National Genetics Education and Development Centre

Assessing the clinical significance of a new variant allele

Perspectives

Genetic mutations may lead to formation of inactive metabolic enzymes (see *'The Genomic Basis of Therapeutics: Part 2 When usual doses lead to adverse effects: Polymorphisms of metabolic enzymes'*). New variant alleles are reported at regular intervals. There is then a need to assess the functional and clinical significance of such variants. Stopping a medication is often not an option and minor effects on extent of drug exposure (pharmacokinetics) can be managed clinically.

Example

CYP2C19 is an important enzyme involved in the metabolism of many widely used drugs. Recently a variant allele CYP2C19*17, which is associated with increased enzyme activity was discovered. The other well known variants of CYP2C19 are associated with reduced activity or loss of function.

How important is this variant likely to be clinically?

The metabolic ratio is given by the molar concentration of omeprazole divided by the concentration of the hydroxylated metabolite as shown in the figure. A higher ratio shows reduced metabolism. The figure clearly shows that the more significant variants are CYP2C19*2 and CYP2C19*3. For most drugs CYP2C19*17 is unlikely to be clinically relevant. CYP2C19*17 exerts a considerably smaller effect than CYP2C19*2 or CYP2C19*3.

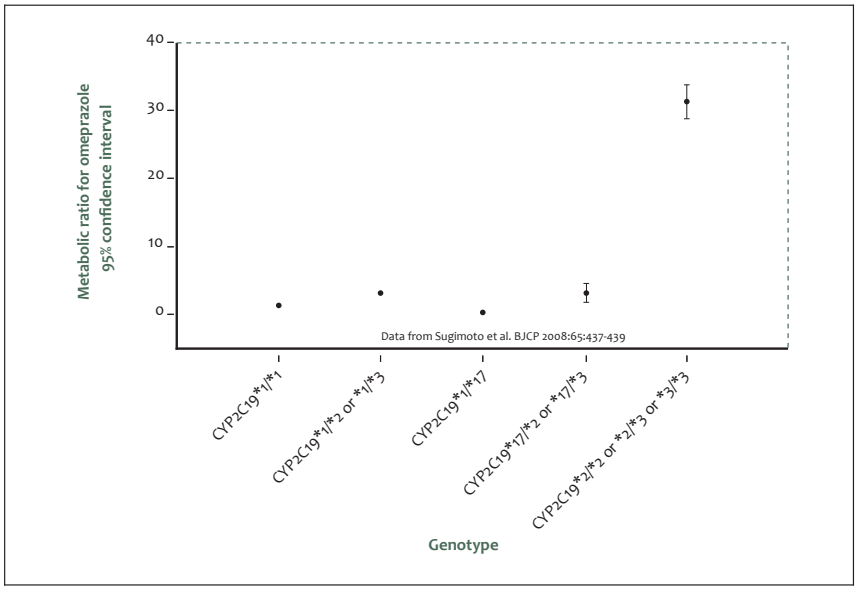

Fig. 1 Metabolic ratio for omeprazole as a function of CYP2C19 genotype

Further reading

Li Wan Po A, Girard T, Farndon P et al. Pharmacogenetics of CYP2C19: functional and clinical implications of a new variant CYP2C19*17. Br J Clin Pharmacol 2010; 69:222-230.