# Exome sequencing for drug adverse reaction analysis

# An application

- Gréen H, Hasmats J, Kupershmidt I, Edsgärd D, de Petris L, Lewensohn R, *et al*. **Using Whole-Exome Sequencing to Identify Genetic Markers for Carboplatin and Gemcitabine-Induced Toxicities**. Clin Cancer Res. 2016 Jan 15;22(2):366-73. doi: 10.1158/1078-0432.CCR-15-0964. Epub 2015 Sep 16. PubMed PMID: 26378035.

# Abstract(1)


- PURPOSE: **Chemotherapies** are associated with significant **interindividual variability** in therapeutic effect and **adverse drug reactions**. In lung cancer, the use of **gemcitabine** and **carboplatin** induces grade 3 or 4 **myelosuppression** in about a quarter of the patients, while an equal fraction of patients is basically unaffected in terms of myelosuppressive side effects. We therefore set out to identify **genetic markers for gemcitabine/carboplatin-induced myelosuppression**.
- EXPERIMENTAL DESIGN: We **exome sequenced** 32 patients that suffered extremely high **neutropenia** and **thrombocytopenia** (grade 3 or 4 after first chemotherapy cycle) or were virtually unaffected (grade 0 or 1).
- The genetic differences/polymorphism between the groups were compared using six different bioinformatics strategies:
  - (i) whole-exome nonsynonymous single-nucleotide variants association analysis,
  - (ii) deviation from Hardy-Weinberg equilibrium,
  - (iii) analysis of genes selected by a priori biologic knowledge,
  - (iv) analysis of genes selected from gene expression meta-analysis of toxicity datasets,
  - (v) Ingenuity Pathway Analysis, and
  - (vi) FunCoup network enrichment analysis

# Abstract (2)

- RESULTS: A total of **53 genetic variants that differed among these groups were validated in an additional 291 patients** and were correlated to the patients' myelosuppression.
- In the validation, we identified **rs1453542 in OR4D6** (P = 0.0008; OR, 5.2; 95% CI, 1.8-18) as a marker for gemcitabine/carboplatin-induced neutropenia
- and **rs5925720 in DDX53** (P = 0.0015; OR, 0.36; 95% CI, 0.17-0.71) as a marker for thrombocytopenia.
  - Patients homozygous for the minor allele of rs1453542 had a higher risk of neutropenia, and for rs5925720 the minor allele was associated with a lower risk for thrombocytopenia.
- CONCLUSIONS: We have identified two new genetic markers with the potential to predict myelosuppression induced by gemcitabine/carboplatin chemotherapy.

# Check list

- Summarize the six bioinformatics methods and the results.
- Look up the allele frequencies and genotype frequencies for rs1453542  and rs5925720 in a Japanese population.
  - Use dbSNP of NCBI.
- Estimate the number of patients who get gemcitabine/carboplatin chemotherapy in Japan.
  - Estimate the number of patients who may be benefited from the genetic tests for these alleles.