Exome sequencing for drug adverse reaction analysis
An application

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.