

MEETING ABSTRACT

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Identification of a genetic variant associated with treatment outcome in ovarian cancer: the potential role of cholesterol metabolism as a determinant of response to chemotherapy

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Cell-based models have shown that response to chemotherapy has a heritable component. We hypothesized that in order to identify loci associated with treatment outcome we should focus on cases known to have had uniform chemotherapy for epithelial ovarian cancer. We therefore performed a two-stage genome-wide association study (GWAS) of progression free survival (PFS) following first line carboplatin/paclitaxel chemotherapy in ovarian cancer cases. In the first stage, we genotyped (Illumina Omni1) 183 Australian cases selected using an extreme phenotype design, and also included data on 134 cases from the TCGA and 68 from Mayo Clinic. In this stage, 260 cases had 'uniform' treatment ("primary" group: at least 4 cycles of carboplatin 5-6 AUC and paclitaxel 135-175 mg/m² every three weeks) and 125 cases ("secondary") had an unknown amount of carboplatin/paclitaxel chemotherapy. In the 2nd stage we genotyped 156 of the top ranking genotyped and imputed SNPs in 4660 cases (1080 'primary' and 1433 'secondary') from 11 sites in OCAC. The additive allelic association with the PFS was assessed in a Cox Proportional Hazards model, adjusting for study site, histological subtype, grade, stage and residual disease. For the SNPs

with low minor allele frequencies, we ran permutations to correct the asymptotic p-values. One SNP clearly replicated in the 2nd stage. The associations in both stages were strongest in the "primary" group (1st stage results for this imputed SNP: hazard Ratio (HR) per minor allele=6.30, 95% CI=[4.26, 9.30], two-sided asymptotic p-value=1.88e-6, permuted p-value=4.46e-5; 2nd stage: HR per minor allele=3.37, 95% CI=[2.48, 4.62], one-sided asymptotic p-value=5e-5, permuted p-value=2.9e-4; meta-analysis p-value corrected by permutation=1.7e-7).

Furthermore, an independent cell-based GWAS conducted using HapMap lymphoblastoid cell lines showed that a more common SNP (MAF~4.5%) in moderate LD with our reported SNP ($r^2 \sim 0.28$), was associated with carboplatin sensitivity (p-value=9e-3). Both these SNPs are located in a gene on chromosome 9 that is known to be associated with circulating levels of high-density lipoprotein cholesterol. Low levels of expression of this gene are associated with poor outcome for both progression free (P=.017) and overall survival (P=.001) from serous ovarian cancer in The Cancer Genome Atlas.

We are now genotyping a panel of rare and common SNPs in this gene in additional validation cohorts from OCAC and conducting additional experiments to evaluate its biological relevance with respect to treatment

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outcome, including the potential role of cholesterol metabolism as a determinant of response to chemotherapy. Our findings may provide some insight into the suggested role of statins in improving outcome for ovarian cancer.

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