;339:200-212.
32. Junhui Y, Jieyuan Z, Xiaoming W, Chaoyong W, Jichuan C, Yu Q, *et al*. Identification of functional tag single nucleotide polmorphisms within the entire CAT gene and their clinical relevance in patients with noise-induced hearing loss. *International Journal of Clinical Experimental Pathology.* 2015;8:2852-2863.
33. Tian X, Zhang X. A Single Nucleotide Polymorphism (rs1056629) in 3'UTR of MMP-9 is Responsible for a Decreased Risk of Metastatic Osteosarcoma by Compromising its Interaction with microRNA-491-5p. *Cellular Physiology Biochemistry.* 2016;38:1415-1424.
34. K C, H Z, Z H, LE W, W Z, EM S, *et al*. CASP3 polymorphisms and risk of squamous cell carcinoma of the head and neck. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2008;14:6343-6349.
35. Wu Y, Ni J, Qi M, Cao C, Shao Y, Xu L, *et al*. Associations of genetic variation in CASP3 gene with noise-induced hearing loss in a Chinese population: a case–control study. *Environmental Health.* 2017;16:78.

****