CYP genes and haplotypes in personalised medicine

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Brian Tait, Chief Scientific Officer at Haplomic Technologies Pty Ltd, focuses here on CYP genes, haplotypes, and their applications in personalised medicine

Knowing the genetic phase is important as proteins are coded for by genes in a cis transfiguration. When a gene has two or more polymorphisms, it is not possible to assign protein sequences unless the genetic phase is established definitely by family studies. Currently, mathematical approaches (LD-linkage disequilibrium) are used to assign the probability of phase and long-range sequencing (LRS).

LD and LRS, which both address this issue, are not 100% accurate, and the advantage of chromosome sequencing is that there are no limits to the base size of the phase achieved. This is in contrast to LRS, which has limits, at present, in the order of 10-20 k of base length.

Since haplotyping defines protein sequence, how important is it to define gene haplotypes in human disease studies and disease treatment? This question is prompted partly by the data, which suggests that gene expression can be influenced by other sequences that are remote from the target gene and act as promoters and enhancers. Some sequences bind to the 5’ portion of the molecule and are polymorphic.

The 20 mer miRNA molecules bind to the 3’ end of the gene and act as gene silencers. There are many reports of polymorphism in both the non-coding-coding part of the 3’ end of the gene, which binds the miRNA and the miRNA itself. If disease development depends on the gene expression level, then the polymorphism of these gene expression factors becomes of paramount importance. It should be noted that miRNA molecules are often located megabases away from their site of action and that they have been reported, in some cases, to act in a cis manner. This highlights the importance of establishing the genetic phase.

The first iteration of the single chromosome sequencing approach aims to provide HLA haplotype information on unrelated bone marrow donors to enable better HLA matching and improve patient and graft survival. We should note that this paper uses the word haplotyping in a non-traditional sense. Rather than referring to genes shown to be in linkage disequilibrium or on the same chromosome, as shown by family studies, it refers to the LD observed between SNPs that define an allele, mostly not confirmed by family studies.

However, there are other clinical situations where highly polymorphic genes are involved and where haplotyping (or genetic phasing) is important in understanding the impact of polymorphisms on gene function. Such a system is the CYP family of genes that control

the metabolism of many drugs, originally termed the P450 genes.

CYP gene polymorphisms

In humans, 57 families of CYP (p450 genes) are divided into 49 subfamilies. The products of these genes have enzymatic effects on many metabolic pathways, particularly from a clinical viewpoint, drug metabolism.

CYP gene nomenclature

The CYP genes have a defined nomenclature. A description is found on the PharmVar website . Essentially, the first two digits give the family number, e.g. CYP2, the third digit provides the subfamily with, for example, CYP2D and the fourth is the gene number, e.g. CYP2D6. For two CYP genes to belong to the same family, they have to share a minimum 40% amino acid sequence, while to belong to the same sub-family, they must share a minimum of 55% amino acid sequence. Since CYP2D6 is involved in the metabolism of approximately 20% of prescribed medications, this gene will be a major focus of this paper.

CYP2D6 is found on the short arm of human chromosome 22 and is located near 22q13.2. Also located nearby are CYP2D7 and CYP2D8, which are pseudogenes and make identifying the extensive polymorphism difficult. CYP2D6 polymorphisms include insertions and deletions, along with SNPs and structural variation. Structural variants include duplications, multiplications, and deletions of the entire gene and hybrid/ fusion genes. The multiplications can result in at least three copies of the CYP2D6 gene on one haplotype. The hybrid genes consist of the initial part of CYP2D6 followed by part of the CYP2D7 or CYP2D6 gene , making it a highly polymorphic gene.

CYP2D6 in drug metabolism and efficiency

In a recent review, Ianni et al. examined drug-gene interactions in various conditions. They reported that CYP2D6 was involved in over 25% of the metabolism of drugs used by prescription by older patients.

Nahid et al., in a recent study, investigated the comparative metabolic capabilities of CYP2D6 alleles CYP2D6*1, CYP2D6*2, CYP2D6*10, and CYP2D6*17 in the metabolism of tramadol and how these allelic variants responded to inhibition by common CYP2D6 inhibitors. They found that CYP2D6 alleles *2,*10 and *17) displayed different enzymatic activity towards tramadol, a drug commonly used in pain relief. They also demonstrated that the alleles *1 and *2 are more susceptible to inhibition than other alleles. Could part of this variation be due to the action of miRNA molecules?

In a metanalysis, Moore et al. investigated 5-HT3 antagonists, such as the drugs ondansetron, dolasetron and tropisetron, which are used effectively as anti-mimetics to reduce vomiting in cancer patients who are undergoing chemotherapy. Approximately

30% of ondansetron is metabolised by the products of the CYP2D6 gene with additional roles for CYP3A, CYP1A1and CYP1A2, whereas for the other two drugs, the figure is approximately 90%.

In a meta-analysis, this group demonstrated that postoperative nausea and vomiting (PONV) was associated with the CYP2D6 genotype in an analysis of 20 studies.

Ribeiro et al. concluded that the AA genotype of rs16947: G>A (one of allele *2 core variants) and AA of rs1065852:G>A (one of allele *10 core variants) was associated with decreased function and therefore affected the final outcome with ondansetron treatment.

In a recent review in 2022, Rykova et al. were able to show that there were SNPs in the 3' untranslated region of the CYP genes which have a direct impact on the binding of mi RNA molecules, hence reducing or eliminating the inhibitory effect these molecules have on expression. CYP2D6 was not one of the genes shown to possess these SNPs.

CYP3A5, a key metaboliser of tacrolimus, was shown to have such polymorphism in the 3' untranslated region. rs15524 affects the binding potential of human miRNA-500 found on chromosome x.

In the 3' untranslated region of the CYP2B6 gene, there is a SNP, rs707265 G allele, the change creating miR- 1623/4269 and 3622a 5p binding sites, absent in the A allele suggesting a role for miRNA molecules in CYP2B6 involvement in the metabolism of methadone as shown by Ipe et al.

CYP3A7 has been shown to influence the metabolism of tacrolimus in a study involving 138 liver transplant patients . The CYP3A7 SNP, rs10211 AA, was shown to be associated with twice the level of tacrolimus than seen with the AG and GG genotypes due to a reduction in CYP3A7 activity as postulated by Dong et al.. To fully utilise the information obtained by CYP allele typing, for all patients, will involve the definition of the alleles by family studies or single chromosome sequencing. LRS or LD does not pass muster.

Numerous studies have been conducted about Caucasian patients, and it is well-known that genetic linkage groups vary from ethnic group to ethnic group.

In addition, the LD groups can differ in disease patients and ethnically matched controls in human disease studies. The impact of the numerous miRNA molecules, which are often coded by non-coding portions of genes on different chromosomes to the target gene, will require genetic phasing to appreciate the full impact of their effect on the expression of the target gene. The PHARMVAR website has stressed the importance of establishing the genetic phase (haplotyping) in CYP genes .

Conclusions

Determining relevant CYP alleles before treatment in individual patients results in rapidly decreasing unwanted drug side effects, so-called personalised medicine (PM). Before the full extent of PM can be realised, alleles need to be sequenced in a single chromosome

sequencing platform, and the complex areas of polymorphisms are defined as alleles. This step will have to be done in all racial groups studied.

In addition, the 3’ region of the CYP gene sequence has to be linked to the appropriate miRNA, as the level of expression of the CYP gene is critical to its function. The non-coding region of the gene that produces the miRNA will also be sequenced on a single chromosome sequencing platform to enable the phase. The future of PM is exciting, and single chromosome sequencing will be a part of it.

References

1. Kitcharoen K. et al. 2006. Human Immunology; 67(3); pp.238-246.
2. Petersdorf E. et al 2007. PLoS Medicine; 4(1); p. e8.
3. Maskalana, M. et al 2020. Human Immunology 81 pp12-17.
4. Pharmacogene Variation Consortium (PharmVar) at https://www.pharmvar.org/
5. –
    1. Gaedigk et al. 2021, CPT 110:542-545 (PMID 34091888.
    2. Gaedigk et al. 2020, CPT 107:43-46 (PMID 31758698.
    3. Gaedigk et al. 2019, CPT 105:29-32.
    4. Gaedigk et al. 2018, CPT 103(3):399-401 (PMID 29134625.
6. Ianni et al.2025 Clin. and Translational Science Volume18, Issue 2.
7. Gebauer et al 2012 Cold Spring Harb. Perspect. Biol. 4: a012245).
8. Nahid et al 2025 Clin Transl. Sci. 18: e70059.;pp1-9. https://doi.org/10.1111/cts.7.
9. Moore et al. 2025 Clinical and Translational Science v18 (2) https://doi.org/10.1111/cts.70108
10. Riberio 2024 Braz. J. Anesthesiol. 74(3):744423. doi: https://doi.org/10.1016/j.bjane.2023.02.00225.
11. Rykova et al 2022. Int. J. Mol. Sci, 23, 13725. https://doi.org/10.3390/ijms232213725
12. Ipe et al 2018 Front Genet., 9, 2.
13. Dong et al. 2022. Gene, 809, 146007.