PATHWAY-DRIVEN MOLECULAR AUTOPSY OF TRAMADOL-EXPOSED INDIVIDUALS

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In 2005 a 13-day old neonate was found deceased; the cause of death was morphine poisoning but manner of death was unknown. An infanticide investigation determined the death was accidental after genotyping cytochrome p450 family 2 subfamily D polypeptide 6 (*CYP2D6*). The mother had been prescribed codeine for post-partum pain, and her genetic make-up was such that she was an ultra-rapid metabolizer (UM) of codeine. As a UM she produced a toxic concentration of circulating morphine that was subsequently delivered to the child during breastfeeding. This case demonstrates how post-mortem genotyping of metabolically relevant targets may aid in civil/criminal investigations. CYP2D6 is responsible for ~30% of phase I metabolism of drugs/toxins. The gene is typically interrogated with restriction enzyme reactions and/or single nucleotide variant (SNV) genotyping to identify haplotypes or star (*) alleles. The combination of *CYP2D6* * alleles forms a diplotype which has been correlated with rate of drug metabolism in various populations. While predictive, there are many population groups exhibiting diplotype-phenotype discordance. It is known that drug ADME-R (**a**bsorption, **d**istribution, **m**etabolism, and **e**xcretion and **r**esponse) are the result of protein pathways, not the activity of a single protein. It is likely that this discordance is due to lack of information as diagnostics focus on a single protein or targeted SNVs of a single gene in the pathway. A predictive model was developed which employs representative proteins/genes along the tramadol ADME-R pathways. *CYP2D6* classifies individuals into metabolizer phenotypes (MP) with high accuracy; however, addition of uridine diphosphate glucuronosyltransferase, family 1, polypeptide B7 (*UGT2B7*), ATP binding cassette, subfamily B, number 1 (*ABCB1*), opioid receptor mu 1 (*OPRM1*), and catechol-O-methyltransferase (*COMT*) increase classifier accuracy. Feature selection and supervised machine learning demonstrate the utility of a substantially reduced number of SNVs that predict MP with accuracies comparable to those using the entire exome of these five genes. Consequently, either massively parallel sequencing or small multiplexed capillary electrophoresis panels may be developed for clinical diagnostics and/or medico-legal death investigations. This presentation will describe the field of molecular autopsy, the genetic component(s) and bioinformatic advances for predicting MP, and the findings of genetic association studies from a cohort of Finns exposed to tramadol prior to death.