Research Article

Single-Nucleotide Polymorphisms in XPO5 are Associated with Noise-Induced Hearing Loss in a Chinese Population

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Objectives. The purpose of this study was to investigate the correlation between single-nucleotide polymorphism (SNP) in 3′UTR of XPO5 gene and the occurrence of noise-induced hearing loss (NIHL), and to further explore the regulatory mechanism of miRNAs in NIHL on XPO5 gene.

Methods. We conducted a case-control study involving 1040 cases and 1060 controls. The effects of SNPs on XPO5 expression were studied by genotyping, real-time polymerase chain reaction (qPCR), cell transfection, and the dual-luciferase reporter assay.

Results. We genotyped four SNPs (rs2257082, rs11077, rs7755135, and rs1106841) in the XPO5 gene. The rs2257082 AG/GG carriers have special connection to an increased risk of noise-induced hearing loss compared to the AA carriers. The rs11077 TG/GG carriers had a significantly increased association with NIHL susceptibility than the TT carriers. There was a higher risk of NIHL in the XPO5 gene rs7755135 CC carriers than in the TT carriers. No statistically significant correlation was obtained with respect to SNP rs1106841. Functional experiments showed that the rs11077 change might inhibit the interaction between miRNAs (miRNA-4763-5p, miRNA-5002-3p, and miRNA-617) and XPO5, with rs11077G allele resulting in overexpression of XPO5.

Conclusion. The genetic polymorphism, rs11077, within XPO5 is associated with the risk of noise-induced hearing loss in a Chinese population.

1. Introduction

Noise-induced hearing loss (NIHL) refers to progressive sensorineural hearing impairment caused by patients exposed to a noisy environment. NIHL has become a major public health problem with industrialization, the increase in social noise, and the prolongation of life expectancy. Based on the global disease burden report issued by the WHO in 2005, occupational noise-associated hearing loss accounts for 16% of adult hearing loss worldwide, which is about 4 million disability-adjusted life years (DALYs) [1]. There are greater than 10 million workers employed in high-noise environments in China, of which at least 10% have different levels of hearing loss. Although environmental factors play a vital part in the development of NIHL, population epidemiologic studies have shown that, with the exception of the influence of other confounding factors, hereditary factors account for up to 50% of the variability in hearing loss after noise exposure [2,3].

MicroRNAs (miRNAs) are highly-conserved, endogenous noncoding single-stranded RNAs with posttranscriptional regulatory functions that are found in eukaryotes and consist of approximately 22 nucleotides (nt) [4,5]. Greater than 700 kinds of miRNAs have been identified in humans and regulate at least 30% of protein-coding gene expression [6,7]. miRNAs are transcribed into primary transcripts of miRNAs (pri-miRNAs) in the nucleus by RNA polymerase II and then further assimilated by RNase III Drosha to form a...
hairpin structure of approximately 60- to 70-nt precursor miRNAs (pre-miRNAs) [8,9]. Pre-miRNAs are transported from the nucleus to the cytoplasm under the synergistic action of transport receptor exportin-5 (XPO5). It is believed that single-nucleotide polymorphisms (SNPs) exist in the binding sites of the gene encoding miRNAs and related target genes, which can directly or indirectly affect gene expression and protein function [10].

Recent studies have confirmed that the abnormal expression of miRNAs is related to many diseases, including auditory diseases [111]. There is increasing evidence that the imbalance of miRNAs in NIHL affects the expression of target genes and further affects the necessary cellular processes, including cell metabolism, proliferation, differentiation, and apoptosis [12,13]. Compared with the control group, the expression of miRNA-24, miRNA-185-5p, and miRNA-451a increased significantly in the NIHL group [14]. Li et al. [15] reported that the serum miRNA-1229-5p level of male workers suffering from NIHL was significantly higher than the control group.

XPO5 exists in the nuclear membrane and participates in the transport of pre-miRNAs. Previous results have indicated that overexpression of XPO5 enhances the activity of miRNAs, and under- or nonexpression of XPO5 results in a decrease in the nuclear output of pre-miRNAs [16,17]. SNPs associated with miRNAs in the XPO5 3′ untranslated region (3′ UTR) affect the risk of disease in the synthesis pathway of miRNAs [18]. Currently, there is a lack of research on the relationship between XPO5 and the risk of NIHL development; however, several studies have demonstrated that the transporter, XPO5, is involved in the miRNA pathway. The structural changes of XPO5 may cause abnormal expression of the miRNA, leading to tumorigenesis [19–21], which may also be the case in the hearing system. Based on bioinformatics prediction and statistical analysis, we found that SNPs in XPO5 may play a potential role in NIHL. In this study, we focused on the SNPs located in the binding region of miRNAs and XPO5. For significant SNPs, we performed functional validation to evaluate the potential function of these SNPs on XPO5.

2. Materials and Methods

2.1. Study Population Collection. In the current study, a total of 1040 cases and 1060 controls were recruited from the Yizheng Branch of the SAIC Volkswagen Automobile Co., Ltd. The subjects were engaged in steady-state noise work for a long time, and the exposure period of noise was not less than 1 year. Workers exposed to noise did not have any history of disease or current illness that might affect their hearing, nor of the long-term use of ototoxic drugs. The definition of hearing loss was as follows: the subject’s audiogram falls at high frequencies; the average hearing threshold of high frequencies in both ears is ≥25 dB; and the high frequencies are greater than the low frequencies. Normal hearing refers to a subject’s high and low frequency threshold ≤25 dB. NIHL cases and controls were matched, including age, gender, smoking status, and noise exposure time. This study was approved by the Ethics Committee of Jiangsu Centers for Disease Control and Prevention, and all of the subjects signed the informed consent in person. Considering the use of data analysis, the private information of subjects involved in the study was encrypted.

2.2. SNP Selection. SNP loci located in the XPO5 gene were found from NCBI dbSNP (http://www.ncbi.nlm.nih.gov/SNP) and ENSEMBL (http://www.ensembl.org/). The principles for screening SNPs are indicated as follows: (a) XPO5 binding site; (b) minor allele frequency (MAF) > 0.05; (c) p of Hardy–Weinberg equilibrium (HWE) > 0.05; and (d) linkage disequilibrium (LD) of r² > 0.8. Four SNPs (rs2257082, rs11077, rs7755135, and rs1106841) were selected as candidate SNPs because the target gene (XPO5) was associated with the pathogenesis of NIHL.

2.3. Genetic Analysis. Peripheral blood samples from the subjects were stored in Vacutainers® containing the anticoagulant, (ethylenediaminetetraacetic acid) EDTA. The total DNA template was extracted using a DNA extraction kit (QIAGEN, Duesseldorf, Germany). Five percent samples were randomly sampled for quality control of duplicate genotyping, and the reproducibility of SNPs was 100%.

2.4. Plasmid Construction. Human miRNA-4763-5p, miRNA-5002-3p, and miRNA-617 were cloned into the expression vector pcDNA3.1 (+) to generate stably-transfected human embryonic kidney cell lines (HEK293T) using forward primers (GAATCTGGTCACCTGATGGGA) and reverse primers (GTGCCTGAAGTGGAGCCCTTGA). The plasmid containing the sequence of the wild-type or mutant miRNA-4763-5p, miRNA-5002-3p, or miRNA-617 binding XPO5, was cloned into the luciferase reporter vector (pGL3-CMV-LUC-MCS). The successfully constructed expression vector was inoculated into LB (Luria–Bertani) medium and cultured on a shaking table (220 rpm) at 37°C for 24 h. The plasmids were extracted and sequenced using a high-purity plasmid extraction kit (QIAGEN).

2.5. Reagents, Cell Culture, and Transfection. The HEK293T cell lines used in this study were obtained from NovoBio Scientific (Shanghai, China). All cells were preserved in Dulbecco’s Modified Eagle’s medium (DEME) fortified with 10% fetal bovine serum (FBS) and placed in a humidified atmosphere with 5% CO₂ at 37°C. mRNA-4763-
For luciferase analysis, 2.6. Luciferase Reporter Assay. HEK293T cells were transfected with luciferase vectors containing T wild-type or G-mutant XPO5 fragments and miRNAs (miRNA-4763-5p, miRNA-5002-3p, and miRNA-617) were collected and cultured in medium and washed twice with phosphate-buffered saline (PBS). The cells were fully lysed by adding 100 μl of 1× passive lysis buffer (PLB; Promega, Madison, WI, USA) to each well. Luciferase activity measurement was carried out on the basis of the operating instructions of the luciferase reporter assay system (Promega, Madison, WI, USA). The activity of Renilla luciferase was normalized to that of Firefly luciferase. All transfections were in triplicate.

2.7. Statistical Analysis. Frequencies of alleles and genotypes at SNP loci were obtained by direct counting. The association of genotype and gene frequency between the case and control groups was determined by a chi-square test. An unconditional univariate logistic regression model was used to analyze the odds ratios (ORs) and their 95% confidence intervals (95% CIs) and to evaluate the correlation between the genotype and gene frequency between the case and control groups. The characteristics of selected SNPs at SNP loci were obtained by direct counting. The association to NIHL. SPSS 19.0 was used for statistical analysis.

As illustrated in Table 3, the rs2257082 AG/GG carriers showed an increased risk of NIHL compared to the AA carriers in the dominant model (adjusted OR = 1.55, 95% CI: 1.23–1.95, p < 0.001). The rs11077TG/GG carriers had a significantly increased association with NIHL susceptibility than TT carriers in the dominant (adjusted OR = 1.93, 95% CI: 1.48–2.52, p < 0.001) and recessive models (adjusted OR = 3.03, 95% CI: 1.19–7.76, p < 0.001). There was a higher risk of NIHL in the XPO5 gene rs7755135T carrier than CC carriers in the codominant (adjusted OR = 2.70, 95% CI: 1.53–4.77, p < 0.001) and recessive models (adjusted OR = 2.42, 95% CI: 1.40–4.19, p < 0.001). No statistically significant correlation was obtained for SNP rs1106841 in any of the models (codominant, dominant, or recessive models). In the allele model, the rs11077G carriers (adjusted OR = 1.63, 95% CI: 1.30–2.03) had a significantly higher risk for NIHL (p < 0.001) and rs7755135T carriers (adjusted OR = 1.12, 95% CI: 1.01–1.39) had a significantly higher risk for NIHL (p = 0.037). The results indicated that XPO5SNPs rs2257082, rs11077, and rs7755135 may have a connection to NIHL.

3.3. Analysis of High-Frequency Hearing Threshold Shift (HFTS) in Selected SNPs. The data of all subjects in Figure 1 described that the HFTS of the XPO5rs2257082 AA genotype was mainly in the range of 28.48 ± 17.62 dB, and those of the AG and GG genotypes were in the range of 27.76 ± 14.24 dB and 31.64 ± 15.34 dB, respectively. The HFTS in the GG genotypes of rs2257082 were significantly higher than in the AA genotypes (p = 0.006). For rs11077, the TT genotype was mainly in the range of 27.96 ± 15.77 dB, and the TG and GG genotypes were 30.96 ± 13.98 dB and 41.91 ± 21.16 dB, respectively. The HFTS in the rs11077GG and TG genotype subjects were significantly higher than in the TT genotypes (p < 0.001 and p = 0.0015, respectively). The rs7755135 CC genotype was mainly in the range of 28.05 ± 16.28 dB, while the CT and TT genotypes were in the range of 28.90 ± 13.47 dB and 37.27 ± 18.12 dB, respectively. The TT genotype exhibited a significantly greater HFTS risk compared with the CC and CT genotypes (p < 0.001 and p < 0.001, respectively); however, the HFTS of the AA, AC, and CC genotypes of rs1106841 were mainly 29.01 ± 17.10 dB, 27.85 ± 14.13 dB, and 29.87 ± 15.31 dB, respectively. There were no significant differences in HFTS among the AA, AC, and CC genotypes (p = 0.106, p = 0.076, and p = 0.520, respectively).

3.4. Analysis of SNP (rs2257082, rs11077, rs7755135, and rs1106841) Haplotype Distribution. Figure 2 showed that the linkage disequilibrium of XPO5rs2257082, rs11077, rs7755135, and rs1106841
rs7755135 and rs1106841. Table 4 summarizes the haplotype frequencies of SNPs analyzed between NIHL cases and control groups. Five common haplotypes (frequency > 3%) were selected from four SNPs, which accounted for 90% of haplotype variation. The GGTA and GTCC haplotypes (rs2257082-rs11077-rs7755135-rs1106841) were associated with an increased risk of NIHL (OR = 1.54, 95% CI: 1.30–1.194, p < 0.001; OR = 1.46, 95% CI: 1.18–1.81, p < 0.001). The GTCA haplotype was associated with a decreased risk of NIHL (OR = 0.81, 95% CI: 0.68–0.96, p = 0.02).

3.5. Predicted miRNAs That Potentially Bind to XPO5rs11077.
To demonstrate whether or not the rs11077SNP affects the prediction of miRNA binding to XPO5, we performed a bioinformatics analysis of XPO5. The results indicated that XPO5rs11077 is located in a potential binding region for incorporation of miRNAs, including miRNA-4763-5p, miRNA-5002-3p, and miRNA-617. XPO5 contains the binding site of predicted miRNAs, as shown in Figure 3.

3.6. SNPs Interfered with the Interaction between miRNA (miRNA-4763-5p, miRNA-5002-3p, and miRNA-617) and XPO5. Transient transfection was carried out in vitro, and the expression of related activities was analyzed and measured by the dual-luciferase reporting system to illustrate whether or not the SNPsrs11077T>G variant affected the binding of XPO5 to miRNAs (miRNA-4763-5p, miRNA-5002-3p, and miRNA-617). Figure 4 indicates that constructs containing the G allele of XPO5 combined with miRNA-4763-5p, miRNA-5002-3p, and miRNA-617 mimics significantly increased luciferase activity compared with the T allele in HEK293T (p < 0.01, p < 0.05, and p < 0.01, respectively). These data suggested that miRNA-4763-5p, miRNA-5002-3p, and miRNA-617 may directly target XPO5 with the rs11077G allele.

4. Discussion
NIHL is one of the most common occupational diseases that seriously affect human health [11]. Globally, the incidence of NIHL is on the rise. The pathogenesis of NIHL has not been fully clarified [22]. An etiologic investigation showed that chronic ear diseases, alcohol consumption, smoking, and occupational factors are related to the occurrence and development of NIHL, but different individuals vary in their sensitivity to individual causes.

Currently, studies on miRNAs and hearing loss have demonstrated that these miRNAs can be used as potential biomarkers to indicate NIHL [15,23]. In a study involving miRNA-15a-1 and miRNA-18a in the development of the...
ear structure of zebrafish, it was found that the number of hair cells in the deformed body decreased, and the inner ear structure was abnormal [24]. MiR-34 mediates hearing impairment associated with cell death in the inner ear of a mouse model [25].

XPO5 is related to the nuclear output of miRNAs [26]. A synergistic effect exists between Ran-GTP and transport receptor XPO5, which transports pre-miRNAs from the nucleus to the cytoplasm [27,28]. After digestion and double helix unwinding, pre-miRNAs bind with the RNA-induced silencing complex (RISC), which contains GEMIN3 and GEMIN4, to synthesize RISC-miRNA complexes [20]. The binding of RISC to the specific sequence of the 3′UTR of target mRNAs results in the inhibition of the cleavage or translation of the mRNA, which interferes with the protein synthesis of the target gene at the posttranscriptional level [29,30]. Reducing the expression of XPO5 can decrease the expression of miRNAs, which may lead to the occurrence and development of hearing loss.

Considering the effect of age on hearing, we matched people in our study. Mizoue et al. [31] have proved that smoking can increase the risk of NIHL. To eliminate the interference of cigarette smoking, the matching included cigarette smoking. When binding of miRNAs to target sequences occurs at or near the miRNA junction in the 3′UTR, the SNPs have an effect by establishing or eliminating the binding sites of miRNAs in target genes, thus losing the original regulatory function and producing significant genetic effects. Accordingly, we systematically investigated the

| Table 3: Distribution of four polymorphisms and the association with NIHL. |
|-------------------------------------------------|
| **Genetic models** | **Genotypes** | **Cases** | **n = 1040** | **Controls** | **n = 1060** | **p** | **Adjusted OR (95% CI)** | **Holm** | **SidakSS** | **SidakSD** |
|-------------------|---------------|----------|--------------|--------------|--------------|-----|---------------------------|---------|-----------|-----------|
| rs2257082         | Codominant    | AA       | 324          | 380          | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | AG       | 546          | 515          | 2.69E-4      | 1.54 (1.22–1.94) |
|                   |               | GG       | 160          | 158          | 1.51E-3      | 1.73 (1.23–2.44) |
|                   | Dominant      | AA       | 324          | 380          | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | AG/GG    | 706          | 673          | 2.09E-4      | 1.55 (1.23–1.95) |
|                   | Recessive     | AA/AG    | 870          | 895          | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | GG       | 160          | 158          | 0.26         | 1.16 (0.89–1.51) |
| Alleles           |              | A        | 1194         | 1275         | 0.09         | 1.11 (0.98–1.26) |
|                   | G             | 866      | 831          |              |              |     |                           |         |           |           |
| rs11077           | Codominant    | TT       | 835          | 921          | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | TG       | 186          | 129          | 8E-6         | 1.85 (1.41–2.43) |
|                   |               | GG       | 15           | 6            | 7.1E-3       | 3.66 (1.42–9.41) |
|                   | Dominant      | TT       | 835          | 921          | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | TG/GG    | 201          | 135          | 1E-6         | 1.93 (1.48–2.52) |
|                   | Recessive     | TT/TG    | 1021         | 1050         | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | GG       | 15           | 6            | 2.04E-2      | 3.03 (1.19–7.76) |
| Alleles           |              | T        | 1856         | 1971         | 1.00 (ref)   |     |                           |         |           |           |
|                   | G             | 216      | 141          |              |              |     |                           |         |           |           |
| rs7755135         | Codominant    | CC       | 689          | 735          | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | CT       | 305          | 302          | 0.12         | 1.19(0.95–1.49) |
|                   |               | TT       | 40           | 20           | 6.19E-4      | 2.70(1.53–4.77) |
|                   | Dominant      | CC       | 689          | 735          | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | CT/TT    | 345          | 322          | 0.04         | 1.26(1.01–1.57) |
|                   | Recessive     | CC/CT    | 994          | 1037         | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | TT        | 40           | 20           | 1.65E-3      | 2.42(1.40–4.19) |
| Alleles           |              | C        | 1683         | 1772         | 1.00 (ref)   |     |                           |         |           |           |
|                   | T             | 385      | 342          |              |              |     |                           |         |           |           |
| rs1106841         | Codominant    | AA       | 467          | 491          | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | AC       | 483          | 463          | 0.18         | 1.16(0.93–1.44) |
|                   |               | CC       | 85           | 98           | 0.88         | 0.97(0.67–1.40) |
|                   | Dominant      | AA       | 467          | 491          | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | AC/CC    | 568          | 561          | 0.22         | 1.15(0.92–1.42) |
|                   | Recessive     | AA/AC    | 950          | 954          | 1.00 (ref)   |     |                           |         |           |           |
|                   |               | CC        | 85           | 98           | 0.35         | 0.86(0.62–1.18) |
| Alleles           |              | A        | 1417         | 1445         | 1.00 (ref)   |     |                           |         |           |           |
|                   | C             | 653      | 659          | 0.88         | 1.01(0.89–1.15) |

*Adjusted for age, sex, smoking, and drinking in the logistic regression model.
potential correlation between the genetic polymorphism of XPO5 and NIHL in the Chinese population and discovered SNPs (rs2257082, rs11077, and rs7755135) in the XPO5 gene. Our data showed that the frequencies of the rs2257082GG, rs11077GG, and rs7755135TT of the XPO5 gene were significantly increased in NIHL cases compared to the control group. Therefore, we speculated that the rs2257082, rs11077, and rs7755135 loci SNPs of the XPO5 gene were associated with NIHL risk. Haploid analysis revealed that the GGTA and GTCC haplotypes (rs2257082-rs11077-rs7755135-rs1106841) increased the risk of NIHL, and the GTCA haplotype was associated with a decreased risk of NIHL. The results support our hypothesis that XPO5 polymorphism may be related to NIHL susceptibility.

miRNAs can degrade or inhibit protein translation by means of complete or incomplete complementary pairing with target gene mRNA. Therefore, miRNAs play a significant role in posttranscriptional regulation of gene expression. The mutation of the binding site of the target gene of miRNAs will affect the biosynthesis or biological function of miRNAs, which will lead to the disorder of cellular function and eventually result in the occurrence of diseases. SNPs can have a profound impact on miRNA function, including transcription, maturation, and target specificity [32], and it can also affect the occurrence of NIHL [33]. Recent studies have shown that SNPs in XPO5 gene may be related to the risk of esophageal cancer, colorectal cancer, and renal cancer [34–36]. The A>C polymorphism of XPO5 gene will reduce the risk of CAD (coronary artery disease), which may be due to the influence on the expression of mature miRNAs and their gene function [37]. At the same time, functional SNPs in miRNA biogenetic pathway genes have been confirmed to be related to the increased risk of NIHL [33,38]. Based on all the above studies, we analyzed the relationship between the functional sites of XPO5 of miRNA processing gene and NIHL, and its effect on miRNA expression. In this study, luciferase reporter assays preliminarily verified whether miRNA interacted with target gene XPO53'UTR and further determined the site of interaction between miRNA and target gene XPO53'UTR.
In addition to the interaction of multiple factors, rs11077 had the most significant correlation with NIHL compared with other loci. We selected rs11077 for functional verification. By virtue of the mutations located in the secondary structure of miRNA, as well as the number of mutants that can be detected, we investigated the possible effects of these mutations on target genes. First, we predicted potential targets based on bioinformatics programs (TargetScan, Microinspector, and miRanda). Meanwhile, considering the complementation, evolutionary conservation, accessibility, and thermal stability of the target gene locus (rs11077) to miRNA, we included these miRNAs (miRNA-4763-5p, miRNA-5002-3p, and miRNA-617) and conduct subsequent studies on luciferase activity. Alternatively, miRNAs contain binding sites that match the seed region of XPO5 perfectly. Importantly, miRNA-4763 has recently been shown to contribute specifically to multidrug resistance in human cancer cells [32]. Wang et al. [33] reported that downregulation of miRNA-4763-3p expression increased the susceptibility to gastric cancer by targeting MDR. It was also predicted that the potential regulatory pathway of XPO5 rs11077, and the binding ability of miRNA-4763-5p/miRNA-5002-3p would be affected when the T wild-type allele mutated into the G allele [34]. The results of luciferase reporter gene activity analysis in our study showed that the translation level of luciferase-UTR was controlled by miRNA-4763-5p, miRNA-5002-3p, and miRNA-617 compared with the T-allele miRNA-4763-5p and the miRNA-617, the G allele
resulted in increased luciferase expression. This finding indicated that the mutation allele of rs11077 affected the binding of miRNAs (miRNA-4763-5p, miRNA-5002-3p, and miRNA-617) to XPO5.

5. Conclusion

In summary, our study provides evidence for the first time that the SNPrs11077G allele and the haplotype (rs2257082, rs11077, rs7755135, and rs1106841) had an association with the risk of NIHL in a Chinese population. It was also verified that the regulation of XPO5 expression by miRNA-4763-5p, miRNA-5002-3p, and miRNA-617 might be achieved by SNPrs11077.

Data Availability

The data sets supporting the results of this article are included within the article.

Ethical Approval

The participant’s private information has been encrypted by Jiangsu Provincial Center for Disease Control and Prevention (CDC). This study conforms to the Helsinki Declaration and was exempted from the review of institutional ethics by the Research Ethics Committee of Jiangsu CDC.

Consent

All presentations of reports must have consent for publication.

Conflicts of Interest

The authors declare that they have no conflicts of interests.

Authors’ Contributions

Ning Wang and Boshen Wang designed and conducted the study. Jiadi Guo and Suhao Zhang analyzed the data and generated the figures. Ning Wang, Boshen Wang, Jiadi Guo, Suhao Zhang, Lei Han, Juan Zhang, and Baoli Zhu wrote the manuscript. Baoli Zhu revised the manuscript. All authors finally reviewed and approved the manuscript.
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