# CASE STUDY

## INDIVIDUAL SUSCEPTIBILITY

BY TOXLEARN4EU
FUNDED BY ERASMUS+

## Problem Based Learning (PBL)

## WP5 – Risk assessment, policy and risk communication

**Topic:** CASE: Individual susceptibility

Toxic effects of drugs – a matter of vulnerability?!

**Part A:**

The death of an apparently healthy Toronto newborn, who died last year from opiate toxicity that was present in breast milk, has renewed the debate over prescribing Tylenol-3 to breastfeeding mothers. After the baby's death, doctors at Toronto Hospital issued a warning that codeine given for postnatal pain can produce deadly concentrations of morphine in breast milk.

Tariq Jamieson was delivered vaginally at full term and healthy weight — everything appeared normal. His mother Rani suffered some lingering pain from an episiotomy, so she was prescribed 2 tablets of Tylenol-3 twice daily — a common pain treatment for mothers who have just given birth. Doctors halved the dose after 2 days due to constipation and somnolence.

Tariq developed increasing lethargy from the 7-day mark, and at 11 days was the child was brought to a pediatrician due to concerns about his skin color and poor feeding. He had, however, regained his birth weight. Two days later the family called an ambulance. Responders found the infant cyanotic and lacking vital signs. Attempts at resuscitation failed.

On postmortem analysis, the child was found to have a blood concentration of acetaminophen of 5.9 µg/mL and morphine 70 ng/mL. This morphine concentration is about 6 times higher than would normally be considered safe in a neonate.

Tylenol-3 contains 500 mg of acetaminophen and 30 mg of codeine. Not all patients metabolize codeine at the same rate. Ms. Jamieson was genotyped and found to carry three copies of the CYP2D6 gene. This essentially made her a so-called ultra-rapid metabolizer of codeine to morphine, leading to an unexpectedly fast build-up of the opiate in her breast milk.

Also other factors might be involved. It is well known that other drugs and nutrition (e.g. grapefruit juice) can modify the action of codeine and knowledge regarding this clinical problem is advancing. The contribution of these factors to Tariq`s death is not known.

**Part B:**

Students at Maastricht university in the Netherlands determined their individual CYP2D6 genetic variant. Sample collection is very simple and requires only a buccal swab, from which sufficient DNA can be obtained to determine the CYP2D6 gene variant by real time polymerase chain reaction (RT-PCR) assays.

The data of these students can be found in the excel file as supplementary material.

Evaluate the data as follows:

- Calculate the distribution of the CYP2D6 gene variants (absolute counts and percentage of total population) in the student population.
- Calculate the distribution of the CYP2D6 phenotypes (absolute counts and percentage of total population) in the student population.
- Visualize all these data in a suitable graphs (e.g. 4 different bar charts). Pay attention to correctly label the x- and y-axes.
- Does the distribution of the gene variants and metabolizer phenotypes differ from your expectations on basis of literature? Elaborate at least 3 reasons which could contribute to the fact that the data of the student population differ from literature data.

**Information sources:**

General chapter on pharmacogenomics in Rang & Dale, Katzung et al. and/or Goodman & Gilman`s.

Feero WG, Guttmacher AE, & Collins FS. (2010). Genomic medicine-an updated primer. The New England Journal of Medicine, 362(21), 2001-2011.

P. A. H. M. Wijnen, R. A. M. op den Buijsch, M. Drent, P. M. J. C. Kuijpers, C. Neef, A. Bast, O. Bekers, G. H. Koek. Review article: the prevalence and clinical relevance of cytochrome P450 polymorphisms, Alimentary Pharmacology & Therapeutics, 26, s2, 2007; https://doi.org/10.1111/j.1365-2036.2007.03490.x

Gasche Y. et al. 2004. Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism. The New England Journal of Medicine 351(27):2827–31.

Ingelman-Sundberg M. 2005. Genetic Polymorphisms of Cytochrome P450 2D6 (cyp2d6): Clinical Consequences, Evolutionary Aspects and Functional Diversity. The Pharmacogenomics Journal 5(1):6–13.

Petrović, J., Pešić, V. & Lauschke, V.M. Frequencies of clinically important CYP2C19 and CYP2D6 alleles are graded across Europe. Eur J Hum Genet 28, 88–94 (2020). https://doi.org/10.1038/s41431-019-0480-8

Relevant website:

· Pharmacogene Variation Consortium: https://www.pharmvar.org/gene/CYP2D6