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## Abstract Submission No.: A-1497

# Variant analysis Impacts on Nephrotoxicity induced Platinum Compound by Molecular Simulation and Network Interaction

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**Objectives :** Platinum compound (cisplatin, carboplatin, oxaliplatin) has remained a backbone antineoplastic agent used to treat various cancers. Approximately one-third of patients develop any kind of nephrotoxicity after a single dose of 50–100 mg/m$^2$ cisplatin. Non-genetic risk factors for cisplatin-induced nephrotoxicity have been identified, including older age, low functional status, malnourishment, hypovolemia, etc. However, studies that have investigated genetic contributions to the development of cisplatin-induced nephrotoxicity have shown inconsistent findings. This study evaluated the relationship between genetic risk factors and cisplatin-induced nephrotoxicity by investigating genetic risk variants not previously studied through molecular simulation and network interaction
**Methods :** We identified of gene that associated with platinum compound by using KEGG, Genecard and PharmKGB. Gene variant of selected enzyme was chosen based on the domain where the mutation occurs and causes protein change, from NCBI and Ensembl. Genetic variants were analyzed by using SIFT and Polyphen-2 to predict their impact on protein structures and functions. The SNPs sequence was investigated using BLAST to predict any difference. The possible active sites of the protein were predicted and visualize the interacting residues of the ligand-receptor complex.
**Results :** We found that 353 genes associated to nephrotoxicity induced platinum compound. Based on selection criteria: protein coding gene, Score>10, and association with PK PD, we choose 4 genes (ERCC1, ERCC2, SLC22A2, ABCC2). Through molecular simulation, it has been found that 2 deleterious variant are rs316019 (SLC22A2) with S/A amino acid replacement (SIFT:0, Polyphen: 0.37, AF: 0.8626), and rs3740066(ABCC2) with I/M amino replacement (SIFT:0, Polyphen:0). Others SNP considered benign and tolerated, are: rs11615 (ERCC1), rs13181 (ERCC2), rs8187710 and rsrs2273697 (ABCC2).
**Conclusions :** In this study we found that SLC22A2 and ABCC2 have essential association with nephrotoxicity induced platinum compound, especially rs316019 and rs3740066. Understanding the potential contribution of genetic variants may assist further clinical investigation in population.

Figure 1 APCN_page-0001.jpg

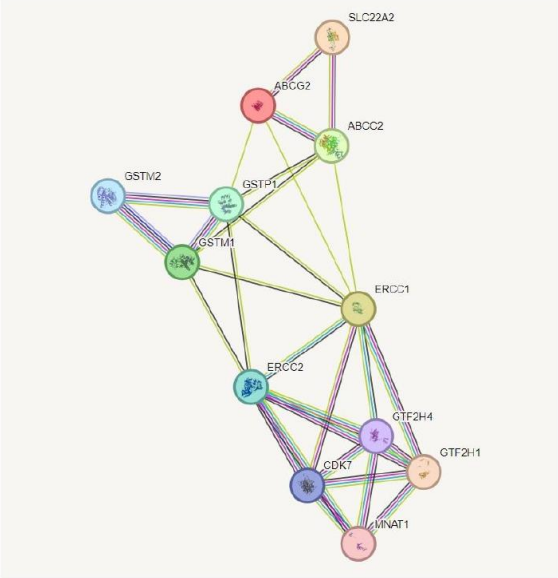


Figure 1. STRING of multiple genes that associated with nephrotoxicity induced Platinum

Figure 1 APCN_page-0001.jpg

Table. 1. Molecular analysis of various SNP

| Variant | alelle | gene | biotype | protein position | amino acid | ref alelle | | SIFT | Polyphen | AF | Description |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11615 | G | ERCC1 | protein_coding | 118 | N | A | A/G | 1 | - | 0.6689 | Benign |
| rs13181 | G | ERCC2 | protein_coding | 673 | K/Q | T | T/A/G | **0.45** | **0** | 0.2366 | benign/likely_benign, not_provided, benign |
| rs13181 | G | ERCC2 | protein_coding | 751 | K/Q | T | T/A/G | **0.37** | **0** | 0.2366 | benign/likely_benign, not_provided, benign |
| rs316019 | T | SLC22A2 | protein_coding | 249 | S/T | A | A/C/T | **1** | **0.012** | - | - |
| rs316019 | C | SLC22A2 | protein_coding | 270 | S/A | A | A/C/T | **0** | **0.37** | 0.8626 | deleterious |
| rs3740066 | G | ABCC2 | protein_coding | 1324 | I/M | C | C/G/T | **0** | **0.822** | - | deleterious |
| rs8187710 | A | ABCC2 | protein_coding | 1515 | C/Y | G | G/A | **0.35** | **0** | 0.0679 | Benign |
| rs2273697 | A | ABCC2 | protein_coding | 417 | V/I | G | G/A | **0.15** | **0.031** | 0.1865 | Benign |