Case Study 3: Thiopurines

Another example of possible applications of pharmacogenetics is the metabolism of thiopurine drugs such as 6-mercaptopurine and the prodrug azathiopurine. Thiopurines are commonly used as anti-cancer agents and are increasingly used to help treat inflammatory diseases such as inflammatory bowel disease (IBD).

Thiopurines are enzymatically converted into active versions which take action on the cancer or reduce immune response. However levels of these anti-cancer agents are controlled in the body by an enzyme called thiopurine S-methyltransferase or TPMT. This enzyme ensures that levels of the thiopurine products do not rise too high, by metabolising them into inactive forms, which in turn prevents potential toxic damage to the bone marrow, which is known as myelosuppression.

There are two main genetic versions of the TPMT gene which are codominantly inherited, one for low- and high-level enzyme activity. Because every human has two versions of the same gene there are three possible phenotypes or identifiable characteristics:

1. Inherit two copies of the gene which indicate low enzyme activity. At risk of myelosuppression. Affects approximately 1/300 patients who receive thiopurine treatment. Very low or no dose administered. Represents 0.3% of population.
2. Inherit one copy of the gene which indicates low enzyme activity and one copy of the gene which indicates high enzyme activity. Intermediate level of enzyme activity. Low dose administered. Represents 11% of population.
3. Inherit two copies of the gene that indicate high enzyme activity. Normal dose administered. Represents 89% of population.


Implementing a pharmacogenetic test for patients before they receive thiopurine treatment may ensure that the correct drug, in terms of those who have two copies of the low activity gene, may be given alternatives to prevent an adverse drug reaction (myelosuppression) and to ensure the correct dose is given, as those who have one high and one low activity gene may not require the same level of dose when compared to those who have two copies of the high activity gene.