LETTER to the EDITOR

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Genetic Landscape of Tinnitus in Cisplatin-Treated Testicular Cancer Patients: Implications for Personalized Medicine and Auditory Health Surveillance

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Dear Editor

Cisplatin, a widely used chemotherapeutic agent for testicular cancer, is associated with significant ototoxicity, leading to tinnitus and hearing loss in many patients [1]. Research shows that approximately 74% of testicular cancer survivors report some ototoxic effects, with 68% experiencing tinnitus and 59% suffering from hearing loss rates considerably higher than in the general population [1, 2]. Genetic factors play a significant role in tinnitus risk, with genome-wide association studies (GWAS) estimating the heritability of bilateral tinnitus at approximately 56% [1, 3]. While initial studies on cisplatin-treated survivors found no significant genetic variants, they did identify associations with cisplatin dosage and pre-existing hearing conditions. Additionally, gene-set enrichment analyses have connected metabolic pathways involving oxidative stress and endoplasmic reticulum stress to the onset of tinnitus, as cisplatin triggers ER stress in auditory cells. Various risk factors contribute to tinnitus in these patients, including cumulative cisplatin dose, age, coexisting conditions like hypercholesterolemia and hypertension, and the use of psychotropic medications [2]. Understanding these factors is crucial for developing strategies to prevent or manage tinnitus in cancer survivors.

We analyzed the genetic basis of tinnitus risk in cisplatin-treated testicular cancer patients using data from recent GWAS. This involved genetic data from large, publicly available biobanks and consortia, such as the Children's Oncology Group and the Genomics of Drug Sensitivity in Cancer project. Standardized assessments were conducted to evaluate tinnitus prevalence and severity among patients. Genome-wide genotype data were generated using Illumina SNP chips, applying quality control to exclude samples and variants with low call rates, Hardy-Weinberg equilibrium violations, or substantial missing data. SNPs associated with tinnitus risk were identified through GWAS meta-analysis and confirmed in independent cohorts, with a significance threshold of $p < 5 \times 10^{-8}$ for genome-wide significance.

A pivotal study by El Charif et al. (2019) in Clinical Cancer Research examined the genetic components of tinnitus among cisplatin-treated testicular cancer patients. Using a genome-wide genotyping array on a sample of 154 cases and 608 controls of European ancestry, the researchers assessed 7,225,561 quality-controlled SNPs to elucidate the genetic landscape related to cisplatin-induced tinnitus. Although lacking a replication sample, the study revealed novel mechanisms behind tinnitus and emphasized the importance of genetic predispositions in enhancing treatment outcomes for cancer patients. This research not only advances the understanding of cisplatin's auditory toxicity but also paves the way for personalized treatment strategies for affected individuals [1].

Various genetic variants were notably linked to tinnitus, with rs141382055-A showing the strongest association (P-value: 3 x 10^-6; OR: 5.7029), suggesting a strong susceptibility link. Other significant variants included rs6671895-T (P-value: 1×10^{-6}; OR: 4.3219), rs7606353-G (P-value: 2×10^{-6}; OR: 4.2043), rs117764890-C (P-value: 6×10^{-6}; OR: 3.4188), and rs12026039-G (P-value: 4×10^{-6}; OR: 3.5248), all associated with genes pertinent to tinnitus and cisplatin response. Additional variants like rs73231578-T, rs10842948-T, rs7532231-A, rs6552561-A, and rs498518-A corroborated these findings with P-values ranging from 4×10^{-6} to 9×10^{-6} and ORs from 1.8521 to 2.9383. These results underscore the genetic predisposition to tinnitus in this patient group and indicate that multiple genomic regions may play a role, providing insights for future studies on underlying mechanisms.

The complex genetic architecture of tinnitus is evident from several SNPs demonstrating low P-values, indicating statistical significance. Specifically, the variant rs141382055-A, linked to the gene *PIP4K2A*, suggests that its carriers have a heightened likelihood of developing tinnitus post-cisplatin treatment, reinforced by high-OR variants like rs6671895-T (MIR3659HG). The implicated genes, including *THAP3P1, ADRA1A*, and *LINC* genes, illustrate a multifaceted genetic environment influencing auditory processing and susceptibility to ototoxicity. For instance, ADRA1A's relationship with tinnitus points to adrenergic pathways potentially affected during cisplatin therapy. The involvement of long intergenic non-coding RNAs (like LINC00184 and LINC01132) suggests their regulatory role in tinnitus pathology, possibly affecting gene expression linked to auditory health.

The consistent identification of these variants across studies not only indicates their association with tinnitus in cancer treatment but also raises inquiries about hereditary predispositions. Understanding these genetic influences is vital for personalized medicine, enabling genetic testing to identify individuals at higher risk of tinnitus from certain chemotherapies. This could inform clinical practices,

tailoring treatment plans to minimize debilitating auditory side effects. Furthermore, this research highlights the need for monitoring auditory health in cancer patients on cisplatin and encourages interdisciplinary approaches combining genetics, audiology, and oncology. Future studies should focus on mouse models and human cohorts to further clarify the biological mechanisms behind these associations and explore therapeutic interventions to mitigate tinnitus risk in vulnerable populations.

In conclusion, identifying genetic variants linked to tinnitus risk in cancer patients treated with cisplatin marks a significant advancement in understanding the interplay between genetics and environmental factors impacting auditory health. This research sheds light on genetic predispositions to tinnitus, emphasizing the necessity for personalized medicine approaches that better assess and mitigate the auditory side effects of chemotherapy. By integrating genetic insights into clinical practice, healthcare providers can develop customized treatment plans that prioritize auditory health, thereby improving the quality of life for cancer patients. Continued interdisciplinary research in genetics, audiology, and oncology is vital to unraveling the complexities of tinnitus and formulating effective strategies for its monitoring and management in at-risk populations. Ongoing studies aim to delve deeper into the genetic landscape associated with cisplatin-induced tinnitus, GWAS to larger cohorts and exploring the shared genetic architectures between cisplatin-related and non-cisplatin-related tinnitus cases. Ultimately, this research has the potential to lead to the creation of otoprotective strategies that could be administered alongside cisplatin, reducing the risk of auditory complications.

Declarations

Ethics approval and consent to participate: This article does not involve any studies with human participants or animals conducted by the authors; therefore, consent to participate is not applicable.

Authors' Contributions Statement

Concept and design: Maedeh Barahman, Amirhossein Shahbazi; Data analysis and interpretation: Melina Pourkazemi, Ali Massoudi; Manuscript drafting: Maedeh Barahman, Amirhossein Shahbazi; Critical review and statistical analysis: Ali Massoudi, Hossein Neamatzadeh; Administrative support: Melina Pourkazemi, Hossein Neamatzadeh.

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