**Supplementary Table 1.** Details of the missense SNPs of SRY protein.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **No.** | **Variant ID** | **Chr: bp** | **Alleles** | **AA** | **AA position** | **Mutation** |
|  | [rs1271064684](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=832192) | Y:2787590 | G/A | A/V | 5 | A5V |
|  | [rs104894971](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84286) | Y:2787551 | C/T | S/N | 18 | S18N |
|  | [rs1262320780](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=814712) | Y:2787533 | T/A | N/I | 24 | N24I |
|  | [rs1206716616](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=703308) | Y:2787519 | G/A | R/W | 29 | R29W |
|  | [rs1556370576](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=700598804) | Y:2787515 | C/A | R/I | 30 | R30I |
|  | [rs1459783583](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=1209467) | Y:2787504 | A/G | F/L | 34 | F34L |
|  | [rs767481926](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=300775) | Y:2787456 | C/T | E/K | 50 | E50K |
|  | [rs1223685980](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=737077) | Y:2787449 | C/T | S/N | 52 | S52G |
|  | [rs1325077544](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=940112) | Y:2787450 | T/C | S/G | 52 | S52N |
|  | [rs762003265](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=281510) | Y:2787434 | T/C | Q/R | 57 | Q57R |
|  | [rs773764555](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=322837) | Y:2787430 | A/C | D/E | 58 | D58E |
|  | [rs104894957](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84276) | Y:2787425 | A/G | V/A | 60 | V60L |
|  | [rs764249635](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=289467) | Y:2787426 | C/G | V/L | 60 | V60A |
|  | [rs104894969](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84284) | Y:2787412 | C/T | M/I | 64 | M64I |
|  | [rs1326404572](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=942916) | Y:2787404 | A/T | F/Y | 67 | F67Y |
|  | [rs104894968](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84283) | Y:2787401 | A/G | I/T | 68 | I68T |
|  | [rs763174397](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=285698) | Y:2787399 | C/G | V/L | 69 | V69L |
|  | [rs776339584](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=331895) | Y:2787385 | A/C | D/E | 73 | D73E |
|  | [rs1057519627](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=602404) | Y:2787377 | C/A | R/L | 76 | R76L |
|  | [rs770778716](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=312346) | Y:2787353 | C/G | R/T | 84 | R84T |
|  | [rs746931713](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=228512) | Y:2787350 | A/T | M/K | 85 | M85K |
|  | [rs1556370554](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=700599346) | Y:2787338 | T/G | E/A | 89 | E89A |
|  | [rs104894959](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84278) | Y:2787334 | G/C | I/M | 90 | I90M |
|  | [rs104894974](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84289) | Y:2787320 | C/T | G/E | 95 | G95R |
|  | [rs104894972](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84287) | Y:2787321 | C/G | G/R | 95 | G95E |
|  | [rs1166279862](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=622433) | Y:2787307 | T/A | K/N | 99 | K99N |
|  | [rs104894964](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84279) | Y:2787287 | T/A | K/I | 106 | K106I |
|  | [rs104894956](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84275) | Y:2787278 | A/G | F/S | 109 | F109S |
|  | [rs104894966](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84281) | Y:2787267 | C/T | A/T | 113 | A113T |
|  | [rs771449441](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=314717) | Y:2787240 | C/T | E/K | 122 | E122K |
|  | [rs104894973](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84288) | Y:2787224 | T/A/C | Y/F | 127 | Y127F |
|  | [rs375342012](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=194010) | Y:2787221 | T/C | K/R | 128 | K128R |
|  | [rs104894976](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=84291) | Y:2787207 | G/A | R/W | 133 | R133W |
|  | [rs754623064](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=255570) | Y:2787136 | T/G | E/D | 156 | E156D |
|  | [rs748958243](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=235713) | Y:2787113 | T/C | Y/C | 164 | Y164C |
|  | [rs1194771063](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=679535) | Y:2787060 | G/A | H/Y | 182 | H182Y |
|  | [rs1019354171](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=554727) | Y:2787053 | G/A | P/L | 184 | P184L |
|  | [rs780561417](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=346723) | Y:2787044 | T/C | N/S | 187 | N187S |
|  | [rs756606002](https://www.ensembl.org/Homo_sapiens/Variation/Summary?db=core;g=ENSG00000184895;r=Y:2786855-2787699;t=ENST00000383070;vf=262525) | Y:2787015 | G/A/T | R/C | 197 | R197C |

**Supplementary Table 2.** Comparative parameters of five SRY protein generation tools, Rosetta, Lomets, RaptorX, PhyRe2, and I-TASSER, in terms of QMEAN scores, side chains, and Ramachandran plots of PROCHECK tools.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Method** | **Parameter** | **A) Rosetta** | **B) Lomets** | **C) RaptorX** | **D) PhyRe2** | **E) I-TASSER** |
| Normalized score in QMEAN tool | QMEAN | -0.87 | -7.28 | -4.42 | -4.39 | -16.68 |
| Cβ | -2.02 | -3.42 | -5.11 | -5.27 | -5.66 |
| All atoms | -0.99 | -2.99 | -2.83 | -2.91 | -6.12 |
| Solvation | 0.32 | -1.07 | -0.33 | -1.54 | -5.01 |
| Torsion | -0.53 | -6.15 | -3.16 | -2.35 | -13.58 |
| Side chain parameters in PROCHECK tool | a. %-tag residues in A, B, L | Worse | Inside | Better | Worse | Worse |
| b. Omega angle st dev | Inside | Inside | Better | Inside | Worse |
| c. Bad contacts/100 residues | Better | Worse | Better | Inside | Inside |
| d. zeta angle st dev | Inside | Inside | Better | Better | Inside |
| e. H-bond energy st dev | Inside | Inside | Better | Worse | Inside |
| f. overall G-factor | Better | Inside | - | Inside | Worse |
| Plot statics of Psi/Phi Ramachandran plot in PROCHECK tool | Residues in most favoured regions | 164 (88.6%) | 163 (88.1%) | 67 (85.9%) | 91 (49.2%) | 91 (49.2%) |
| Residues in additional allowed regions | 21 (11.4%) | 15 (8.1%) | 7 (9.0%) | 58 (31.4%) | 58 (31.4%) |
| Residues in generously allowed regions | 0 (0.0%) | 3 (1.6%) | 4 (5.1%) | 26 (14.1%) | 26 (14.1%) |
| Residues in disallowed regions | 0 (0.0%) | 4 (2.2%) | 0 (0.0%) | 10 (5.4%) | 10 (5.4%) |
| Number of non-glycine and non-proline residues | 185 (100%) | 185 (100%) | 78 (100.0%) | 185 (100%) | 185 (100%) |
| Number of end-residues | 2 | 2 | 3 | 2 | 2 |
| Number of glycine residues | 4 | 4 | 3 | 4 | 4 |
| Number of proline residues | 13 | 13 | 5 | 13 | 13 |
| Total number of residues | 204 | 204 | 87 | 204 | 204 |

**Supplementary Table 3.** The mechanisms of the possible effects of the amino acid residues of the most three damaging missense SNPs of SRY protein. A) Post-translation modification prediction, B) Receptor binding prediction. Symbols phos., ubi., meth., SUMO., O-GalNAc., O-GlcNAc., N-Gly., K-Ace., and N-t-ace. refer to phosphorylation, ubiquitination, methylation, sumoylation, *O-N*-acetylgalactosamination, *O-N*-acetylglucosamination, *N*-glycosylation, *K*-acetylation, and *N-t*-acetylation, respectively.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **A) Post-translational modifications** | | | | | | | | | |
| **AA Change** | **Phos.** | **Ubi.** | **Meth.** | **SUMO.** | **O-GalNAc.** | **O-GlcNAc.** | **N-Gly.** | **K-Ace.** | **N-t-Ace.** |
| I90 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| F109 | -0.796 | 0 | 0 | 0 | 0 | -0.2653 | 0 | 0 | 0 |
| Y127 | 3.059 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **B) Binding with ligands/receptors** | | | | | | | | | |
|  | **RaptorX** | **COACH** | **TM-SITE** | **S-SITE** | **COFACTOR** | **FINDSITE** | **ConCavity** |  |  |
| I90 |  | - | - | - | - | - | - |  |  |
| F109 | - | - | - | - | - | - | - |  |  |
| Y127 | - | - | - | - | - | - | - |  |  |