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Association Analysis of Candidate Gene Polymorphisms and Tinnitus in Young Musicians

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Abstract

Introduction: Subjective tinnitus, a perception of phantom sound, is a common otological condition that affects almost 15% of the general population. It is known that noise-induced hearing loss (NIHL) and tinnitus exhibit a high level of comorbidity in individuals exposed to intense noise and music. However, the influence of genetic variants associated with NIHL on tinnitus remains elusive. We hypothesized that young musicians carrying genetic variants associated with NIHL would exhibit a higher prevalence of tinnitus than their counterparts.

Methods: To test this hypothesis, we analyzed the database by Bhatt et al. (2020) (originally developed by Phillips et al., 2015) that investigated the genetic links to NIHL in young college-aged musicians. The present study identified 186 participants (average age = 20.3 yrs, range = 18–25 yrs) with normal tympanometry and otoscopic findings and with no missing data. We included 19 single nucleotide polymorphisms in 13 cochlear genes that were previously associated with NIHL. The candidate genes include: KCNE1, KCNQ1, CDH23, GJB2, GJB4, KCNJ10, CAT, HSP70, PCDH70, MYH14, GRM7, PON2, and ESRRB.

Results: We find that individuals with at least one minor allele of rs163171 (C > T) in KCNQ1 exhibit significantly higher odds of reporting tinnitus compared to individuals carrying the major allele of rs163171. KCNE1 rs2070358 revealed a suggestive association ($p = 0.049$) with tinnitus, but the FDR corrected p-value did not achieve statistical significance ($p < 0.05$). A history of ear infection and sound level tolerance showed a statistically significant association with tinnitus. Music exposure showed a suggestive association trend with tinnitus. Biological sex revealed a statistically significant association with distortion product otoacoustic emissions SNR measures.

Conclusions: We concluded that KCNQ1/KCNE1 volta-gegated potassium ion channel plays a critical role in the pathogenesis of NIHL and tinnitus. Further research is required to construct clinical tools for identifying genetically predisposed individuals well before they acquire NIHL and tinnitus.

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Keywords

Genetic; Genome-wide association; Genomics; Hearing loss; Noise; Noise-induced hearing loss; Tinnitus

Tinnitus, a phantom perception of sound in the absence of an external sound source, is a prevalent hearing disorder. Over 50 million US adults experience some form of tinnitus, and almost 20 million people struggle with clinical manifestations of chronic tinnitus, while 2 million have extreme and debilitating cases (1). About 10% of young adults experience chronic tinnitus (2-5). About 15% of workers exposed to occupational noise experience chronic tinnitus (6). Tinnitus is the most prevalent service-connected disability (7). The US military spends over $3.5 billion on tinnitus-related costs annually; this amount is likely to increase drastically (8). Tinnitus can cause anxiety, stress, depression, cognitive dysfunction, social isolation, and insomnia leading to poor quality of life (9-11).

The phenotypic spectrum of tinnitus is likely to be influenced by a combination of environmental, genetic, and lifestyle-related factors (12). Environmental and health-related variables, such as loud noise/music exposure, hearing loss, persistent middle ear infection, smoking, stress, head injury, exposure to certain ototoxic medications, and systemic diseases are known risk factors for tinnitus (2-4,13). In older adults, tinnitus is often associated with noise-induced hearing loss (NIHL), other forms of hearing loss (e.g., presbycusis), cochlear dysfunction, stress, occupational noise exposure, leisure-time noise/music exposure, smoking, head injury, ototoxic drugs, depression, and history of the middle ear or sinus infections, severe neck injury, migraine or systematic diseases (e.g., hypertension, hyperlipidemia) (14-16). Noise/music exposure is a predominant environmental risk factor for tinnitus (2-4). However, it is estimated that only 3% of the cases are exclusively attributable to noise/music exposure (17). Almost 50% of the cases cannot be attributed to any known causes (18). A longitudinal twin study exploring the genetic contribution to tinnitus suggested a moderate genetic influence on tinnitus (19). Therefore, there is a need to identify genetic factors underlying tinnitus perception.

Table 1 presents a list of major case–control studies investigating the genetic influence on tinnitus. The case–control studies investigated potential candidate gene set, which included the genes essential for cardiovascular physiology (ACE, ADD1), ion recycling in the inner ear (i.e., KCNE1, KCNJ10, SLC12A2, GJB family), serotonin receptor and transporters (e.g., SLC6A4), and neurotrophic factors (e.g., BDNF, GDNF) (Table 1). A genome-wide association study (GWAS) investigating 4,000,000 single nucleotide polymorphisms (SNPs) could not obtain any statistically significant associations with tinnitus. The study reported novel target genes and SNPs, showing promising association trends to tinnitus (20). A recent GWAS using the UK biobank database identified 6 genome-wide significant loci and 27 genes in the discovery cohort. The study replicated 3 of 6 loci and 8 of 27 genes in a replication sample (21).

While it is known that NIHL and tinnitus exhibit a high level of comorbidity in individuals exposed to high levels of noise/music (e.g., 32)(32), the influence of genetic variants associated with NIHL on tinnitus remains elusive. We hypothesized that young musicians

carrying genetic variants related to NIHL would exhibit a higher prevalence of tinnitus than their counterparts. To test this hypothesis, we analyzed the database by Phillips et al. (33) that investigated the genetic links to NIHL in young college-aged musicians. This population is exposed to a traumatic level of music regularly (e.g., 34,35)(34,35), but it exhibits an absence of age-related confounding variables (e.g., systemic diseases) and exposure to ototoxic agents. This unique combination is suitable to investigate the genetic influence on NIHL and related hearing health concerns (e.g., tinnitus). This study aimed to examine the relationship between selected genetic variants and measures of tinnitus in a sample of young musicians.

METHODS

Participants

The present study evaluated the database by Phillips et al. (33), which included phenotype and genotype data of 640 music students aged 18 to 25 years. The data were collected in the academic year 2010 to 2012. All participants were music majors with daily music exposure that included individual practice and ensemble practice. Audiometric testing was conducted, and participants were asked to complete an online survey inquiring about demographic details, music exposure, tinnitus, and other audiological details. The cohort for the present study was chosen from the initial sample of 640 young adults (34). The present study identified 186 participants (average age = 20.3 yrs, range = 18–25 yrs) from the initial sample of 640 young adults with normal tympanometry and otoscopic findings and with no missing genetic and phenotype data. Bhatt et al. (36) conducted an association analysis of candidate SNPs (those included in the present study) and audiological measures of NIHL. We evaluated the association between the candidate SNPs (i.e., SNPs associated with NIHL – further details can be found in Bhatt et al. (36)) and tinnitus. Here we briefly present the relevant testing procedures. The study details can be found in our previous reports (33,36).

Prerequisite Testing

All participants underwent otoscopic examination. Participants with normal findings were tested with immittance audiometry. We performed tympanometry using a 226-Hz probe tone with Maico MI 24 (MAICO Diagnostics, Eden Prairie, MN). Participants with normal otoscopic findings and normal immittance measures (i.e., tympanometric compliance value ranging from 0.33 to 1.75 cm^3, ear canal volume ranging from 0.8 to 1.8 cm^3, middle-ear pressure ranging from −50 to 25 daPa in both ears) were considered for the statistical analysis.

Hearing Threshold Measurement

All audiometric measures were collected in a sound-treated booth meeting the ANSI standards (ANSI S3.1-1999). Audiometric thresholds were obtained at 250; 500; 1,000; 2,000; 3,000; 4,000; 6,000; and 8,000 Hz (GSI-61, Eden Prairie, MN) with TDH-39 supra-aural headphones (Telephonics, Farmingdale, NY), using the modified Hughson-Westlake procedure. We found 186 individuals with complete audiometric, genetic, and survey data from the initial database.

Distortion Product Otoacoustic Emissions

The details about the recording procedure can be found in Bhatt et al. (2020). In brief, distortion product otoacoustic emissions were measured using an ERO-SCAN OAE screener (MAICO Diagnostics, Eden Prairie, MN). DPOAEs were measured for primary levels of 65/55 dB SPL with F2/F1 = 1.22. DPOAEs were measured for F2 frequency ranging from 1,500 to 10,000 Hz at nine data points (i.e., 1,500; 2,000; 3,000; 4,000; 5,000; 6,000; 7,000; 8,000; and 10,000 Hz). DPOAEs were measured for 2 seconds at each F2 frequency while participants were seated comfortably in a sound-treated booth meeting ANSI standards (ANSI S3.1-1999). The database contained DPOAE data for 165 participants from 186 participants meeting the inclusion criteria of the study.

Questionnaire Data

The survey included an assessment of three areas: demographic details, medical and audiological history, music exposure history, tinnitus, and sound level tolerance (SLT).

1. Demographic details: The questionnaire inquired about age, sex, and ethnicity. Response choices for sex included male/female/no disclosure. Ethnicity was evaluated with a question, “Please indicate your predominant racial ancestry. Use percentages that add up to 100%.” The response choices included African/European/East Asian/Middle Eastern/Native American/Polynesian/South Asian. Ethnicity was classified: European American and others (including multiracial).

2. Medical and audiological history: These questions addressed the history of hearing loss, medical conditions such as meningitis, high blood pressure, head injury, diabetes, mumps, heart trouble, malaria, scarlet fever, and others.

3. Music exposure history: The music exposure was calculated using the methods described in Bhatt et al. (36). In brief, we used questionnaire data about musical instruments (average hours/wk and a total number of years), ensembles (average hours/wk and a total number of years), and music player use (average hours/wk, typical volume control settings, and a total number of years) to calculate the overall music exposure value for each participant. Music exposure was divided into four categories using the quartile range – low, mid, high, very high.

4. Tinnitus phenotype: The survey inquired about tinnitus using the following question – “Do you have ringing, static, or a hissing sound in your ears?” The answer choices include Yes/No. If the participants answered positively, they were asked to indicate the affected side (Right/Left/Both) and were injured to indicate when they hear tinnitus (Occasionally/After practice/After noise/Constantly). The individuals responding positively to the question, “Do you have ringing, static, or a hissing sound in your ears?” were identified as cases, and those responding “no” to the question were considered controls for the statistical analysis.

5. The survey inquired about SLT with the following question – “Do loud sounds hurt your ears?” The participants were required to answer Yes/No.

Genotyping Data

The genotyping details can be found in Phillips et al. (33). In brief, the buccal cell samples (Isohelix: Boca Raton, FL) were collected and DNA was extracted for SNP genotyping and validation (GeneSeek; Lincoln, NE) on the Sequenom MassARRAY iPLEX platform. We identified a subset of SNPs from the original database that has been associated with NIHL in the previous studies (36). SNPs with the minor allele frequency >0.001 and with no missing data were included. The present study included 19 SNPs in 13 cochlear genes that were previously associated with NIHL. These include two SNPs in KCNE1 (rs2070358, rs1805127) (25,37), one SNP in KCNQ1 (rs163171) (38), one SNP in CDH23 (rs1227051) (39), two SNPs in GJB2 (rs9552098, rs3751385) (25), one SNP in GJB4 (rs755931) (25), one SNP in KCNJ10 (rs1130183) (25), two SNPs in CAT (rs475043, rs12273124) (25,40), three SNPs in HSP70 (rs1043618, rs1061581, rs2227956) (41), one SNP in PCDH70 (rs7095441) (42), two SNPs in MYH14 (rs667907, rs588035) (42), one SNP in GRM7 (rs11928865) (43) (associated with age-related hearing loss), one SNP in PON2 (rs987539) (44), and one SNP in ESRRB (rs61742642) (33).

Statistical Analysis

The statistical analysis was performed with the SPSS software (version 25, SPSS, INC). A binomial logistic regression analysis was performed to identify the predictors for tinnitus. The regression model included biological sex, SLT, history of ear infection, and 19 SNPs as the dependent variables. SNPs were coded into two categories (dominant genetic model) – participants carrying major allele (e.g., CC genotype), and those with at least one minor allele (e.g., CT or TT genotypes). The odds ratio and Chi-square statistics, and Pearson's productmoment correlation coefficients were calculated to examine the relationship between the experimental variables.

RESULTS

The study sample included 99 males and 87 females. One hundred six participants (57%) reported tinnitus perception. Among individuals with tinnitus, 95 participants reported ringing, seven participants reported hissing, and four reported other types of tinnitus perception. Among participants with tinnitus, 20 individuals reported tinnitus perception in only one ear, and 87 reported tinnitus perception in both ears. One hundred seventy individuals reported predominant European ancestry, 56 individuals reported a history of ear infection, and 22 individuals reported that they smoked tobacco at least once in their lifetime. Fifty-six participants (about 30%) reported a history of ear infections.

Comparison of Audiometric Thresholds Between Individuals With and Without Tinnitus

The repeated measure ANOVAs were performed to identify the group difference in the audiometric thresholds between individuals with and without tinnitus. The analysis was performed with six independent variables and two dependent variables – tinnitus and biological sex. The analyses revealed that the main effect of tinnitus ($F[1,171] = 1.3$, $p = 0.25$) and biological sex ($F[1,171] = 1.8$, $p = 0.17$) were not significant for the right ear. Similarly, we could not obtain statistically significant main effect for tinnitus ($F[1,171] = 1.2$, $p = 0.27$) and biological sex ($F[1,171] = 3.5$, $p = 0.06$) for the left ear. The interaction

effect between the dependent variables was found to be significant (F[1,171] = 5.29, p = 0.02). The estimated marginal means for the interaction effect revealed that male participants with tinnitus (marginal mean = 5.16 dB) and without tinnitus (marginal mean = 7.8 dB) revealed a higher mean difference. Female participants with tinnitus (marginal mean = 5.4 dB) and without tinnitus (marginal mean = 4.5 dB) showed lower mean difference. The repeated measure ANOVAs revealed no significant difference between the SLT groups in both ears ($p > 0.05$). Figure 1 presents audiometric results between the experimental groups.

Comparison of DPOAEs Between Individuals With and Without Tinnitus

We performed repeated measure ANOVAs with 9 within-subject factors (DPOAE frequency bands) and two between-subject factors – biological sex and tinnitus. The results revealed that gender showed significant main effect for right (F[1,160] = 16.04, $p < 0.0001$) and left (F[1,160] = 7.19, $p = 0.008$) ears. The main effect for tinnitus was not significant for both ears ($p > 0.05$). Similarly, the repeated measure ANOVAs revealed no significant difference between the SLT groups in both ears ($p > 0.05$). Figure 2 presets audiometric results between the experimental groups.

Association Between Tinnitus and Hearing Health-Related Variables

We performed Chi-square analyses to identify the association between tinnitus and hearing health-related variables. Tinnitus revealed statistically significant association with SLT (χ^2[1, N = 186] = 4.18, $p = 0.041$) and a history of ear infection (χ^2[1, N = 186] = 6.81, $p = 0.009$). No significant relationship was obtained for biological sex, music exposure, self-reported ethnicity, family history of hearing loss, and smoking. Figure 3 presents the association between tinnitus and hearing health-related variables.

Results of the Regression Analyses

We performed binomial logistic regression analysis with tinnitus as an independent variable and 24 dependent variables – sex, ethnicity, SLT, music exposure, history of ear infection, and 19 SNPs in 13 cochlear genes listed in methods. We applied false discovery rate corrections to the p-value to correct for multiple comparisons. History of ear infection (odds ratio [OR] = 0.29, $p = 0.004$, 95%CI = 0.12–0.66) and KCNQ1 rs163171 (OR = 2.83, $p = 0.004$, 95%CI = 1.38–5.78) were found to be associated with tinnitus (Fig. 3). These associations remained statistically significant after FDR correction. SLT (OR = 2.1, $p = 0.04$, 95%CI = 1.03–4.27) and KCNE1 rs2070358 (OR = 0.41, $p = 0.049$, 95%CI = 0.17–0.99) showed suggestive associations not statistically significant after FDR correction. The overall model resulted in a statistically significant Chi-square value ($p = 0.02$) and a Cox and Snell R^2 value of 0.193. No other predictors were associated with tinnitus. We performed a Chi-square analysis to rule out a possibility of population stratification due to self-reported ethnicity. Self-reported ethnicity revealed no significant association with KCNQ1 SNP rs163171 (χ^2[1, N = 186] = 0.051, $p = 0.82$) and tinnitus (χ^2[1, N = 186] = 1.25, $p = 0.26$). We performed a similar regression analysis for SLT as a dependent variable (Table 2). Sex (OR = 3.8, $p = 0.0004$, 95%CI = 1.81–8.04) and tinnitus (OR = 2.01, $p = 0.046$, 95%CI = 1.01–3.99) revealed statistically significant association with SLT. No other audiological and genetic variables showed an association with SLT.

DISCUSSION

The present study evaluated tinnitus in a sample of young adults (N = 186). We hypothesized that individuals carrying SNPs associated with NIHL would exhibit a significantly higher prevalence of tinnitus as these conditions are highly comorbid. Our results showed that individuals with at least one minor allele of rs163171 (C > T) in the KCNQ1 gene exhibit significantly higher odds of reporting tinnitus compared to individuals carrying the major allele of rs163171. Our analysis further revealed that a history of ear infection and SLT showed a statistically significant association with tinnitus. Music exposure showed a promising association trend with tinnitus, but the *p*-value failed to achieve statistical significance. Biological sex revealed a statistically significant association with DPOAE SNR measures. The main effects of tinnitus on hearing thresholds and DPOAE SNR were not statistically significant.

Association of the KCNQ1 Variant With Tinnitus

Potassium ion recycling is a necessary process for maintaining endolymphatic potential (45). KCNQ1 (Potassium Voltage-Gated Channel Subfamily Q Member 1) and KCNE1 (Potassium Voltage-Gated Channel Subfamily E Regulatory Subunit 1) form a voltage-gated potassium channel that is expressed in the marginal cell membrane of the stria vascularis (46). KCNQ1/KCNE1 channel is necessary to maintain potassium ions in endolymph to sustain endolymphatic potential, essential for cochlear transduction (e.g., 47)(47). Individuals with Jervell & Lange-Nielsen syndrome have KCNQ1 or KCNE1 mutations resulting in cardiac arrhythmia and hearing loss (48-51). SNP in KCNQ1 (rs163171) was associated with NIHL in factory workers (38). This SNP revealed a significant association with tinnitus in the present study. KCNE1 rs2070358 revealed a promising pattern of association ($p = 0.049$) with tinnitus, but the FDR corrected *p*-value could not achieve the statistical significance (adjusted $p < 0.05$). Our previous study showed that the KCNE1 SNP was significantly associated with DPOAE SNR in young musicians (Bhatt et al., 2020). Collectively, the results suggest the involvement of KCNQ1/KCNE1 voltage-gated potassium ion channel in the pathogenesis of NIHL and tinnitus.

Subjective tinnitus has been associated with a larger platelet count and volume (52-56). Interestingly, the minor allele of KCNQ1 rs163171 has been associated with larger platelet count, mean platelet volume, and other inflammatory markers (57). We hypothesized that individuals with the minor allele of KCNQ1 rs163171 might be more susceptible to noise damage due to inefficient inflammatory response following noisy events (e.g., music ensemble) resulting in tinnitus. KCNQ1 rs163171 is located in the noncoding (intronic) region of the KCNQ1 gene (https://www.ncbi.nlm.nih.gov/snp/rs163171) A recent GWAS investigating a genome-wide association to tinnitus using the UK Biobank database that identified most SNPs in the noncoding (intronic) regions from the genes associated with tinnitus (21). The biological mechanism underlying tinnitus and intronic SNPs largely remains unexplored (52). However, it is known that the genetic elements responsible for maintaining biological functions are likely to be regulated by epigenetic factors. The investigation of epigenetic factors on tinnitus is essential to acquire mechanistic insight into KCNQ1-related susceptibility to tinnitus.

KCNQ1 did not reveal a statistically significant association with tinnitus in the large-scale GWAS (21). This observation might be attributed to the differences in the tinnitus phenotyping process and the study population. The present study evaluated audiometric hearing thresholds to identify those with “normal” audiograms while the large-scale GWAS was dependent on the self-reported measure of hearing difficulties (21). The study population of young musicians does not exhibit age-related confounding factors (e.g., systemic diseases) that can often obscure the phenotype–genotype association analysis. Young musicians with routine exposure to traumatic sound levels are likely to facilitate the identification of genetic variants with a small effect size. Given that the KCNQ1 variant was not associated with tinnitus in a large-scale GWAS, we expect that its effect size would be smaller in the general population. Further research is required to investigate the role of the KCNQ1/KCNE1 channel in the pathogenesis of tinnitus and NIHL.

Association of Tinnitus With Other Audiometric Measures

Tinnitus revealed a statistically significant association with SLT and a history of ear infection. These results are consistent with other studies (2-5,15). We could not obtain a statistically significant main effect for tinnitus on DPOAE and audiometric measures. It is possible that the conventional audiometry evaluating hearing thresholds at the octave frequencies and DPOAE measured using discrete primary tone combination are not sensitive to detect physiological dysfunction between the tested frequencies (58). The audiometric “notch” configuration in the high-resolution audiometry has been associated with tinnitus in individuals with conventional hearing thresholds within normal limits, suggesting that the cochlear hearing loss that remains undetected with the conventional audiometry might play a role in tinnitus genesis (59). Therefore, the present study cannot rule out the cochlear dysfunction in individuals with tinnitus.

Young musicians are exposed to traumatic sound levels at occupational and recreational settings on a regular basis (34-35). Recent animal studies have shown moderate noise exposures that produce a large temporary threshold shift, but no permanent threshold shift could induce irreversible damage to inner hair cells ribbon synapses (60-62). Noise-induced cochlear synaptopathy preferentially damages auditory nerve fibers with a low spontaneous-firing rate (SR) and high threshold (63). Low SR fibers show larger dynamic ranges (64), are essential for processing temporal information at the suprathreshold levels (65-67) and are less vulnerable to masking (68). Noise-induced cochlear synaptopathy could compromise auditory acuity in complex listening environments without affecting hearing sensitivity (69). Noise-induced cochlear synaptopathy might reduce the cochlear output, which might cause an elevation in the central gain contributing to tinnitus (70). Musicians with high noise exposure exhibit a reduction in their auditory brainstem response wave I amplitude (71). The proxy measures of cochlear synaptopathy remained unexplored in the present study. Therefore, we could not rule out the auditory neural dysfunction in our participants with normal audiograms. We hypothesized that the reduction in cochlear gain due to impaired functioning KCNQ1/KCNE1 voltage-gated potassium ion channel (as evident by reduced DPOAE SNR) (36) might cause maladaptive consequences resulting in abnormally increased central gain contributing to tinnitus genesis.

Experimental Caveats

We evaluated an existing database with limited genotype and phenotype data. Our study evaluated sex, ethnicity, and music exposure to account for population stratification while investigating the genetic association to tinnitus and SLT. However, it should be noted that fully accounting for population stratification is a major weakness of the candidate gene studies (72). The database did not have an exhaustive set of SNPs associated with NIHL in previous studies (e.g., 73)(73). The study was limited by its small sample size and the survey design for evaluating tinnitus and music exposure. A comprehensive test battery including tinnitus evaluation and physiological measures might be more efficient to identify complex genetic elements that control the phenotypic spectrum underlying tinnitus.

CONCLUSIONS

The study revealed a significant association between SNP rs163171 (C > T) in KCNQ1 and tinnitus. KCNE1 rs2070358 revealed a promising pattern of association ($p = 0.049$) with tinnitus, but the FDR corrected p-value could not achieve the statistical significance ($p < 0.05$). We concluded that KCNQ1/KCNE1 voltage-gated potassium ion channels play a critical role in the pathogenesis of NIHL and tinnitus. Further research is required to construct clinical tools for identifying genetically predisposed individuals well before they are exposed to environmental risk factors (e.g., noise, music) and acquire irreversible damage to their auditory system leading to NIHL and tinnitus.

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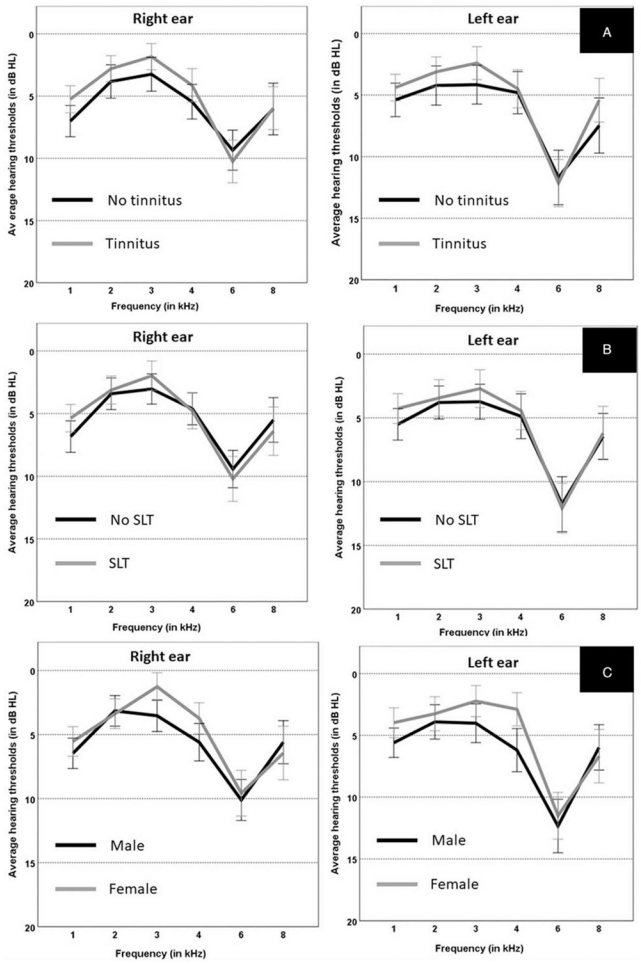

FIG. 1.

Average hearing thresholds as a function of audiometric frequencies between individuals with and without tinnitus (A), sound level tolerance (SLT) (B), and between males and females (C).

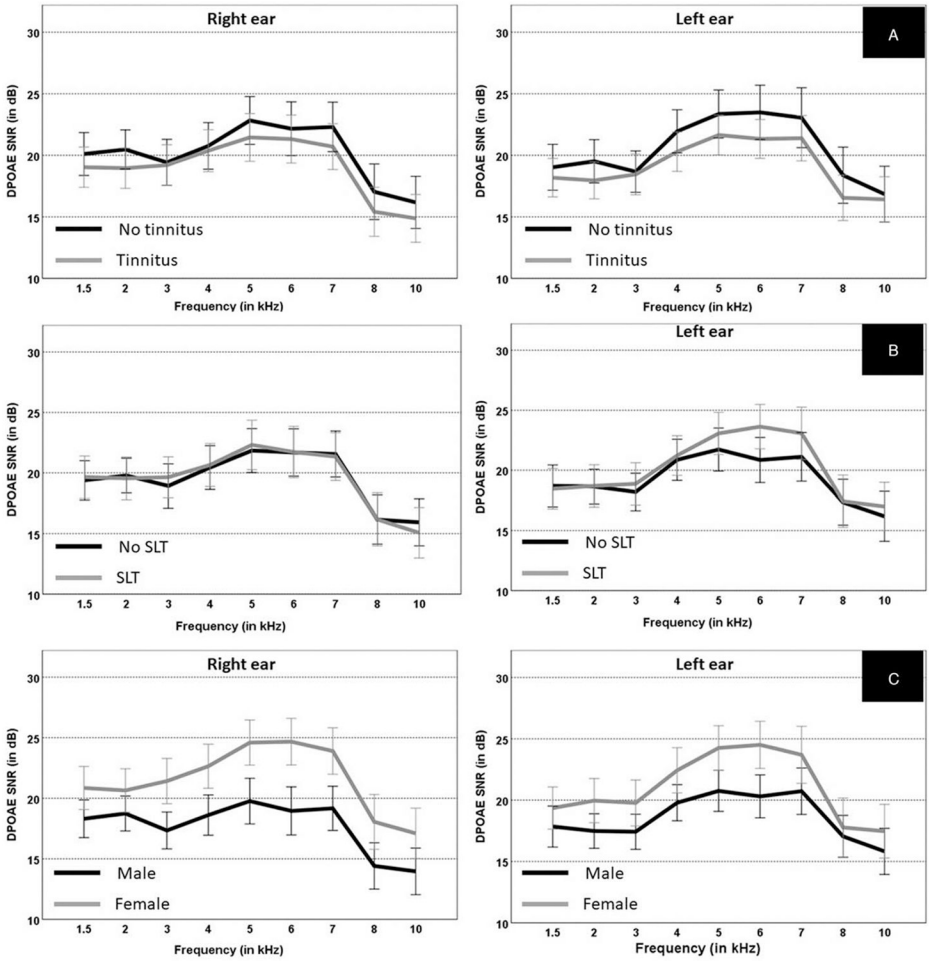

FIG. 2.

Average DPOAE SNR values as a function of audiometric frequencies between individuals with and without tinnitus (A), sound level tolerance (SLT) (B), and between males and females (C). DPOAE, distortion product otoacoustic emissions.

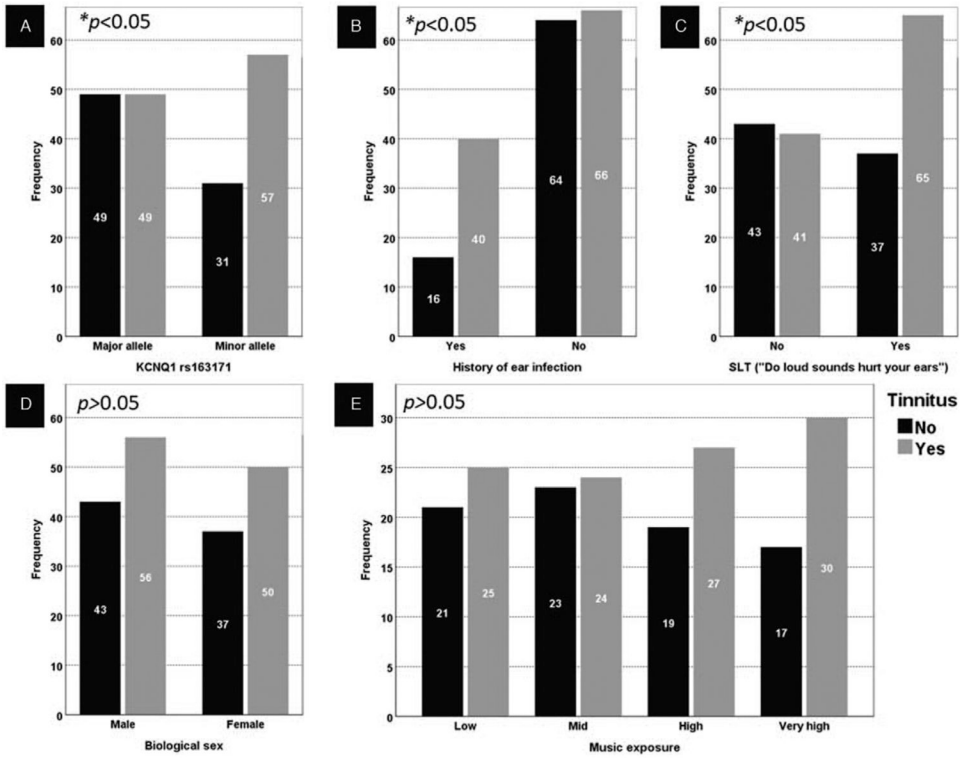

FIG. 3.

(A) Prevalence of tinnitus between individuals with the major and minor allele for KCNE1 rs163171. (B) Prevalence of tinnitus between individuals with and without a history of ear infection. (C) Prevalence of tinnitus between individuals with and without SLT. (D) Prevalence of tinnitus between males and females. (E) Prevalence of tinnitus between individuals with low, mid, high, and very high music exposure levels. SLT, sound level tolerance.

TABLE 1.

A brief review of the studies investigating the genetic influence on tinnitus

Study	Phenotype	Targeted Genes	Major Findings
Clifford et al. (2020) (21)	"Yes" to "Do you get or have you had noises (such as ringing or buzzing) in your head or in one or both ears that last for more than 5 min at a time?"	Genome-wide association study	Six genome-wide significant loci and 27 genes (with 3 of 6 loci and 8 of 27 genes were replicated).
Marchiori et al. (2018) (22)	Tinnitus severity (a score from 0 to 10)	TNFα	TNFα −308 G variant was associated with tinnitus (OR = 2.74; 95%CI: 1.56–4.81; $P < 0.0005$)
Gilles et al. (2017) (20)	"Yes" to "Nowadays, do you ever hear noises in your head or ear(s) (tinnitus) which usually last longer than 5 min?"	Genome-wide association study	No significant association. VDAC1, NKTR, COG3 showed promising main effects.
Yüce et al. (2016) (23)	Patients suffering from chronic for >6 mo. Subjects responded to Strukturiertes Tinnitus-Interview and Tinnitus Handicap Inventory.	ACE, ADD1	ADD1 (G460W) associated with tinnitus
Orenay-Boyacioglu et al. (2016) (24)	Tinnitus perception for at least 3 mo.	GDNF	No significant genetic association was observed.
Pawelczyk et al. (2012) (25)	"Yes" to "Do you suffer from tinnitus?"	K+ ion recycling	KCNE1 rs915539 (with tinnitus); SLC12A2 (rs10089) with tinnitus and NIHL.
Sand et al. (2012) (26)	Tinnitus severity (German version of the Tinnitus Questionnaire)	GDNF, BDNF	GDNF (rs1110149, rs884344, rs3812047) and BDNF (rs2049046, rs6265) genotypes were associated (only in females)
Sand et al. (2012) (27)	Tinnitus severity (German version of the Tinnitus Questionnaire)	KCTD12	KCTD12 (rs34544607)
Sand et al. (2011) (28)	Tinnitus severity (German version of the Tinnitus Questionnaire)	KCNE3	No significant association
Deniz et al. (2010) (29)	Tinnitus perception for more than 1 yr.	SLC6A4	SLC6A4 (5-HTTLPR) was associated with tinnitus
Sand et al. (2010) (30)	Tinnitus severity (German version of the Tinnitus Questionnaire)	KCNE1	No significant association
Kleinjung et al. (2006) (31)	Tinnitus severity (German version of the Tinnitus Questionnaire)	5-HT1A	No significant association

NIHL, noise-induced hearing loss.

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TABLE 2.

Results of the binary logistic regression analyses for tinnitus and sound level tolerance (SLT)

Independent Variables	Outcome: Tinnitus – Yes/No		Independent Variables	Outcome: SLT – Yes/No	
	OR (95%CI)	*p* Value		OR (95%CI)	*p* Value
Sex	1.03 (0.48–2.22)	0.925	Sex	3.81 (1.81–8.04)	0.0004 **
Ethnicity	1.42 (0.37–5.45)	0.603	Ethnicity	0.34 (0.09–1.31)	0.119
History of ear infection	0.29 (0.12–0.66)	0.004 **	History of ear infection	1.29 (0.59–2.80)	0.512
SLT	2.10 (1.03–4.27)	0.041 *	Tinnitus	2.01 (1.01–3.99)	0.046 *
Music exposure	1.14 (0.84–1.55)	0.376	Music exposure	0.90 (0.67–1.21)	0.510
KCNE1 rs2070358	0.41 (0.17–0.99)	0.049 *	KCNE1 rs2070358	1.61 (0.73–3.56)	0.233
KCNE1 rs1805127	2.12 (0.86–5.18)	0.100	KCNE1 rs1805127	0.97 (0.42–2.23)	0.961
KCNQ1 rs163171	2.83 (1.38–5.78)	0.004 **	KCNQ1 rs163171	1.18 (0.60–2.32)	0.623
CDH23 rs1227051	1.42 (0.69–2.93)	0.340	CDH23 rs1227051	0.90 (0.45–1.82)	0.790
GJB2 rs9552098	0.98 (0.25–3.71)	0.978	GJB2 rs9552098	0.99 (0.29–3.40)	0.994
GJB2 rs3751385	0.53 (0.15–1.89)	0.332	GJB2 rs3751385	0.82 (0.25–2.66)	0.747
GJB4 rs755931	0.52 (0.14–1.94)	0.337	GJB4 rs755931	2.23 (0.65–7.60)	0.200
KCNJ10 rs1130183	0.67 (0.21–2.10)	0.497	KCNJ10 rs1130183	0.50 (0.16–1.52)	0.225
CAT rs475043	1.38 (0.63–3.05)	0.417	CAT rs475043	1.75 (0.82–3.75)	0.146
CAT rs12273124	1.67 (0.43–6.37)	0.453	CAT rs12273124	1.06 (0.30–3.68)	0.917
HSP70 rs1043618	0.51 (0.11–2.36)	0.394	HSP70 rs1043618	0.66 (0.14–2.98)	0.596
HSP70 rs1061581	0.92 (0.20–4.23)	0.918	HSP70 rs1061581	1.42 (0.32–6.30)	0.645
HSP70 rs2227956	0.95 (0.42–2.16)	0.919	HSP70 rs2227956	0.64 (0.29–1.40)	0.267
PCDH15 rs7095441	0.59 (0.29–1.22)	0.160	PCDH15 rs7095441	1.04 (0.52–2.08)	0.907
MYH14 rs667907	0.61 (0.14–2.51)	0.495	MYH14 rs667907	1.89 (0.43–8.21)	0.394
MYH14 rs588035	1.33 (0.32–5.40)	0.690	MYH14 rs588035	0.40 (0.09–1.74)	0.225
GRM7 rs11928865	0.59 (0.28–1.23)	0.160	GRM7 rs11928865	0.92 (0.45–1.87)	0.827
PON2 rs987539	1.14 (0.55–2.35)	0.718	PON2 rs987539	0.76 (0.37–1.54)	0.455
ESRRB rs61742642	2.21 (0.81–6.04)	0.120	ESRRB rs61742642	0.83 (0.32–2.15)	0.703

* p value < 0.05.

** Remained significant after applying the FDR correction (for $\alpha = 0.05$).