**Supplementary Table 3. SWAAT analysis of CYP missense variant structural consequence.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene** | **Mutation** | **SWAAT prediction**a | **SWAAT red-flag protein structural consequences** |
| *CYP2A13* | I331T | X |  |
| *CYP2A13* | R257C | X | exposed hydrophilic introduced, salt bridge breakage |
| *CYP2B6* | P167A | X |  |
| *CYP2B6* | K139E | X | Salt bridge formation |
| *CYP2B6* | G110V | X |  |
| *CYP2B6* | R336C | X | exposed hydrophilic introduced, Salt bridge breakage |
| *CYP2B6* | R487C |  | exposed hydrophilic introduced |
| *CYP2B6* | Q172H | X | buried charge introduced, Salt bridge formation |
| *CYP2B6* | I328T | X |  |
| *CYP2B6* | M198T | X |  |
| *CYP2B6* | I114T | X |  |
| *CYP2B6* | R29S |  |  |
| *CYP2B6* | R487S | X |  |
| *CYP2B6* | V183G | X |  |
| *CYP2B6* | T168I | X | buried exposed switch |
| *CYP2B6* | R29P | X |  |
| *CYP2B6* | K262R |  |  |
| *CYP2B6* | E148D | X |  |
| *CYP2B6* | A279P |  |  |
| *CYP2C19* | E122A |  | exposed hydrophilic introduced |
| *CYP2C19* | V374I | X | buried exposed switch |
| *CYP2D6* | R62W | X | exposed hydrophilic introduced, Salt bridge breakage |
| *CYP2D6* | H167Q | X |  |
| *CYP2D6* | N166D |  |  |
| *CYP2D6* | T107N | X | buried exposed switch |
| *CYP2D6* | P469A | X | buried exposed switch |
| *CYP2D6* | T107S | X | buried exposed switch |
| *CYP2D6* | L460V | X |  |
| *CYP2D6* | R129L |  | exposed hydrophilic introduced |
| *CYP2D6* | D337G |  |  |
| *CYP2D6* | E410K |  |  |
| *CYP2D6* | V119M | X |  |
| *CYP2D6* | A90V | X |  |
| *CYP2D6* | E418Q |  | salt bridge breakage |
| *CYP2D6* | E383K |  | salt bridge breakage |
| *CYP2D6* | H352R |  |  |
| *CYP2D6* | P325L | X | large helical penality in alpha helix |
| *CYP2D6* | T107I | X |  |
| *CYP2D6* | H478Y |  |  |
| *CYP2D6* | T470A |  |  |
| *CYP2D6* | A122S | X |  |
| *CYP2D6* | R388H | X | salt bridge formation |
| *CYP2D6* | R201H |  | salt bridge breakage |
| *CYP2D6* | E418K | X | salt bridge breakage |
| *CYP2D6* | L91M | X |  |
| *CYP2D6* | G479R | X |  |
| *CYP2D6* | P268S | X |  |
| *CYP2D6* | P34S | X |  |
| *CYP2D6* | V136I |  |  |
| *CYP2D6* | R365H | X | buried salt bridge breakage, salt bridge breakage |
| *CYP2D6* | V338M | X |  |
| *CYP2D6* | I109V | X |  |
| *CYP2D6* | G42R |  |  |
| *CYP2D6* | V104A | X |  |
| *CYP2D6* | R269Q | X | salt bridge breakage |
| *CYP2D6* | A482G |  |  |
| *CYP2D6* | T261I | X |  |
| *CYP2D6* | E278K |  |  |
| *CYP2D6* | E155K |  |  |
| *CYP2D6* | A482T | X |  |
| *CYP2D6* | R173C |  | exposed hydrophilic introduced |
| *CYP2D6* | A449D | X |  |
| *CYP2D6* | Q151E | X |  |
| *CYP2D6* | Y355C | X |  |
| *CYP2D6* | H94R | X |  |
| *CYP2D6* | F120I | X |  |
| *CYP2D6* | R88P | X |  |
| *CYP2D6* | S168A |  |  |
| *CYP2D6* | N285S |  |  |
| *CYP2D6* | F481V | X |  |
| *CYP2D6* | M279K | X | salt bridge formation |
| *CYP2D6* | H478P |  |  |
| *CYP3A4* | I334T | X |  |
| *CYP3A4* | A369S | X |  |
| *CYP3A4* | I118V | X |  |
| *CYP3A4* | G56D | X | buried glycine replaced, buried charge introduced |
| *CYP3A4* | L372F | X |  |
| *CYP3A4* | R162W | X | exposed hydrophilic introduced, salt bridge breakage |
| *CYP3A4* | P218R | X | large helical penalty in alpha helix |
| *CYP3A4* | S222P | X |  |
| *CYP3A4* | P415L | X |  |
| *CYP3A4* | Y318C | X |  |
| *CYP3A4* | R162Q |  | salt bridge breakage |
| *CYP3A4* | M444T | X |  |
| *CYP3A4* | L292P | X |  |
| *CYP3A4* | H323Q | X | salt bridge breakage |
| *CYP3A4* | I426V | X |  |
| *CYP3A4* | F113I | X |  |
| *CYP3A4* | T185S | X |  |
| *CYP3A4* | F189S | X | buried exposed switch |
| *CYP3A4* | R130Q | X |  |
| *CYP3A4* | V170I | X |  |
| *CYP3A4* | T362M | X |  |
| *CYP3A4* | P466S | X |  |
| *CYP3A4* | Q200H |  |  |
| *CYP2C8* | K399R |  |  |
| *CYP2C8* | R139K |  |  |
| *CYP2C9* | E272G | X | salt bridge breakage |
| *CYP2C9* | P489S | X |  |
| *CYP2C9* | R144C | X | buried charge replaced, buried exposed switch |
| *CYP2C9* | N457S |  |  |
| *CYP2C9* | I359L | X |  |
| *CYP2C9* | R125L |  | exposed hydrophilic introduced |
| *CYP2C9* | D397A | X | exposed hydrophilic introduced, salt bridge breakage |
| *CYP2F1* | Q266H | X | buried charge introduced |
| *CYP2F1* | D218N | X | buried exposed switch |
| *CYP2F1* | P490L | X |  |
| *CYP2F1* | S38P |  |  |
| *CYP2J2* | D342N |  | salt bridge breakage |
| *CYP2J2* | G312R | X | buried exposed switch, large helical penality in alpha helix |
| *CYP2J2* | T143A |  |  |
| *CYP2J2* | N404Y | X |  |
| *CYP2J2* | P351L | X |  |
| *CYP2J2* | P115L | X | buried exposed switch, large helical penalty in alpha helix |
| *CYP2J2* | I192N | X | buried hydrophilic introduced |
| *CYP2J2* | R158C | X | exposed hydrophilic introduced, salt bridge breakage |
| *CYP2R1* | L99P | X | buried proline introduced |
| *CYP2S1* | P466L | X |  |
| *CYP2S1* | L230R | X |  |
| *CYP2S1* | S61N | X |  |
| *CYP2S1* | R380C |  | exposed hydrophilic introduced |
| *CYP2W1* | V432I |  |  |
| *CYP2W1* | Q482H |  |  |
| *CYP3A5* | F446S | X | buried exposed switch |
| *CYP3A5* | L82R | X | buried hydrophilic introduced, buried charge introduced |
| *CYP3A5* | I456V | X |  |
| *CYP3A5* | H30Y | X |  |
| *CYP3A5* | Q200R |  |  |
| *CYP3A5* | I488T | X |  |
| *CYP3A5* | T398N | X |  |
| *CYP3A5* | F203C | X |  |
| *CYP3A5* | A337T |  |  |
| *CYP3A5* | Y53C | X |  |
| *CYP3A5* | R28C |  | exposed hydrophilic introduced |

a ‘X’ and blanks represent variants predicted to be deleterious and neutral by SWAAT, respectively.

The likely structural events are based on a set of features that were assessed for structural impact with the likelihood to influence protein function [1].

**References:**

[1]  S. Ittisoponpisan, S. A. Islam, T. Khanna, E. Alhuzimi, A. David, and M. J. Sternberg. Can predicted protein 3d structures provide reliable insights into whether missense variants are disease associated? *Journal of Molecular Biology*, 431(11): 2197–2212, 2019.