**Table S1**. List of genes and SNPs considered in the present study.

| XME | Gene | SNP | Functional Consequence | AA change |
|---|---|---|---|---|
| **Phase I** | *CYP2A6* | rs28399433 - A/C | 2KB Upstream Variant | |
| | *CYP2B6* | rs3745274 - G/T | Missense Variant | Gln172His |
| | *CYP2E1* | rs2070673 - T/A | 2KB Upstream Variant | |
| | *CYP3A5* | rs776746 - C/T | Intron /Splice Acceptor Variant | |
| | *CYP2C19* | rs4244285 - G/A | Synonymous variant | Pro227Pro |
| | | rs12248560 - C/T | 2KB Upstream Variant | |
| **Phase II** | *COMT* | rs165599 - A/G | 3 Prime UTR Variant | |
| | | rs4680 - G/A | Missense Variant | Val158Met |
| | *GSTP1* | rs1695 - A/G | Missense Variant | Ile105Val |
| | *NAT2* | rs1801280 - T/C | Missense Variant | Ile114Thr |
| | | rs1799930 - G/A | Missense Variant | Arg197Gln |
| | | rs1208 - A/G | Missense Variant | Arg268Lys |
| | *UGT1A1* | rs4124874 - T/G | Intron Variant | |
| | *UGT2B7* | rs7662029 - G/A | Intron Variant | |
| | | rs7668258 - C/T | Intron Variant | |
| | *UGT1A6* | rs2070959 - A/G | Missense Variant | Thr181Ala |
| | *UGT1A10* | rs6759892 - T/G | Missense Variant | Ser158Ala |
| **Phase III** | *ABCB1* | rs2032582 - A/C | Missense Variant | Ser893Thr |
| | | rs1128503 - G/A | Synonymous variant | Gly412Gly |
| | *ABCC2* | rs2273697 - G/A | Missense Variant | Val417Ile |
| | | rs3740066 - C/T | Synonymous variant | Ile1324Ile |
| | *ABCG2* | rs2231142 - G/T | Missense Variant | Gln141Lys |
| | *SLC15A2* | rs2257212 - C/T | Missense Variant | Leu350Phe |
| | | rs1143671 - C/T | Missense Variant | Pro409Ser |
| | | rs1143672 - G/A | Missense Variant | Arg509Lys |
| | *SLC22A2* | rs316019 - C/A | Missense Variant | Ala270Ser |
| | | rs316019 - C/A | Missense Variant | Ser270Ala |
| | *SLCO1B1* | rs4149056 - T/C | Missense Variant | Val174Ala |
| | *SLCO1B3* | rs4149117 - G/T | Missense Variant | Ser112Ala |
| | | rs7311358 - A/G | Missense Variant | Met233Ile |
| **Others*** | *DPYD* | rs1801265 - A/G | Missense Variant | Cys29Arg |
| | *ITGB3* | rs5918 - T/C | Missense Variant | Leu59Pro |
| | *PGTS1* | rs5788 - C/A | Synonymous Variant | Gly213Gly |
| | | rs10306114 - A/G | 5 Prime UTR Variant | |
| | *PTGS2* | rs20417 - C/G | 2KB Upstream Variant | |

Underlined SNP were excluded from the analysis after quality control.

* These genes and relative polymorphisms were selected because deeply studied in relation to drug response, so likely affecting the risk or the clinical evolution of several diseases.

**Table S2**. Multinomial logistic analysis for multivariate genetic associations.

| | | *Comparison 1 (Age class 2 *vs* Age class 1) 65-89 years vs <65 years | | Comparison 2 (Age class 3 *vs* Age class 1) 90+ vs <65 years | | Comparison 3 (Age class 3 *vs* Age class 2) 90+ vs 65-89 years | |
|---|---|---|---|---|---|---|---|
| | Gene | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value |
| rs3745274-G/T | *CYP2B6* | 1.09 (0.70-1.67) | 0.702 | 0.62 (0.39-0.99) | 0.045 | 0.54 (0.34-0.84) | 0.006 |
| rs776746-G/A | *CYP3A5* | 1.03 (0.46-2.26) | 0.946 | 1.86 (0.88-3.91) | 0.101 | 1.93 (0.93-4.00) | 0.075 |
| rs4680-G/A | *COMT* | 1.39 (0.84-2.32) | 0.197 | 2.56 (1.56-4.21) | <0.001 | 1.93 (1.20-3.10) | 0.007 |
| rs2273697-G/A | *ABCC2* | 0.97 (0.62-1.53) | 0.914 | 1.28 (0.80-2.03) | 0.30 | 1.30 (0.83-2.05) | 0.253 |

*In each comparison the youngest group was considered as the reference category.

CI = Confidence interval. For both the comparisons 1 and 2 (both using the youngest group as reference category), Odd ratios (ORs) were obtained directly from the equations included in the models; for the comparison 3 (90+ years vs <65 years), ORs were obtained by difference of equations included in the models.