

PgmNr 648: A genome-wide association study of cisplatin-induced tinnitus in adult cancer survivors.

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Despite its efficacy as a curative agent in testicular cancer, cisplatin can result in severe, often permanent toxicities, including tinnitus. Treatment of tinnitus is limited to palliative behavioral modifications and attenuation of associated anxiety and stress. We performed a novel genome-wide association study of cisplatin-induced tinnitus in 835 well-characterized testicular cancer survivors (Median age at assessment: 38 ± 10 (SD) years; median cumulative dose of cisplatin: 400 mg/m^2). There are no external quantitative means to assess tinnitus clinically, therefore, we assessed it as a binary response to the question derived from the validated Scale for Chemotherapy-Induced Neurotoxicity: “Have you suffered in the last 4 weeks from: Ringing in your ears?”, with “not at all” (662) respondents as controls, and “Quite a bit” or “Very much”(173) as cases, excluding “a little bit” respondents (467). We observed a significant association between tinnitus and cisplatin dose by 100 mg/m^2 [OR: 1.36, $p = 0.01$], age by decade [OR: 1.28, $p = 0.003$], noise exposure [OR: 1.7, $p = 4 \times 10^{-6}$], vertigo [OR: 6.4, $p = 1.4 \times 10^{-7}$], use of psychotropic medication (anxiolytics/antidepressants)[OR: 2.4, $p = 0.003$], and difficulty hearing in crowds [OR: 7.9, $p < 10^{-16}$]. Nearly 7.3 million SNPs passed quality control in 835 genetically European individuals. Imputed SNP dosages and covariates including age, noise exposure, cisplatin dose, and 10 genetic principal components were logistically regressed on tinnitus. Intronic SNPs with $p < 1.0 \times 10^{-5}$ were observed in several genes that are associated with hearing loss, neurodegenerative and anxiety disorders. The top signal ($p = 1.5 \times 10^{-6}$) was the

variant rs7606353, about 14kb upstream of *OTOS*; a gene involved in cochlear development and implicated in vestibular disease. Other implicated genes include *OR6B3*, *DPYSL2*, as well as *PPFIBP1*, a gene also associated with tinnitus in Vanderbilt BioVU ($p = 0.002$; 105 cases, 7899 controls). Gene set enrichment analysis revealed that the ten most enriched biological processes (FDR $q < 0.15$) are neurological in origin, including central nervous system axonogenesis ($q = 0.04$). Heritability was assessed using GCTA, revealing potential polygenic architecture ($h^2 = 0.57 \pm 0.48$, $p = 0.10$). Discovering new links between tinnitus, genetic predispositions and interactions with cisplatin therapies can pave the way for more effective preventative strategies or novel treatment options for cancer survivors.

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