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Title: Analysis of *POR* gene mutations in patients with atypical drug responses
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Introduction:
Genetic variation impacts drug metabolism and is a possible factor in adverse drug reactions. Single Nucleotide Polymorphisms, commonly called SNPs, contribute to genetic variation. SNPs are changes in single bases of the DNA sequence which can have an effect on many biological processes, in this case, drug metabolising enzymes.

The POR gene encodes a protein essential for the CYP450 family of enzymes. These enzymes are essential for the metabolism of almost all drugs, from caffeine to opioids to cancer chemotherapy and more. The POR enzyme reactivates the CYP450 enzymes, so it is crucial for their activity. Genetic variation in the POR gene is therefore a possible explanation of multiple adverse drug reactions.

Aim:
This project aims to better understand how POR SNPs might contribute to adverse drug reactions by sequencing the POR gene from a select group of participants known to have experienced adverse drug reactions to multiple drugs.

Impact:
Because of its association with many drug metabolising enzymes, variations present in the POR gene may influence how many different drugs are metabolised, and therefore the kinds of side effects a patient may have. Knowledge of a patient's genetic profile can help inform health care providers of potential problems with prescribing certain medication.

Method:
Polymerase Chain Reaction assays were designed to amplify and sequence the POR gene, particularly the 16 coding regions, using up to 10 different reactions to cover the whole gene. These assays were applied to 24 participants selected from the Understanding Drug Reactions Using Genomic Sequencing (UDRUGS) project, run by the Carney Centre for Pharmacogenomics. Participants were selected based on having adverse reactions to multiple drugs. To analyse the sequence data, bioinformatic techniques were used. Geneious 9.0 was the software program used that produces a visualisation of sequence data to identify SNPs of interest.

Results:
Of the 22 SNPs that were investigated with a potential interest to drug metabolism, two people had none of these SNPS, five people had at least one SNP, seven people had two SNPs, three people had three SNPs, six people had four SNPs, and one person had five SNPs.

The SNP called *28 with ID number rs1057868 has a change in the genetic code from C to T, and is a relatively common SNP with a 33% frequency in the general population. In our cohort we had a higher frequency of 45%. This indicates that people who have adverse drug

reactions may be more likely to carry this SNP. This will require further investigation to determine statistical significance.

Three participants had two particular SNPs, *28 as mentioned above, and one with ID number rs2868177, which changes the genetic code from A to G. In combination, these two POR SNPs affect the activity of CYP2B6, which metabolises anaesthetics and opioids among other drugs.

Conclusion:

The POR gene has many variants and was challenging to sequence in particular regions, especially the promoter region. A larger sample size is needed to investigate statistical significance of multiple SNPs, and further analysis is required in order to understand whether genetic variation in POR is a factor in adverse drug reactions.