Fighting adverse drug reactions (ADR), a cyp450 genetic test panel with reported allele frequencies of cyp2c9, 2c19 and 2d6 in a Danish population

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Aims: Allelic variations in CYP450 2C9, 2C19 and 2D6 genes are relatively frequent, resulting in either slow, intermediate, normal or fast metabolism of many commonly used drugs. Here we provide a tool for finding patients with either a slow or fast liver metabolism of these drugs. A slow metabolism because of one or two non-functional copies can result in the accumulation of high drug concentrations with severe ADR. A faster than normal metabolism of the drugs can lead to no or little effect of the drug, and can help explain a suspicion of non-adherence. Examples of drugs are Tamoxifen, Codeine, and Nortrityline metabolized by 2D6, Warfarin and Phenytoin metabolized by 2C9, and Clopidogrel, Citalopram and Sertraline metabolized by 2C19. Some of these are prodrugs that needs to be metabolized in order to be active. For all of the drugs mentioned, recommended dosing guidelines exist for patients with variations in the CYP genes.

Method: We have established a test panel based on Taqman chemistry, where we can detect the 8 most frequent alleles from 2D6 in addition to detecting deletion/duplications, 4 most frequent alleles from 2C19, and 2 from 2C9.

Results: In 2017 we analyzed 220 individuals for 2D6, 120 individuals for 2C19 and 56 individuals for 2C9. For individuals analyzed for 2D6, 9% have no functional genes and possible ADR. 4% have only one partially functioning 2D6 gene. This genotype leads to decreased enzyme activity, but the clinical consequences cannot be completely determined. Finally, five patients have additional copies of the gene, of which 2 (1% of total) would be characterized as Ultrafast metabolizers (UM). For Individuals analyzed for allelic variants in 2C19, 1% have no functional alleles leading to possible ADR. 22% have one functioning alleles with decreased enzyme activity. This genotype is characterized as an Intermediate metabolizer. 4% carry 2C19 with increased activity from both allels. This will either lead to low concentration of drugs due to higher metabolization, or in case of prodrugs, it will lead to increased levels of the active drug. For individuals analyzed for 2C9, 34% have one partially functioning gene leading to lower enzyme activity, with consequences as mentioned above.

Conclusion: With this panel we cover most CYP alleles that can impact drug metabolism. In the near future, we hope to expand this panel so that even more genes that play a role in ADR can be genotyped. These assays have been established in our laboratory, and are performed every week.