

Supplementary material to:

**The evaluation of *CYP2D6*, *CYP2C9*, *CYP2C19*, and *CYP2B6* phenoconversion in post-mortem casework: the challenge of forensic toxicogenetics**

**Table S1.** List of genotyped variants for *CYP2D6*, *CYP2C9*, *CYP2C19* and *CYP2B6*.

Gene symbol	dbSNP reference (variant allele)	Function
<i>CYP2D6</i> [59,33]	( <i>CYP2D6</i> *1)	Wild type (Normal function)
	rs16947 ( <i>CYP2D6</i> *2)	Normal function
	rs35742686 ( <i>CYP2D6</i> *3)	No function
	rs3892097 ( <i>CYP2D6</i> *4)	No function
	rs5030655 ( <i>CYP2D6</i> *6)	No function
	rs5030656 ( <i>CYP2D6</i> *9)	Decreased function
	rs1065852( <i>CYP2D6</i> *10)	Decreased function
	rs28371706( <i>CYP2D6</i> *17)	Decreased function
	rs28371725( <i>CYP2D6</i> *41)	Decreased function

	rs79292917( <i>CYP2D6</i> *59)	Decreased function
<i>CYP2C9</i> [60]	( <i>CYP2C9</i> *1)	Wild type (Normal function)
	rs179985( <i>CYP2C9</i> *2)	Decreased function
	rs1057910( <i>CYP2C9</i> *3)	No function
	rs28371686 ( <i>CYP2C9</i> *5)	Decreased function
	rs28371685( <i>CYP2C9</i> *11)	Decreased function
<i>CYP2C19</i> [60]	( <i>CYP2C19</i> *1)	Wild type (Normal function)
	rs4244285 ( <i>CYP2C19</i> *2)	No function
	rs4986893 ( <i>CYP2C19</i> *3)	No function
<i>CYP2B6</i> [53,42]	( <i>CYP2C2B6</i> *1)	Wild type (Normal function)
	rs8192709( <i>CYP2B6</i> *2)	Normal function
	rs2279343( <i>CYP2B6</i> *4)	Increased function
	rs3211371( <i>CYP2B6</i> *5)	Normal function
	rs12721655( <i>CYP2B6</i> *8)	No function

	rs3745274( <i>CYP2B6</i> *9)	Decreased function
	rs28399499( <i>CYP2B6</i> *18)	No function
	rs34826503( <i>CYP2B6</i> *19)	Decreased function
	rs34223104 ( <i>CYP2B6</i> *22)	Increased function

**Table S2.** General parameters useful for CYP2D6, CYP2C9, CYP2C19 and CYP2B6 to determine the g-phenotype starting from the activity\* score (\*only CYP2D6, CYP2C9) and the p-phenotype considering the drugs found in the samples. Starting AS: activity score based on genotype. Adjusted AS: activity score adjusted according to the models described in the literature. g-phenotype: genotype-based phenotype. p-phenotype: phenoconversion-induced phenotype. IM: intermediate metabolizers, NM: normal metabolizers, PM: poor metabolizers, UM: ultrarapid metabolizers. For homogeneous classification UM was converted in EM: extensive metabolizers (for CYP2B6).

<i>CYP2D6</i>				
Starting AS	g-phenotype	Inhibitor (multiplicative factor)	Adjusted AS	p-phenotype
0	gPM	strong (0)	0	PM
		Moderate \ weak (0,5)	0	PM
$0 < x < 1.25$	gIM	strong (0)	0	PM
		Moderate \ weak (0,5)	$0,13 < x < 0,5$	IM
$1.25 \leq x \leq 2.25$	gNM	strong (0)	0	PM
		Moderate \ weak (0,5)	$0,63 < x < 1,13$	IM
> 2.25	gUM	strong (0)	0	PM
		Moderate \ weak (0,5)	>1,25	NM

<i>CYP2C9 and CYP2C19</i>			
Starting AS*	g-phenotype	p-phenotype with Inhibitor	p-phenotype with Inducer
0 < x < 0,5	gPM	PM	PM
1 < x < 1,5	gIM	PM	NM
2	gNM	PM	UM
> 2	gUM	IM	UM
<i>CYP2B6</i>			
	g-phenotype	p-phenotype with inhibitor	p-phenotype with inducer
-	gPM	PM	IM\EM
-	gIM	PM	high IM\EM
-	gNM	low IM\PM	EM
-	gEM	high IM	EM
*only CYP2C9			

**Table S3. Specifications of the samples included in the study.** Case number (n) (PHG: phenoconversion), gender, age, ethnicity, Cause (CoD) and Manner of death (MoD) as well as toxicological results including ethanol of the post-mortem cases analysed.

Case n.	Gender	Age	Ethnicity	Past history	CoD	MoD	Ethanol (g/l)	Toxicological results (ng/ml)
PHG1	M	43	European	Unknown	Asphyxia	Suicide	-	Tramadol 904.7
PHG2	F	52	European	Psychiatric disease, drug abuse	Acute intoxication by multiple substances	Suicide	-	Morphine 491.6, THC 3.8, citalopram 389.3 nordazepam 189.9 diazepam 222.6 quetiapine 451.5
PHG3	F	37	European	Drug abuse, epilepsy	Acute intoxication by morphine	Accident	-	Morphine 500, dextromethorphan, hydromorphone, clotiapine 26

<b>PHG4</b>	F	55	European	Psychiatric disease	Acute intoxication by multiple substances	Suicide	-	Codeine 749, tramadol 788, oxycodon 352, O-desmethyltramadol, oxymorphone, paracetamol
<b>PHG5</b>	F	32	European	-	Acute intoxication by multiple substances	Accident	-	Cocaine 6,393, methadone 1,679, chlorpromazine 60.2, desalkylfluorazepam 64.8, diazepam 40 ng/ml, nordazepam 53.5 mirtazapine 186.6
<b>PHG6</b>	M	37	European	Unknown	Acute intoxication by multiple substances	Accident	-	Morphine 315, codeine 46, paroxetine 35.5, norketamine, dextromethorphan, hydromorphone
<b>PHG7</b>	M	44	European	Unknown	Acute intoxication by multiple substances	Accident	0.18	Cocaine 3,796, mirtazapine > 2000, paroxetine 1,217.9, lorazepam 277.6 trazodone 2,158.6
<b>PHG8</b>	M	31	European	Psychiatric disease	Blunt trauma	Accident	-	Clozapine 943.3, haloperidol 21.1, diazepam 198.6, nordazepam 287.7
<b>PHG9</b>	M	51	European	Hepatitis C	Blunt trauma	Accident	2.34	Amitriptyline, nortriptyline
<b>PHG10</b>	M	36	European	Unknown	Burning	Suicide	-	Diazepam 153.6, nordazepam 257.7 fluoxetine < 600, desalchylflurazepam 206.5, trazodon 176.8, norfluoxetine
<b>PHG11</b>	M	35	European	Psychiatric disease, hepatitis C, neurological disease	Acute intoxication by multiple substances	Accident	-	Cocaine 2,265, methadone 255.6, diazepam 15.9, venlafaxine 569.6, o-desmethylvenlafaxine 194.3
<b>PHG12</b>	M	69	European	Psychiatric disease	Blunt trauma	Accident	0.80	Paroxetine 269, ketamine, midazolam 72
<b>PHG13</b>	M	30	Mediterranean	Unknown	Acute intoxication by multiple substances	Accident	0.67	Methadone 1,065, morphine 19, diazepam 187, nordazepam 192, temazepam traces, olanzapine >145; citalopram >259
<b>PHG14</b>	F	47	European	Psychiatric disease	Blunt trauma	Accident	-	Methadone 347, fluoxetine 3,235, nordiazepam, olanzapine 957.14, paracetamol, trazadon 107.2, diazepam, desmethylolazapine 25.9, clotiapine traces
<b>PHG15</b>	M	35	Mediterranean	-	Acute intoxication by	Accident	-	Methadone 441.9, promazine 44, diazepam traces, mirtazapine 5.9, tramadol traces

					multiple substances			
<b>PHG16</b>	M	53	Arabian Peninsula	Psychiatric disease, drug abuse	Sudden cardiac death	Natural	2.76	Nordiazepam 42.1, lidocaine, mirtazapine 130.4, metoprolol, amiodarone 29.9, diazepam 98.3, clotiapine 10.7
<b>PHG17</b>	M	40	European	Psychiatric disease	Asphyxia	Accident	-	7-aminoclonazepam 54.1, levomepromazine 36.7, quetiapine 91.3, norquetiapine 224.4, valproic acid 4.8 microgram/ml
<b>PHG18</b>	M	80	European	-	Sudden cardiac death	Natural	-	Amitriptyline 126.0, nortriptyline 64.2, sertraline 208.1, N-desmethylsertraline 192.2, promazine traces, trazodon traces, lorazepam 328.8
<b>PHG19</b>	M	85	European	-	Blunt trauma	Accident	-	Fentanyl, lidocaine, paracetamol, promazine
<b>PHG20</b>	M	57	European	-	Sudden cardiac death	Natural	0.11	Paroxetine 259.2, alprazolam 26.4
<b>PHG21</b>	M	44	European	Psychiatric disease	Acute intoxication by olanzapine		-	Olanzapine > 2000 ng/m; desmethylolanzapine 92.1 ng/ml
<b>PHG22</b>	M	58	European	Drug abuse	Acute intoxication by multiple substances	Accident	-	Methadone 297, levomepromazine, 83 paroxetine 126.1, quetiapine, norquetiapine, ephedrine, pseudoephedrine
<b>PHG23</b>	M	43	European	Psychiatric disease, epilepsy	Acute intoxication by multiple substances	Suicide	-	Methadone 77.7, morphine 1,069.2, nordazepam 144.7, diazepam 33.7, oxazepam 49.8, temazepam 23.2
<b>PHG24</b>	M	44	European	-	Acute intoxication by multiple substances	Accident	-	Cocaine 1,380, methadone 80, morphine 582, codeine 43
<b>PHG25</b>	M	41	European	-	Acute intoxication by methadone	Accident	0.67	Methadone 437.14
<b>PHG26</b>	F	32	European	Drug abuse	Acute intoxication by multiple substances	Accident	-	Cocaine 5,915, methadone 1,523, chlorpromazine 45.7, 52.6, diazepam 53 ng/ml, nordazepam 46.2 mirtazapine 157.6

<b>PHG27</b>	M	26	European	Drug abuse	Acute intoxication by methadone	Accident	-	Methadone 905.9
<b>PHG28</b>	M	25	European	-	Acute intoxication by multiple substances	Accident	-	Methadone 33, morphine 158
<b>PHG29</b>	M	56	European	Drug abuse, HIV	Acute intoxication by multiple substances	Accident	-	Cocaine 137, methadone 506, diazepam 999, nordazepam 910
<b>PHG30</b>	M	31	European	Psychiatric disease, alcohol abuse	Acute intoxication by multiple substances	Accident	-	Methadone 342.5
<b>PHG31</b>	M	30	Mediterranean	Alcohol abuse	Acute intoxication by multiple substances	Accident	0.67	Methadone 1,065, morphine 52, diazepam 187, nordazepam 192, temazepam traces, olanzapine >145, citalopram >259
<b>PHG32</b>	F	31	European	Drug abuse	Blunt trauma	Suicide	-	Methadone 1,112.4, THC 2.1, diazepam 60.5, nordazepam 78.5, mirtazapine 11.4
<b>PHG33</b>	M	28	Arabian Peninsula	Psychiatric disease, drug abuse	Acute intoxication by methadone	Accident	-	Methadone 441.9, promazine 44, diazepam traces, mirtazapine 5.9, tramadol traces
<b>PHG34</b>	M	40	European	Drug abuse	Acute intoxication by multiple substances	Accident	-	Cocaine 138, methadone 503, paroxetine 43, trazodone 291, aripiprazole 52
<b>PHG35</b>	M	46	European	Drug abuse	Acute intoxication by multiple substances	Accident	-	Methadone 272, morphine 621.8, codeine 46.3, phenacetin

**Table S4. Genotype, g-phenotype and p-phenotype for CYP2D6, CYP2C9, CYP2C19, CYP2B6.** Case number (n), PHG: phenoconversion, g-phenotype: phenotype based on genotype, p-phenotype: phenoconversion-induced phenotype. na: not applicable because both inhibitors and inducers are present, nd=not determined, \*=samples containing inhibitors (lidocaine and olanzapine) but information on their strength is lacking in the literature.

Case n.	Genotype CYP2D6	g-phenotype CYP2D6	p-phenotype CYP2D6	GenotypeCYP2C9	g-phenotype CYP2C9	p-phenotype CYP2C9	Genotype CYP2C19	g-phenotype CYP2C19	p-phenotype CYP2C19	GenotypeCYP2B6	g-phenotype CYP2B6	p-phenotype CYP2B6
PHG1	*1\*2	gNM	IM	*1\*1	gNM	PM	nd	nd	nd	nd	nd	nd
PHG2	*4\*5	gPM	PM	*1\*2	gIM	NM	*1\*1	gNM	PM	*1\*6	gIM	high-IM\EM
PHG3	*1\*1	gNM	NM	*1\*1	gNM	NM	*1\*2	gIM	NM	*1\*5	gNM	NM
PHG4	*1\*2	gNM	NM	*1\*1	gNM	NM	*1\*1	gNM	NM	*1\*1	gNM	NM
PHG5	*1\*1 x3	gUM	PM	*1\*1	gNM	NM	*1\*1	gNM	PM	*1\*6	gIM	high-IM\EM
PHG6	*1\*1	gNM	PM	*1\*2	gIM	PM	*1\*1	gNM	NM	*1\*4	gEM	high-IM
PHG7	*1\*1 x3	gUM	PM	*1\*2	gIM	NM	nd	nd	nd	*1\*9	gIM	PM
PHG8	*10\*10	gIM	PM	*1\*1	gNM	NM	nd	nd	nd	*1\*4	gEM	EM
PHG9	*2\*2 x3	gUM	UM	*1\*1	gNM	NM	nd	nd	nd	*1\*4	gEM	EM
PHG10	*2\*2	gNM	PM	*1\*2	gIM	PM	nd	nd	nd	*1\*6	gIM	high-IM\EM
PHG11	*2\*2	gNM	PM	*1\*1	gNM	NM	*1\*2	gIM	PM	*1\*6	gIM	high-IM\EM
PHG12	*1\*41 x3	gUM	PM	*2\*3	gPM	PM	*1\*2	gIM	NM	*1\*6	gIM	PM
PHG13	*1\*2 x4	gUM	IM	*1\*1	gNM	PM	*1\*1	gNM	PM	*1\*1	gNM	EM
PHG14	*2\*2	gNM	PM	*1\*1	gNM	PM	*1\*1	gNM	PM	*1\*6	gIM	high-IM\EM



PHG1 5	*1\*1	gNM	IM	*1\*1	gNM	NM	*1\*1	gNM	PM	*1\*5	gNM	EM
PHG1 6	*41\*41	gIM	IM	*1\*1	gNM	PM	*1\*1	gNM	PM	*1\*4	gEM	EM
PHG1 7	*1\*4	gIM	PM	*1\*2	gIM	PM	*1\*1	gNM	PM	*1\*4	gEM	EM
PHG1 8	*4\*41	gIM	IM	*1\*1	gNM	PM	*1\*2	gIM	PM	*1\*6	gIM	PM
PHG1 9	*2\*41	gNM	IM or PM*	*1\*2	gIM	NM	*1\*2	gIM	NM	*1\*7	gIM	IM
PHG2 0	*4\*10	gIM	PM	*1\*3	gIM	PM	*1\*1	gNM	NM	*1\*1	gNM	lowIM\PM
PHG2 1	*1\*1	gNM	IM or PM*	*1\*1	gNM	NM	*1\*1	gNM	PM	*1\*1	gNM	NM
PHG2 2	*2\*2	gNM	PM	*1\*1	gNM	PM	*1\*1	gNM	NM	*1\*1	gNM	na
PHG2 3	*2\*4	gIM	PM	*1\*2	gIM	na	*1\*1	gNM	na	*1\*5	gNM	EM
PHG2 4	*1\*4	gIM	IM	*1\*1	gNM	UM	*1\*1	gNM	PM	*1\*5	gNM	EM
PHG2 5	*1\*4	gIM	IM	*1\*1	gNM	NM	*1\*1	gNM	NM	*1\*7	gIM	high- IM\EM
PHG2 6	*1\*1	gNM	PM	*1\*1	gNM	NM	*1\*1	gNM	PM	*1\*6	gIM	high- IM\EM
PHG2 7	*2\*41	gNM	IM	*1\*1	gNM	NM	*2\*2	gPM	NM	*2\*5	gNM	EM

<b>PHG2 8</b>	*1\*4	gIM	IM	*1\*1	gNM	NM	*1\*1	gNM	NM	*1\*7	gIM	high- IM\EM
<b>PHG2 9</b>	*1\*1	gNM	PM	*1\*1	gNM	NM	*1\*1	gNM	PM	*1\*1	gNM	EM
<b>PHG3 0</b>	*2\*4	gIM	IM	*1\*2	gIM	NM	nd	nd	nd	*1\*22	gEM	EM
<b>PHG3 1</b>	*1\*2	gNM	IM	*1\*1	gNM	PM	nd	nd	nd	*1\*1	gNM	EM
<b>PHG3 2</b>	*1\*4	gIM	IM	*2\*2	gIM	PM	*1\*1	gNM	PM	*1\*6	gIM	na
<b>PHG3 3</b>	*1\*2	gNM	IM	*1\*1	gNM	NM	*1\*2	gIM	PM	*1\*5	gNM	EM
<b>PHG3 4</b>	*2\*2 x4	gUM	PM	*1\*2	gIM	PM	*1\*1	gNM	PM	*1\*6	gIM	na
<b>PHG3 5</b>	*1\*1	gNM	IM	*1\*1	gNM	NM	*1\*1	gNM	NM	*1\*4	gEM	EM