**Supplementary Table 2. CYP star allele/haplotype NMA analysis.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Star Allele/ Haplotype** | **Haplotype Combined ∆∆G**  **(kcal·mol-1)** | **Predicted haplotype structural effect** | **CPIC functional classification** | **Variants defining haplotype** | **Variant Combined ∆∆G (kcal·mol-1)** | **Predicted variant functional effect** |
| *CYP2F1\*3.001* | -0,9262366 | stabilising |  | D218N | -1,3777422 | stabilising |
| Q266H | -0,723825 | stabilising |
| P490L | 0,0932706 | neutral |
| *CYP2F1\*4.001* | -1,9834974 | stabilising |  | S38P | -1,0562565 | stabilising |
| D218N | -1,3777422 | stabilising |
| *CYP2W1\*5.001* | -2,5236142 | stabilising |  | V432I | -1,2753342 | stabilising |
| Q482H | -2,2823947 | stabilising |
| *CYP2A13\*10* | 0,78203736 | destabilising | function not assigned | R257C | -1,2127802 | stabilising |
| I331T | 0,7707903 | destabilising |
| *CYP2B6\*6* | -0,0601104 | neutral | decreased function | Q172H | 0,1040712 | neutral |
| K262R | -0,892796 | stabilising |
| *CYP2B6\*26* | 0,6662888 | destabilising | decreased function | K262R | -0,892796 | stabilising |
| Q172H | 0,1040712 | neutral |
| P167A | 0,5176808 | destabilising |
| *CYP2B6\*7* | -0,0601104 | neutral | decreased function | Q172H | 0,1040712 | neutral |
| K262R | -0,892796 | stabilising |
| R487C | -0,2383712 | neutral |
| *CYP2B6\*19* | 1,541516 | destabilising | decreased function | Q172H | 0,1040712 | neutral |
| K262R | -0,892796 | stabilising |
| R336C | 0,9760368 | destabilising |
| *CYP2B6\*37* | 2,4683328 | destabilising | no function | Q172H | 0,1040712 | neutral |
| K262R | -0,892796 | stabilising |
| V183G | 1,8464656 | destabilising |
| *CYP2B6\*13* | 0,680704 | destabilising | no function | Q172H | 0,1040712 | neutral |
| K262R | -0,892796 | stabilising |
| K139E | 0,4096768 | neutral |
| *CYP2B6\*20* | 0,480356 | neutral | decreased function | K262R | -0,892796 | stabilising |
| Q172H | 0,1040712 | neutral |
| T168I | 0,4562848 | neutral |
| *CYP2B6\*18.002* | 0,3749488 | neutral | no function | K262R | -0,892796 | stabilising |
| I328T | 0,5430336 | destabilising |
| *CYP2C8\*3* | -1,1189533 | stabilising | function not assigned | R139K | -0,7715336 | stabilising |
| K399R | -1,1561408 | stabilising |
| *CYP2C9\*35* | 1,01259728 | destabilising | no function | R125L | -0,5396152 | stabilising |
| R144C | 0,98538 | destabilising |
| *CYP2C9\*71* | -0,098842 | neutral | uncertain function | E272G | -1,0414296 | stabilising |
| P489S | 0,258998 | neutral |
| *CYP2C9\*61* | 0,23829624 | neutral | decreased function | R144C | 0,98538 | destabilising |
| N457S | -1,4287908 | stabilising |
| *CYP2C9\*18* | -1,735581 | stabilising | uncertain function | I359L | -0,373158 | neutral |
| D397A | -1,419416 | stabilising |
| *CYP2D6\*70* | 0,5700364 | destabilising | uncertain function | V338M | -3,0965856 | stabilising |
| V136I | -3,8637948 | stabilising |
| V119M | -2,7709664 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*10* | 1,7397212 | destabilising | decreased function | P34S | 1,6259646 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*102* | -0,2623378 | neutral | unknown function | A90V | 0,4736306 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*103* | -0,1932294 | neutral | unknown function | A90V | 0,4736306 | neutral |
| N166D | 0,0691084 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*104* | -0,1539084 | neutral | unknown function | EA156V | 0,5734845 | destabilising |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*105* | -1,441462 | stabilising | unknown function | F366S | -0,7403708 | stabilising |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*108* | -0,3916966 | neutral | unknown function | H352R | -0,1330613 | neutral |
| Y355C | -0,199837 | neutral |
| *CYP2D6\*111* | 1,1128658 | destabilising | uncertain function | G111S | 1,8310522 | destabilising |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*114* | 2,09231 | destabilising | no function | G169R | 1,1208338 | destabilising |
| P34S | 1,6259646 | destabilising |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*117* | -1,0210867 | stabilising | unknown function | D337N | -0,3191279 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*12* | -0,8583694 | stabilising | no function | G42R | -0,1602156 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*121* | -0,665719 | stabilising | unknown function | H167Q | -0,2637018 | neutral |
| N166D | 0,0691084 | neutral |
| R296C | -0,8365892 | stabilising |
| S168A | 0,1494804 | neutral |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*125* | -1,1629252 | stabilising | unknown function | R296C | -0,8365892 | stabilising |
| R450H | -0,455428 | neutral |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*126* | -0,2621316 | neutral | unknown function | R296C | -0,8365892 | stabilising |
| S135F | 0,5092978 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*127* | 3,09417 | destabilising | unknown function | R365H | 5,105954 | destabilising |
| Y355C | -0,199837 | neutral |
| *CYP2D6\*128* | 0,0112326 | neutral | uncertain function | R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| V68G | 0,7135996 | destabilising |
| *CYP2D6\*132* | 2,1189126 | destabilising | decreased function | N285S | 0,3652075 | neutral |
| P34S | 1,6259646 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*133* | 0,8011668 | destabilising | uncertain function | G340R | 1,4122186 | destabilising |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*135* | -0,6727194 | stabilising | uncertain function | R296C | -0,8365892 | stabilising |
| RA414C | 0,0189267 | neutral |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*136* | 0,1354938 | neutral | uncertain function | P430L | 0,8323846 | destabilising |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*14* | 0,4613912 | neutral | decreased function | G169R | 1,1208338 | destabilising |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*141* | 2,34104 | destabilising | uncertain function | A482G | -0,1419439 | neutral |
| A482T | 0,2423759 | neutral |
| E410K | 0,2085511 | neutral |
| F481V | -0,6042557 | stabilising |
| G479R | 3,7755842 | destabilising |
| H478P | -0,0169499 | neutral |
| H478Y | 0,2103658 | neutral |
| P469A | 0,5862006 | destabilising |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| T107I | -0,0223625 | neutral |
| T470A | -0,1108578 | neutral |
| *CYP2D6\*142* | 1,7397212 | destabilising | uncertain function | P34S | 1,6259646 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*17* | -0,6321365 | stabilising | decreased function | R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| T107I | -0,0223625 | neutral |
| *CYP2D6\*2* | -0,7025097 | stabilising | normal function | R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*28* | -0,4291658 | neutral | uncertain function | Q151E | 0,2851133 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*29* | -1,4660549 | stabilising | decreased function | R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| V136I | -0,5606376 | stabilising |
| V338M | -0,1908059 | neutral |
| *CYP2D6\*31* | -0,2989764 | neutral | no function | R296C | -0,8365892 | stabilising |
| R440H | 0,4100755 | neutral |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*35* | -0,7025097 | stabilising | normal function | R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*36* | 4,77919 | destabilising | no function | A482G | -0,1419439 | neutral |
| A482T | 0,2423759 | neutral |
| F481V | -0,6042557 | stabilising |
| G479R | 3,7755842 | destabilising |
| H478P | -0,0169499 | neutral |
| H478Y | 0,2103658 | neutral |
| P34S | 1,6259646 | destabilising |
| P469A | 0,5862006 | destabilising |
| S486T | 0,1137541 | neutral |
| T470A | -0,1108578 | neutral |
| *CYP2D6\*37* | 1,8385254 | destabilising | uncertain function | P34S | 1,6259646 | destabilising |
| R201H | 0,098806 | neutral |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*45* | -0,7198924 | stabilising | normal function | E155K | -0,016336 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*46* | -0,7198924 | stabilising | normal function | E155K | -0,016336 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*47* | 1,7397212 | destabilising | no function | P34S | 1,6259646 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*49* | 1,9982854 | destabilising | decreased function | F120I | 0,2430402 | neutral |
| P34S | 1,6259646 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*51* | -0,8386966 | stabilising | no function | E334A | -0,2337296 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*52* | 1,818246 | destabilising | decreased function | E418K | 0,0785263 | neutral |
| P34S | 1,6259646 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*53* | 0,451982 | neutral | normal function | A122S | 0,2099122 | neutral |
| F120I | 0,2430402 | neutral |
| *CYP2D6\*54* | 2,153272 | destabilising | decreased function | P34S | 1,6259646 | destabilising |
| S486T | 0,1137541 | neutral |
| T261I | 0,3158283 | neutral |
| *CYP2D6\*55* | -0,873559 | stabilising | decreased function | K404Q | -0,1710504 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*57* | 4,268034 | destabilising | no function | A482G | -0,1419439 | neutral |
| A482T | 0,2423759 | neutral |
| F481V | -0,6042557 | stabilising |
| G479R | 3,7755842 | destabilising |
| H478P | -0,0169499 | neutral |
| H478Y | 0,2103658 | neutral |
| P34S | 1,6259646 | destabilising |
| P469A | 0,5862006 | destabilising |
| R62W | -0,3098947 | neutral |
| S486T | 0,1137541 | neutral |
| T470A | -0,1108578 | neutral |
| *CYP2D6\*64* | 1,715655 | destabilising | uncertain function | P34S | 1,6259646 | destabilising |
| S486T | 0,1137541 | neutral |
| T107I | -0,0223625 | neutral |
| *CYP2D6\*65* | 0,9272902 | destabilising | uncertain function | P34S | 1,6259646 | destabilising |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*72* | 1,4516606 | destabilising | uncertain function | E383K | -0,1888925 | neutral |
| P34S | 1,6259646 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*73* | -0,5471407 | stabilising | unknown function | R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| V104M | 0,0897606 | neutral |
| *CYP2D6\*82* | -0,7269554 | stabilising | unknown function | H94R | -0,2779012 | neutral |
| I109V | -0,0514441 | neutral |
| L91M | -0,4948216 | neutral |
| T107N | -0,0190416 | neutral |
| T107S | 0,213318 | neutral |
| V104A | 0,0198037 | neutral |
| *CYP2D6\*83* | 3,1973284 | destabilising | uncertain function | A482G | -0,1419439 | neutral |
| A482T | 0,2423759 | neutral |
| F481V | -0,6042557 | stabilising |
| G479R | 3,7755842 | destabilising |
| H478P | -0,0169499 | neutral |
| H478Y | 0,2103658 | neutral |
| P469A | 0,5862006 | destabilising |
| S486T | 0,1137541 | neutral |
| T470A | -0,1108578 | neutral |
| *CYP2D6\*84* | -0,430364 | neutral | uncertain function | P267H | 0,2746138 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*85* | -0,8875665 | stabilising | unknown function | H478Q | -0,2099732 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*86* | 0,5302152 | destabilising | unknown function | E278K | -0,3230848 | neutral |
| M279K | 0,6386012 | destabilising |
| *CYP2D6\*87* | 1,7397212 | destabilising | uncertain function | P34S | 1,6259646 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*88* | 0,13216822 | neutral | uncertain function | S486T | 0,1137541 | neutral |
| V104A | 0,0198037 | neutral |
| *CYP2D6\*94* | 1,4972556 | destabilising | uncertain function | D337G | -0,2071149 | neutral |
| P34S | 1,6259646 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*95* | 2,600268 | destabilising | uncertain function | P34S | 1,6259646 | destabilising |
| R388H | 0,8435396 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*98* | -1,0368608 | stabilising | uncertain function | H463D | -0,3355824 | neutral |
| R296C | -0,8365892 | stabilising |
| S486T | 0,1137541 | neutral |
| *CYP2D6\*99* | 3,266807 | destabilising | no function | P34S | 1,6259646 | destabilising |
| R88P | 1,4958764 | destabilising |
| S486T | 0,1137541 | neutral |
| *CYP2C19\*3* | 0,8806458 | destabilising | no function | I331V | 0,0080425 | neutral |
| W212X | -0,7491536 | stabilising |
| *CYP2C19\*5* | 1,7583514 | destabilising | no function | I331V | 0,0080425 | neutral |
| R433W | 1,75031 | destabilising |
| *CYP2C19\*6* | 0,07683506 | neutral | no function | I331V | 0,0080425 | neutral |
| R132Q | 0,0676725 | neutral |
| *CYP2C19\*8* | 0,5296734 | destabilising | no function | I331V | 0,0080425 | neutral |
| W120R | 0,5185378 | destabilising |
| *CYP2C19\*9* | 0,5719456 | destabilising | decreased function | I331V | 0,0080425 | neutral |
| R144H | 0,56193 | destabilising |
| *CYP2C19\*10* | 0,7448702 | destabilising | decreased function | I331V | 0,0080425 | neutral |
| P227V | 0,730687 | destabilising |
| *CYP2C19\*11* | 0,405794 | neutral | normal function | I331V | 0,0080425 | neutral |
| R150H | 0,1684469 | neutral |
| *CYP2C19\*13* | -0,043127 | neutral | normal function | I331V | 0,0080425 | neutral |
| R410C | -0,0531426 | neutral |
| *CYP2C19\*18* | 0,4445719 | neutral | normal function | I331V | 0,0080425 | neutral |
| R329H | 0,1787067 | neutral |
| *CYP2C19\*19* | -0,4329313 | neutral | decreased function | I331V | 0,0080425 | neutral |
| S51G | -0,4420527 | neutral |
| *CYP2C19\*22* | -0,8205922 | stabilising | no function | I331V | 0,0080425 | neutral |
| R186P | -0,8316689 | stabilising |
| *CYP2C19\*23* | 0,4155246 | neutral | uncertain function | I331V | 0,0080425 | neutral |
| G91R | 0,395687 | neutral |
| *CYP2C19\*24* | -0,020874 | neutral | no function | I331V | 0,0080425 | neutral |
| R335Q | -0,0464056 | neutral |
| *CYP2C19\*26* | 0,07683506 | neutral | decreased function | I331V | 0,0080425 | neutral |
| D256N | 0,0517647 | neutral |
| *CYP2C19\*28* | 0,47827198 | neutral | normal function | I331V | 0,0080425 | neutral |
| V374I | 0,564726 | destabilising |
| *CYP2C19\*31* | -0,0452559 | neutral | uncertain function | I331V | 0,0080425 | neutral |
| H78Y | -0,0532996 | neutral |
| *CYP2C19\*32* | 0,56244312 | destabilising | uncertain function | I331V | 0,0080425 | neutral |
| H99R | 0,551308 | destabilising |
| *CYP2C19\*33* | 0,19557604 | neutral | uncertain function | I331V | 0,0080425 | neutral |
| D188N | 0,1876445 | neutral |
| *CYP2C19\*39* | -0,5709945 | stabilising | function not assigned | I331V | 0,0080425 | neutral |
| E122A | -0,5821295 | stabilising |
| *CYP3A4\*38* | 1,0478738 | destabilising | function not assigned | T363M | 1,0043682 | destabilising |
| M445T | 0,125234 | neutral |

NMA: Normal Mode Analysis

This table presents 92 CYP star alleles together with the defining missense variants for each star allele. Moreover, a CPIC functional classification is included together with the NMA-based combined ∆∆G analysis.