Poster

[P27-10] P27-10: Pharmacokinetics and pharmacogenetics

Chair: Andrew Somogyi, Australia

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[P27-10-4] The use of next-generation sequencing (NGS) data in pharmacogenetics: a software for allele calling based on star nomenclatures

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Background

“Star” nomenclatures available through public databases are commonly used in pharmacogenetics to report patient genotypes. Each variant allele (*2, *3, *etc.*) corresponds to a gene version with one or more Short Nucleotide Variations (SNV) as compared to the reference (*1) allele sequence. Next generation sequencing (NGS) enables determinations of SNV throughout large genome sequences (e.g. gene panels, exome) but does not directly infer variant alleles using star nomenclatures.

Methods

We developed a java software to retrieve SNV belonging to a relevant panel of pharmacogenes (P450, POR, UGT, TPMT, NAT) and to quickly and easily conclude on patient genotypes using star nomenclatures. The software uses VCF (Variant Calling Format) files (i.e. the NGS output file format for storing variants) based on GRCh37 or GRCh38 genomes. It relies on public data extracted from nomenclature websites[1] and the dbSNP database[2]. The software was tested in 16 patients with available exome (n=14) or panel-genes sequencing data (n=2). The variant alleles automatically identified were confirmed trough manual interpretation.

Results

For CYP2D6, all 16 patients had at least one variant allele. Six had a loss-of-function allele: the common *4 allele along with 3 others not routinely screened (*9, *59, 41). 1 patient had the *28 allele with unknown function. Others had normal function alleles, including *2, *34, *39. Minor frequencies were consistent with those reported for Caucasians[3]. In addition, we found 4 SNV in this gene unreported in the P450 nomenclature website, including 3 in the dbSNP[2]. The use of exome data was associated with a limitation: polymorphisms located in introns or promoters cannot be identified, which makes the determination of particular alleles impossible. A more general limitation is that large chromosomal rearrangements (e.g. deletion or duplication) cannot be reported.

Conclusions

An original software was developed to allow a quick determination of relevant variant alleles from NGS raw data. It might be very useful for the clinical implementation of NGS technology in pharmacogenetic labs. The software also differentiates unreported from reported variants which might be useful for research in pharmacogenetics.

[1] http://www.cypalleles.ki.se/;
[2] www.ncbi.nlm.nih.gov/projects/SNP/
[3] http://exac.broadinstitute.org