Genetic variant linked to hearing loss in children treated with common chemotherapy drug

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Amit Bhavsar, Canada Research Chair in Functional Genomic Medicine, led a U of A team that confirmed that children with the genetic variant TCERG1L have three times the risk of hearing loss due to cisplatin treatment compared with those who don't have the variant. Credit: William Au

A University of Alberta research lab has helped identify a genetic

variant that increases the risk of hearing loss in children with cancer who are treated with the widely used drug cisplatin.

Amit Bhavsar, assistant professor in the Department of Medical Microbiology & Immunology and Canada Research Chair in Functional Genomic Medicine, led the U of A team that contributed to the international study, which was published in the journal *Precision Oncology*. Bhavsar's team confirmed the study's genomic findings with a biological investigation using cell-based models.

With significant advances in pediatric cancer care in recent decades, the five-year survival rate for childhood cancer is now almost 80 per cent. But many childhood cancer survivors suffer from serious health complications after chemotherapy. Permanent hearing loss is one of them.

Hearing loss affects half of young patients

Children with solid tumours in the brain, liver and bone are usually treated with cisplatin, a highly effective chemotherapy that has been in use since the 1960s. They are more vulnerable to chemotherapy toxicities than adults—half of children treated with cisplatin suffer irreversible hearing loss.

Hearing loss in young children can have a devastating effect on speech development, psychosocial skills and academic performance, said Bhavsar, and affects quality of life in children of all ages.

The international study began in 2015, spearheaded by the European organization PanCareLIFE. The collaborators looked at how the genetic variations in 770 pediatric patients in Europe and Canada influenced their response to cisplatin. Bhavsar said close to a million variants were examined.

In their first cohort study, the researchers identified a genetic variant in the TCERG1L gene, along with a few other variants, that appeared to increase the risk of cisplatin-induced hearing loss. Two further replication studies—including one involving young cancer patients in Canada—were done, looking at those specific variants. They confirmed the association between the TCERG1L variant and the hearing loss.

The Bhavsar lab joined the project in 2019. Its role was to replicate the statistical findings in a laboratory setting "to see if there was a biological rationale for what they had seen in the cohorts," he explained. The U of A team manipulated the TCERG1L gene in human cell lines to determine how that would affect the cells' response to cisplatin.

Their laboratory findings corroborated the cohort research, concluding that children with the TCERG1L variant have three times the risk of hearing loss due to cisplatin treatment compared with those who don't have the variant. They are the first research group to make this connection.

Predicting who is at risk

Bhavsar said further research is needed. In the case of the TCERG1L gene, which is a transcription regulator, it would be important to investigate other genes regulated by TCERG1L to see what role they play in cisplatin-induced hearing loss.

The hope is that research like this international study will lead to predictive tests that will allow doctors to determine which patients are at higher risk of hearing loss during or after cisplatin treatment. This might change treatment or dose decisions and would at least allow patients and families to be informed in advance of the risks, Bhavsar noted.

More information: A. J. M. Meijer et al, TCERG1L allelic variation

is associated with cisplatin-induced hearing loss in childhood cancer, a PanCareLIFE study, *npj Precision Oncology* (2021). DOI: 10.1038/s41698-021-00178-z