**Supplementary Table 1. Missense variant NMA analysis.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **Mutation** | **Normal Mode Analysis** | | | | **Computational Variant Effect Predictors** | | | |
| **∆∆G (kcal·mol-1)** | **∆∆S**  **(kcal·mol-1·K-1)** | **combined ∆∆G (kcal·mol-1)** | **Prediction**a | **SIFT**a | **PolyPhen-2**a | **CADD**a | **Consensus**a |
| *CYP2A13* | D158E | -0,693498 | 0,012 | -0,27696924 |  |  |  |  |  |
| *CYP2A13* | F453Y | 2,59731 | -0,087 | 1,0844178 | X | X | X | X | X |
| *CYP2A13* | R101Q | -0,137141 | 0,678 | -0,81147358 | X | X | X | X | X |
| *CYP2A13* | R494C | 2,68964 | 1,046 | -0,1494568 |  | X | X | X | X |
| *CYP2A13* | V323L | -0,218444 | -0,104 | 0,03347128 |  | X |  | X | X |
| *CYP2A13* | R257C | -2,3597 | 0,282227 | -1,21278024 | X |  | X |  |  |
| *CYP2A13* | I331T | 1,1793 | -0,288086 | 0,77079032 | X |  |  |  |  |
| *CYP2B6* | A102T | 0,816358 | -0,142 | 0,46925604 |  |  |  |  |  |
| *CYP2B6* | A407T | 0,0666466 | -0,007 | 0,033165708 |  |  |  |  |  |
| *CYP2B6* | G476D | 12,937 | -0,312 | 5,2655 | X | X | X | X | X |
| *CYP2B6* | G99E | 17,3674 | -0,964 | 7,679292 | X | X | X | X | X |
| *CYP2B6* | H247P | 1,78199 | 0,253 | 0,3937962 |  |  |  |  |  |
| *CYP2B6* | I328T | 2,55874 | 0,382 | 0,5444812 | X | X | X | X | X |
| *CYP2B6* | I382N | 4,51067 | 0,789 | 0,8303746 | X |  |  |  |  |
| *CYP2B6* | I391N | 2,9144 | 0,47 | 0,581072 | X | X | X | X | X |
| *CYP2B6* | K139E | 0,332693 | 0,909 | -0,89165666 | X | X | X | X | X |
| *CYP2B6* | K262R | -0,11128 | -0,148 | 0,1234736 |  |  |  |  |  |
| *CYP2B6* | L313I | 2,40625 | 0,154 | 0,741895 | X |  | X |  |  |
| *CYP2B6* | M198T | 2,02589 | 0,719 | -0,0354418 |  | X |  | X | X |
| *CYP2B6* | M459V | 1,17419 | 0,246 | 0,1706722 |  |  |  |  |  |
| *CYP2B6* | M46V | 3,41641 | 0,667 | 0,5511958 | X |  | X |  |  |
| *CYP2B6* | P428T | 3,86486 | -0,429 | 1,9491268 | X | X | X | X | X |
| *CYP2B6* | Q485L | -0,584528 | -0,388 | 0,21243936 |  | X | X | X | X |
| *CYP2B6* | R140Q | 0,0819975 | 0,106 | -0,08756095 |  |  |  |  |  |
| *CYP2B6* | R434Q | 0,466131 | 0,495 | -0,37727022 |  |  |  |  |  |
| *CYP2B6* | R487S | 1,58759 | 0,58 | -0,0463158 |  |  |  |  |  |
| *CYP2B6* | S259R | 0,15035 | 0,003 | 0,053773 |  | X | X |  | X |
| *CYP2B6* | V183I | -0,432545 | -0,259 | 0,1257129 |  |  |  |  |  |
| *CYP2B6* | Q172H | 3,345 | 1,04199 | 0,1040712 |  |  |  |  |  |
| *CYP2B6* | K262R | -0,421 | 0,6543 | -0,892796 | X |  |  |  |  |
| *CYP2B6* | P167A | 2,079 | 0,24316 | 0,5176808 | X | X | X | X | X |
| *CYP2B6* | R487C | 0,17 | 0,27051 | -0,2383712 |  |  |  |  |  |
| *CYP2B6* | R336C | 2,77 | 0,06836 | 0,9760368 | X | X | X | X | X |
| *CYP2B6* | V183G | 4,2 | -0,22363 | 1,8464656 | X | X | X | X | X |
| *CYP2B6* | K139E | -0,102 | -0,40039 | 0,4096768 |  | X | X | X | X |
| *CYP2B6* | T168I | 2,188 | 0,33496 | 0,4562848 |  |  |  |  |  |
| *CYP2B6* | I328T | 1,832 | 0,13672 | 0,5430336 | X | X | X | X | X |
| *CYP2C19* | I331V | 0,560533 | 0,183 | 0,00804254 |  |  |  |  |  |
| *CYP2C19* | W212X | 2,35528 | 1,468 | -0,7491536 | X |  |  |  |  |
| *CYP2C19* | R433W | 2,3425 | -0,768 | 1,75031 | X | X | X | X | X |
| *CYP2C19* | R132Q | 0,269454 | 0,031 | 0,06767252 |  | X | X | X | X |
| *CYP2C19* | W120R | 4,29131 | 0,993 | 0,5185378 | X | X | X | X | X |
| *CYP2C19* | R144H | 1,0455 | -0,147 | 0,56193 | X | X | X | X | X |
| *CYP2C19* | P227L | 1,71065 | -0,072 | 0,730687 | X | X | X | X | X |
| *CYP2C19* | R150H | 0,920755 | 0,162 | 0,1684469 |  |  |  |  |  |
| *CYP2C19* | R410C | 1,78773 | 0,654 | -0,0531426 |  | X | X |  | X |
| *CYP2C19* | R329H | -0,192877 | -0,225 | 0,17870674 |  |  |  |  |  |
| *CYP2C19* | S51G | 0,322177 | 0,504 | -0,44205274 |  |  |  |  |  |
| *CYP2C19* | R186P | 0,558345 | 0,932 | -0,8316689 | X |  |  |  |  |
| *CYP2C19* | G91R | 0,917492 | -0,042 | 0,39568696 |  | X | X | X | X |
| *CYP2C19* | R335Q | 1,10988 | 0,418 | -0,0464056 |  | X | X | X | X |
| *CYP2C19* | D256N | 0,136223 | 0 | 0,05176474 |  | X |  | X | X |
| *CYP2C19* | V374I | 0,413279 | -0,364 | 0,56472602 | X |  |  |  |  |
| *CYP2C19* | H78Y | -1,25142 | -0,377 | -0,0532996 |  |  |  |  |  |
| *CYP2C19* | H99R | -0,520979 | -0,669 | 0,55130798 | X |  |  |  |  |
| *CYP2C19* | D188N | 0,308117 | -0,063 | 0,18764446 |  | X |  | X | X |
| *CYP2C19* | E122A | 0,0390276 | 0,533 | -0,582129512 | X | X |  | X | X |
| *CYP2C8* | A238P | 3,9232 | -0,076 | 1,575936 | X |  |  |  |  |
| *CYP2C8* | G171S | -0,938687 | -0,546 | 0,25481894 |  |  |  |  |  |
| *CYP2C8* | I223M | -0,783911 | -0,159 | -0,11980618 |  |  |  |  |  |
| *CYP2C8* | I244V | 1,07585 | 0,253 | 0,125463 |  |  |  |  |  |
| *CYP2C8* | I264M | -0,261521 | -0,03 | -0,06577798 |  | X | X |  | X |
| *CYP2C8* | I269F | 1,4958 | 0,134 | 0,418324 |  | X | X | X | X |
| *CYP2C8* | I331T | 3,35775 | 0,322 | 0,915305 | X | X | X | X | X |
| *CYP2C8* | I331T | 3,35775 | 0,322 | 0,915305 | X | X | X | X | X |
| *CYP2C8* | K247R | 0,396455 | 0,015 | 0,1338529 |  |  |  |  |  |
| *CYP2C8* | K383N | 1,32454 | 0,589 | -0,1563548 |  | X | X | X | X |
| *CYP2C8* | L361F | 3,84962 | 0,018 | 1,4426956 | X | X |  |  |  |
| *CYP2C8* | R186G | 2,09486 | 1,053 | -0,3833132 |  | X | X | X | X |
| *CYP2C8* | V181I | -0,468388 | -0,368 | 0,23417256 |  |  |  |  |  |
| *CYP2C8* | R139K | -0,5106 | 0,51563 | -0,7715336 | X |  | X |  |  |
| *CYP2C8* | K399R | -0,4808 | 0,86914 | -1,1561408 | X |  |  |  |  |
| *CYP2C9* | A149T | 2,24048 | -0,466 | 1,3733024 | X | X | X | X | X |
| *CYP2C9* | A149V | 2,94853 | -0,344 | 1,5057214 | X |  |  |  |  |
| *CYP2C9* | D191G | 5,14328 | 0,445 | 1,4560464 | X | X | X | X | X |
| *CYP2C9* | D360E | 2,0968 | -0,204 | 1,025264 | X | X |  |  |  |
| *CYP2C9* | D49G | 5,17648 | -0,07 | 2,0454624 | X | X |  | X | X |
| *CYP2C9* | E300V | -0,933367 | -0,013 | -0,34011946 |  |  |  |  |  |
| *CYP2C9* | E326D | 5,00395 | 0,686 | 1,133181 | X | X | X | X | X |
| *CYP2C9* | E354K | 8,01916 | -0,05 | 3,1032808 | X | X | X | X | X |
| *CYP2C9* | F110S | 2,36825 | 0,404 | 0,447455 |  |  |  |  |  |
| *CYP2C9* | G40R | 31,8313 | -0,963 | 13,174454 | X |  |  |  |  |
| *CYP2C9* | G431R | 18,7053 | -0,781 | 7,982734 | X |  |  |  |  |
| *CYP2C9* | G442V | -0,657883 | -0,392 | 0,18904446 |  | X |  | X | X |
| *CYP2C9* | G70R | 10,2831 | -0,593 | 4,571738 | X | X | X | X | X |
| *CYP2C9* | G96A | 0,79321 | -0,21 | 0,5366198 | X |  |  |  |  |
| *CYP2C9* | G96R | 2,21022 | -1,305 | 2,3014836 | X |  |  |  |  |
| *CYP2C9* | G98V | 8,74468 | 0,084 | 3,2288984 | X | X | X | X | X |
| *CYP2C9* | H251R | -0,245571 | 0,055 | -0,15491698 |  | X | X | X | X |
| *CYP2C9* | I207T | 3,01685 | 0,764 | 0,290723 |  | X | X |  | X |
| *CYP2C9* | I222V | 0,584734 | 0,013 | 0,20763892 |  |  |  |  |  |
| *CYP2C9* | I284V | 1,08465 | 0,347 | 0,023527 |  |  |  |  |  |
| *CYP2C9* | I327T | 2,60966 | 0,519 | 0,4103908 |  | X | X | X | X |
| *CYP2C9* | I359T | 2,26965 | 0,228 | 0,607107 | X | X | X | X | X |
| *CYP2C9* | I387V | 0,778488 | 0,056 | 0,23310544 |  |  |  |  |  |
| *CYP2C9* | I434F | -0,333141 | 0,074 | -0,20947358 |  |  | X |  |  |
| *CYP2C9* | K119R | -1,08235 | -0,17 | -0,220893 |  |  |  |  |  |
| *CYP2C9* | L128R | 1,40852 | 0,371 | 0,1197176 |  |  |  |  |  |
| *CYP2C9* | L361I | 0,783158 | -0,135 | 0,44880004 |  |  |  |  |  |
| *CYP2C9* | L362V | 1,54403 | 0,24 | 0,3179314 |  |  |  |  |  |
| *CYP2C9* | L36F | 0,60469 | -0,273 | 0,5355422 | X |  |  |  |  |
| *CYP2C9* | L90P | 6,26266 | 0,372 | 1,9631708 | X |  | X |  |  |
| *CYP2C9* | N204H | 3,42673 | 0,144 | 1,1408774 | X | X |  |  |  |
| *CYP2C9* | N418T | 0,127028 | -0,108 | 0,16923064 |  |  |  |  |  |
| *CYP2C9* | N41D | -0,430025 | -0,064 | -0,0917295 |  | X | X | X | X |
| *CYP2C9* | P163L | 1,8849 | 0,342 | 0,333222 |  | X | X | X | X |
| *CYP2C9* | P227L | 0,604233 | -0,106 | 0,34832854 |  |  |  |  |  |
| *CYP2C9* | P227S | -0,0795527 | -0,167 | 0,156809974 |  | X | X | X | X |
| *CYP2C9* | P279T | 0,793963 | 0 | 0,30170594 |  | X |  |  |  |
| *CYP2C9* | P317S | 1,78971 | 0,215 | 0,4392898 |  | X | X | X | X |
| *CYP2C9* | P337T | 2,61775 | -0,292 | 1,321785 | X | X | X | X | X |
| *CYP2C9* | P346L | 2,11666 | -0,472 | 1,3329708 | X |  |  |  |  |
| *CYP2C9* | P382S | 1,91924 | -0,239 | 0,9969912 | X | X | X | X | X |
| *CYP2C9* | Q214H | 3,17459 | -0,43 | 1,6879442 | X |  |  |  |  |
| *CYP2C9* | Q214L | -0,840573 | -0,124 | -0,18053774 |  | X |  | X | X |
| *CYP2C9* | Q454H | 2,30593 | -0,245 | 1,1506534 | X | X | X | X | X |
| *CYP2C9* | R124Q | -1,87437 | 0,184 | -0,9183406 | X | X | X | X | X |
| *CYP2C9* | R124W | -1,66312 | -0,635 | 0,0792144 |  | X | X | X | X |
| *CYP2C9* | R125C | 0,45835 | 0,058 | 0,109213 |  | X | X | X | X |
| *CYP2C9* | R125H | 0,00512823 | -0,183 | 0,206908727 |  |  | X | X | X |
| *CYP2C9* | R132Q | 0,331003 | -0,011 | 0,13810114 |  | X | X | X | X |
| *CYP2C9* | R132W | 0,250043 | -0,264 | 0,39069634 |  | X | X |  | X |
| *CYP2C9* | R144H | 2,67756 | -0,096 | 1,1249928 | X |  | X | X | X |
| *CYP2C9* | R150C | 1,06524 | 0,56 | -0,2224088 |  |  |  |  |  |
| *CYP2C9* | R150H | 1,11331 | 0,288 | 0,1004978 |  |  |  |  |  |
| *CYP2C9* | R150L | 0,130176 | 0,45 | -0,45453312 |  |  |  |  |  |
| *CYP2C9* | R335Q | 0,72199 | 0,269 | -0,0269238 |  |  | X | X | X |
| *CYP2C9* | R335W | 0,387574 | -0,006 | 0,15399812 |  | X | X | X | X |
| *CYP2C9* | R433W | -0,986376 | -0,53 | 0,21877712 |  | X | X | X | X |
| *CYP2C9* | S280C | -0,120844 | 0,02 | -0,06832072 |  | X |  |  |  |
| *CYP2C9* | S343R | -0,398508 | 0,001 | -0,15255304 |  | X |  |  |  |
| *CYP2C9* | T130M | 2,36101 | -0,066 | 0,9711038 | X | X | X | X | X |
| *CYP2C9* | T130R | 7,36524 | -0,846 | 3,7463112 | X | X | X | X | X |
| *CYP2C9* | T299A | 0,177293 | 0,57 | -0,57102866 | X | X | X | X | X |
| *CYP2C9* | T299R | 2,10234 | -0,963 | 1,8774492 | X | X | X | X | X |
| *CYP2C9* | V76M | 1,55461 | -0,396 | 1,0342718 | X | X | X | X | X |
| *CYP2C9* | R125L | 0,6178 | 0,69141 | -0,5396152 | X | X | X | X | X |
| *CYP2C9* | R144C | 2,9126 | 0,1084 | 0,98538 | X |  | X |  |  |
| *CYP2C9* | E272G | -1,123 | 0,54883 | -1,0414296 | X | X |  |  |  |
| *CYP2C9* | P489S | 2,4805 | 0,61035 | 0,258998 |  | X | X | X | X |
| *CYP2C9* | N457S | -0,2715 | 1,18359 | -1,4287908 | X |  |  |  |  |
| *CYP2C9* | I359L | 1,0875 | 0,70215 | -0,373158 |  |  |  |  |  |
| *CYP2C9* | D397A | -1,8932 | 0,625 | -1,419416 | X | X | X | X | X |
| *CYP2D6* | A226V | 3,16647 | 1,128 | -0,0601014 |  |  |  |  |  |
| *CYP2D6* | C191L | -3,40228 | -0,563 | -0,6623064 | X |  |  |  |  |
| *CYP2D6* | E156A | 2,22624 | 0,967 | -0,2370688 |  | X | X | X | X |
| *CYP2D6* | E215K | 4,42362 | -0,227 | 1,9352156 | X |  |  |  |  |
| *CYP2D6* | F457L | 0,746963 | 0,138 | 0,12928594 |  | X | X | X | X |
| *CYP2D6* | G42E | -0,39499 | 0 | -0,1500962 |  | X | X |  | X |
| *CYP2D6* | G439D | 9,85274 | -0,153 | 3,9154012 | X | X | X | X | X |
| *CYP2D6* | G445R | -0,459624 | -1,51 | 1,51654288 | X | X | X | X | X |
| *CYP2D6* | K147R | 0,143681 | -0,219 | 0,29987878 |  | X |  | X | X |
| *CYP2D6* | L142S | 3,03872 | 0,743 | 0,3225536 |  | X | X | X | X |
| *CYP2D6* | N175S | 0,484066 | 0,181 | -0,01877492 |  |  |  |  |  |
| *CYP2D6* | Q117R | 1,56328 | -0,11 | 0,7172464 | X |  |  |  |  |
| *CYP2D6* | R330P | 1,87993 | 0,796 | -0,1771466 |  | X | X | X | X |
| *CYP2D6* | R344Q | -0,0977968 | -0,305 | 0,304437216 |  |  |  |  |  |
| *CYP2D6* | R441C | 0,11692 | 1,144 | -1,2368504 | X | X | X | X | X |
| *CYP2D6* | R441H | 0,621678 | 0,025 | 0,20823764 |  | X | X | X | X |
| *CYP2D6* | R497H | 0,42382 | -0,324 | 0,5239316 | X | X | X | X | X |
| *CYP2D6* | S488F | -0,982676 | -0,69 | 0,39938312 |  |  |  |  |  |
| *CYP2D6* | T249P | 3,47729 | -0,157 | 1,4972102 | X |  | X |  |  |
| *CYP2D6* | T310A | 0,466573 | 0,683 | -0,58766226 | X | X | X | X | X |
| *CYP2D6* | V136M | -2,70624 | -0,227 | -0,7741312 | X |  |  |  |  |
| *CYP2D6* | V370I | -0,852284 | -0,16 | -0,14466792 |  |  |  |  |  |
| *CYP2D6* | P34S | 4,87717 | 0,203 | 1,6259646 | X | X | X | X | X |
| *CYP2D6* | S486T | -0,0484366 | -0,118 | 0,113754092 |  |  |  |  |  |
| *CYP2D6* | A90V | 0,147028 | -0,373 | 0,47363064 |  |  |  |  |  |
| *CYP2D6* | R296C | 0,843081 | 1,033 | -0,83658922 | X |  |  |  |  |
| *CYP2D6* | N166D | 0,50018 | 0,108 | 0,0691084 |  |  |  |  |  |
| *CYP2D6* | E156V | 0,719275 | -0,268 | 0,5734845 | X | X | X | X | X |
| *CYP2D6* | F366S | 2,32534 | 1,45 | -0,7403708 | X | X | X | X | X |
| *CYP2D6* | H352R | -0,435635 | -0,029 | -0,1330613 |  |  |  |  |  |
| *CYP2D6* | Y355C | 1,56085 | 0,708 | -0,199837 |  | X | X | X | X |
| *CYP2D6* | G111S | 3,77519 | -0,354 | 1,8310522 | X | X | X | X | X |
| *CYP2D6* | G169R | 1,38451 | -0,531 | 1,1208338 | X | X | X | X | X |
| *CYP2D6* | D337N | -0,421284 | 0,142 | -0,31912792 |  |  |  |  |  |
| *CYP2D6* | G42R | -0,42162 | 0 | -0,1602156 |  |  | X | X | X |
| *CYP2D6* | H167Q | 0,355311 | 0,356 | -0,26370182 |  |  |  |  |  |
| *CYP2D6* | S168A | 0,390422 | -0,001 | 0,14948036 |  |  |  |  |  |
| *CYP2D6* | R450H | 0,0954001 | 0,439 | -0,455427962 |  | X | X | X | X |
| *CYP2D6* | S135F | -0,73469 | -0,704 | 0,5092978 | X | X | X | X | X |
| *CYP2D6* | R365H | 13,6283 | 0,065 | 5,105954 | X | X | X | X | X |
| *CYP2D6* | V68G | 5,26442 | 1,149 | 0,7135996 | X | X | X | X | X |
| *CYP2D6* | N285S | 0,893283 | -0,023 | 0,36520754 |  |  |  |  |  |
| *CYP2D6* | G340R | 2,70247 | -0,344 | 1,4122186 | X | X | X | X | X |
| *CYP2D6* | R414C | 0,0498072 | 0 | 0,018926736 |  |  | X |  |  |
| *CYP2D6* | P430L | 1,14417 | -0,355 | 0,8323846 | X |  | X | X | X |
| *CYP2D6* | A482G | 0,215937 | 0,2 | -0,14194394 |  |  |  |  |  |
| *CYP2D6* | A482T | 0,690884 | 0,018 | 0,24237592 |  |  |  |  |  |
| *CYP2D6* | E410K | -0,232234 | -0,265 | 0,20855108 |  |  |  |  |  |
| *CYP2D6* | F481V | 0,605643 | 0,745 | -0,60425566 | X |  |  |  |  |
| *CYP2D6* | G479R | 5,18459 | -1,612 | 3,7755842 | X |  |  |  |  |
| *CYP2D6* | H478P | 0,0320266 | 0,026 | -0,016949892 |  | X | X |  | X |
| *CYP2D6* | H478Y | 0,14391 | -0,139 | 0,2103658 |  |  |  |  |  |
| *CYP2D6* | P469A | 2,17337 | 0,214 | 0,5862006 | X | X | X |  | X |
| *CYP2D6* | T107I | -0,668954 | -0,207 | -0,02236252 |  |  |  |  |  |
| *CYP2D6* | T470A | -0,291731 | 0 | -0,11085778 |  |  |  |  |  |
| *CYP2D6* | Q151E | 0,773877 | 0,008 | 0,28511326 |  |  |  |  |  |
| *CYP2D6* | V136I | -1,52252 | -0,016 | -0,5606376 | X |  |  |  |  |
| *CYP2D6* | V338M | 0,287774 | 0,268 | -0,19080588 |  | X | X | X | X |
| *CYP2D6* | R440H | 0,262725 | -0,277 | 0,4100755 |  |  | X | X | X |
| *CYP2D6* | R201H | 0,00359482 | -0,087 | 0,098806032 |  |  |  |  |  |
| *CYP2D6* | E155K | -0,302358 | -0,088 | -0,01633604 |  |  |  |  |  |
| *CYP2D6* | F120I | 1,52379 | 0,3 | 0,2430402 |  |  |  |  |  |
| *CYP2D6* | E334A | 1,28008 | 0,643 | -0,2337296 |  | X | X | X | X |
| *CYP2D6* | E418K | 0,188964 | -0,006 | 0,07852632 |  |  | X | X | X |
| *CYP2D6* | A122S | 0,204611 | -0,118 | 0,20991218 |  | X | X |  | X |
| *CYP2D6* | T261I | 0,598285 | -0,079 | 0,3158283 |  | X |  |  |  |
| *CYP2D6* | K404Q | 0,66692 | 0,379 | -0,1710504 |  | X | X | X | X |
| *CYP2D6* | R62W | 0,932277 | 0,593 | -0,30989474 |  | X | X | X | X |
| *CYP2D6* | E383K | -0,373296 | 0,042 | -0,18889248 |  | X |  |  |  |
| *CYP2D6* | V104M | -0,981051 | -0,413 | 0,08976062 |  |  |  |  |  |
| *CYP2D6* | H94R | -0,306898 | 0,144 | -0,27790124 |  |  |  |  |  |
| *CYP2D6* | I109V | 0,377463 | 0,174 | -0,05144406 |  |  |  |  |  |
| *CYP2D6* | L91M | -0,612478 | 0,234 | -0,49482164 |  | X | X |  | X |
| *CYP2D6* | T107N | 0,153259 | 0,069 | -0,01904158 |  |  |  |  |  |
| *CYP2D6* | T107S | 0,808942 | 0,084 | 0,21331796 |  |  |  |  |  |
| *CYP2D6* | V104A | 0,668115 | 0,209 | 0,0198037 |  |  |  |  |  |
| *CYP2D6* | P267H | 0,274668 | -0,152 | 0,27461384 |  | X | X | X | X |
| *CYP2D6* | H478Q | -0,231298 | 0,109 | -0,20997324 |  |  |  |  |  |
| *CYP2D6* | E278K | -0,552539 | 0,101 | -0,32308482 |  | X |  |  |  |
| *CYP2D6* | M279K | 1,61274 | -0,023 | 0,6386012 | X | X |  | X | X |
| *CYP2D6* | D337G | 0,135803 | 0,231 | -0,20711486 |  | X |  | X | X |
| *CYP2D6* | R388H | 2,35542 | 0,046 | 0,8435396 | X |  |  |  |  |
| *CYP2D6* | H463D | 1,09752 | 0,672 | -0,3355824 |  | X |  | X | X |
| *CYP2D6* | R88P | 4,64978 | 0,242 | 1,4958764 | X | X | X | X | X |
| *CYP2D6* | H324P | 5,18382 | 0,201 | 1,7447316 | X | X | X | X | X |
| *CYP2F1* | D218N | -1,682791 | 0,65918 | -1,37774218 | X |  |  |  |  |
| *CYP2F1* | Q266H | 1,01377 | 0,99023 | -0,723825 | X | X |  |  |  |
| *CYP2F1* | P490L | 2,21995 | 0,66992 | 0,0932706 |  | X |  |  |  |
| *CYP2F1* | S38P | -0,281256 | 0,84766 | -1,05625648 | X |  |  |  |  |
| *CYP2W1* | V432I | -0,498 | 0,969727 | -1,27533424 | X |  |  |  |  |
| *CYP2W1* | Q482H | -0,929 | 1,722656 | -2,28239472 | X |  |  |  |  |
| *CYP2W1* | P488L | 0,950687 | -0,232 | 0,62110106 | X |  |  |  |  |
| *CYP2W1* | E58A | -0,104029 | 0,324 | -0,40241102 |  | X | X | X | X |
| *CYP2W1* | A181T | 12,9333 | -0,68 | 5,676254 | X |  |  |  |  |
| *CYP2W1* | A125T | 1,70379 | -0,351 | 1,0405602 | X |  |  |  |  |
| *CYP3A4* | A370S | 0,45083 | -0,192 | 0,3863554 |  |  |  |  |  |
| *CYP3A4* | D174H | 0,228664 | -0,376 | 0,50801232 | X |  |  |  |  |
| *CYP3A4* | F113I | 2,101 | 0,515 | 0,22158 |  |  |  |  |  |
| *CYP3A4* | F189S | 6,26981 | 1,37 | 0,8481278 | X | X | X | X | X |
| *CYP3A4* | G56D | 2,04455 | -0,068 | 0,853089 | X | X | X | X | X |
| *CYP3A4* | H324Q | 1,32278 | 0,471 | -0,0248636 |  | X | X | X | X |
| *CYP3A4* | I118V | 0,572509 | 0,661 | -0,52276658 | X |  |  |  |  |
| *CYP3A4* | I335T | 1,87632 | 0,521 | 0,1294816 |  | X | X | X | X |
| *CYP3A4* | I427V | 0,642671 | 0,138 | 0,08965498 |  | X |  |  |  |
| *CYP3A4* | L293P | 0,986763 | 0,698 | -0,40679006 |  |  | X |  |  |
| *CYP3A4* | L373F | 5,22524 | -0,436 | 2,4739112 | X | X |  |  |  |
| *CYP3A4* | P218R | 1,14656 | -0,24 | 0,7044928 | X | X | X | X | X |
| *CYP3A4* | P416L | 6,31746 | -0,642 | 3,1196748 | X | X | X | X | X |
| *CYP3A4* | P467S | 2,69737 | 0,187 | 0,8155606 | X | X |  |  |  |
| *CYP3A4* | Q200H | 0,424505 | 0 | 0,1613119 |  |  |  |  |  |
| *CYP3A4* | R130Q | -0,231126 | 0,711 | -0,88414788 | X | X | X | X | X |
| *CYP3A4* | R162Q | 0,332387 | 0,288 | -0,19625294 |  |  |  |  |  |
| *CYP3A4* | R162W | 0,896397 | -0,231 | 0,59935086 | X | X | X | X | X |
| *CYP3A4* | S222P | 3,42096 | 0,04 | 1,2551648 | X |  |  |  |  |
| *CYP3A4* | T185S | 1,74183 | 0,187 | 0,4524554 |  | X | X | X | X |
| *CYP3A4* | V170I | -0,16228 | -0,188 | 0,1488936 |  |  |  |  |  |
| *CYP3A4* | Y319C | 4,23306 | 1,008 | 0,4796028 |  | X | X | X | X |
| *CYP3A4* | T363M | 0,600548 | -0,693 | 1,00436824 | X | X | X |  | X |
| *CYP3A4* | M445T | 1,5203 | 0,404 | 0,125234 |  | X | X | X | X |

a ‘X’ and blanks represent variants predicted to be deleterious and neutral, respectively, by the prediction tools

NMA: Normal Mode Analysis

This table presents all 261 missense variants analysed in this study, together with their FoldX and ENCoM-derived energy scores. A combined ∆∆G (combination of ENCoM and FoldX) is presented, from which a prediction of the effect of each variant is made based on the threshold (-0.5 < combined ∆∆G < 0.5) [1]. Predictions from commonly used Ensembl Variant Effect Predictor (VEP; https://www.ensembl.org/ToolsVEP) [2] plugins as well as a consensus (2 from 3 rule) has been included for comparison with combined ∆∆G predictions.

**References:**

[1] V. Frappier and R. J. Najmanovich. A coarse-grained elastic network atom contact model and its use in the simulation of protein dynamics and the prediction of the effect of mutations. *PLoS computational biology*, 10(4):e1003569, 2014.

[2] W. McLaren, L. Gil, S. E. Hunt, H. S. Riat, G. R. Ritchie, A. Thormann, P. Flicek, and F. Cunningham. The ensembl variant effect predictor. *Genome biology*, 17(1): 1–14, 2016.