

Evaluating the significance of new pharmacogenetic associations

Perspectives

One of the major objectives of pharmacogenetic studies is to identify genetic predictors of drug-response. For efficacy, the study design should ideally be a randomised controlled trial. However, for adverse effects, reports often take the form of case reports, given the rarity of most severe adverse effects with licensed drugs. The challenge for the clinician is then to assess how clinically meaningful any reported association is.

Example

In a recent report (1), an association was shown between HLA*B1502 (coding for a human leukocyte antigen) and Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), two potentially life-threatening skin reactions. The case-control study of patients on carbamazepine included 42 patients with SJS/TEN and 42 drug-tolerant patients (see Figure 1).

HLA-B*1502 Positive	SJS/TEN		Total
	Cases	Controls	
Yes	37	5	42
No	5	37	42
Total	42	42	84

Fig.1 Case-control data on carbamazepine-associated SJS/TEN

From this table, the sensitivity (SN), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) were 88%, 88%, 1.9% and 100%, based on a prevalence of SJS/TEN of 0.27%. How to calculate the test metrics from the observed data is explained in the accompanying factsheet '*The Genomic Basis of Therapeutics: Part 10, Calculating screening test-performance metrics*'.

What can you infer from these test characteristics about the value of genotyping for the HLA variant to prevent SJS/TEN?

Practical implications

- Not all patients (1 in 10) with SJS/TEN will be identified by the test for the HLA variant
- Some patients (1 in 10) without the variant will still develop SJS/TEN
- Of 100 patients with the variant only 2 are expected to develop the complication
- Virtually every patient without the HLA variant will also be free of this complication, as expected from the low incidence of SJS/TEN anyway
- Whether the test is worthwhile or not also depends on the prevalence of the variant allele in the target population. In the Thai population, this is about 8%, the Japanese 0.1% and in most Caucasian populations, virtually non-existent.
- Recent drug regulatory advice (2008) recommends testing for the variant allele in Thai, Han Chinese and Hong-Kong Chinese patients before prescribing carbamazepine when no alternative drug is appropriate. With similar strength of evidence for an association between the variant allele and phenytoin-induced SJS/TEN more recent advice (2010) is less supportive of screening.

Further reading

(1) Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Chen P, Lin SY, Chen WH, et al. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. *Epilepsia* 2010.