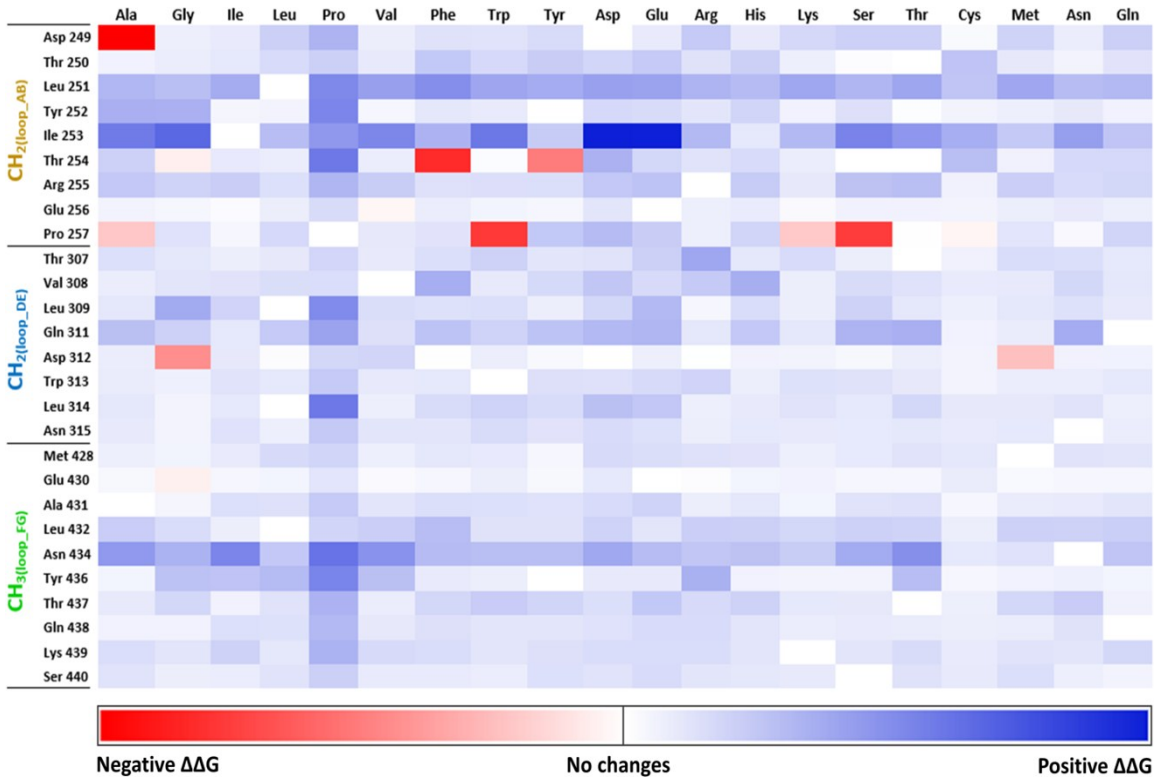
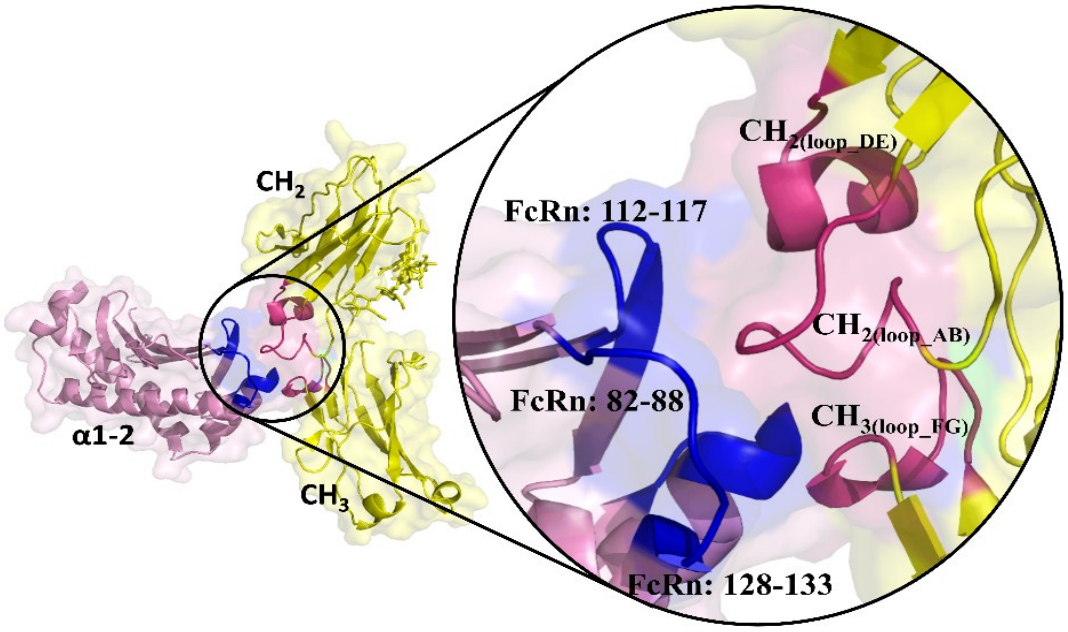
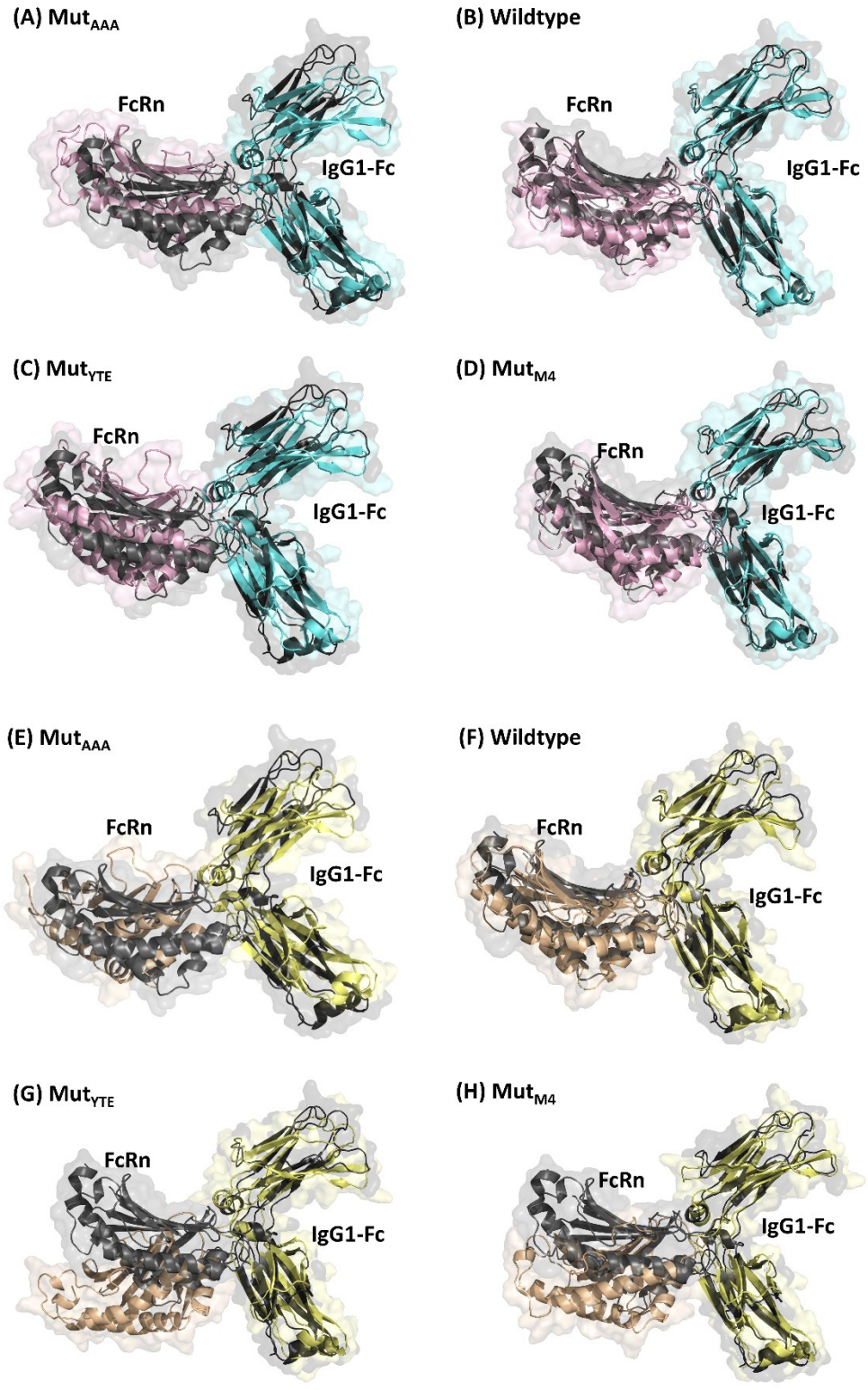
**Supplementary Figures**




**Supplementary Figure S1.** Heat map binding free energy ($\Delta\Delta G_{bind}$) comparison upon the mutation with 19 other amino acids of the Fc interacting residues (with FcRn).




**Supplementary Figure S2.** The overview of Fc-FcRn complex structure zoomed in interacting interface with Fc (yellow), Fc interacting interface (magenta), FcRn heavy chain (light pink), FcRn interacting interface (blue). Labeled residues were used in binding free energy calculation. Figure was prepared using Pymol (DeLano, 2003).




**Supplementary Figure S3.** The superimposition of the MD representative structures at pH 6.0 (A-D) and pH 7.5 (E-H) with the crystal structure (PDB ID 4NOU; Fc: black & FcRn: grey ribbon presentation). The IgG1-Fc (A, E) $Mut_{AAA}$-FcRn, (B, F) WT-FcRn, (C, G) $Mut_{YTE}$-FcRn, and (D, H) $Mut_{M4}$-FcRn complexes were represented as Fc: cyan & FcRn: pink ribbon presentation at pH 6 and Fc: yellow & FcRn: orange ribbon presentation at pH 7.5. Figure was prepared using Pymol (DeLano, 2003).

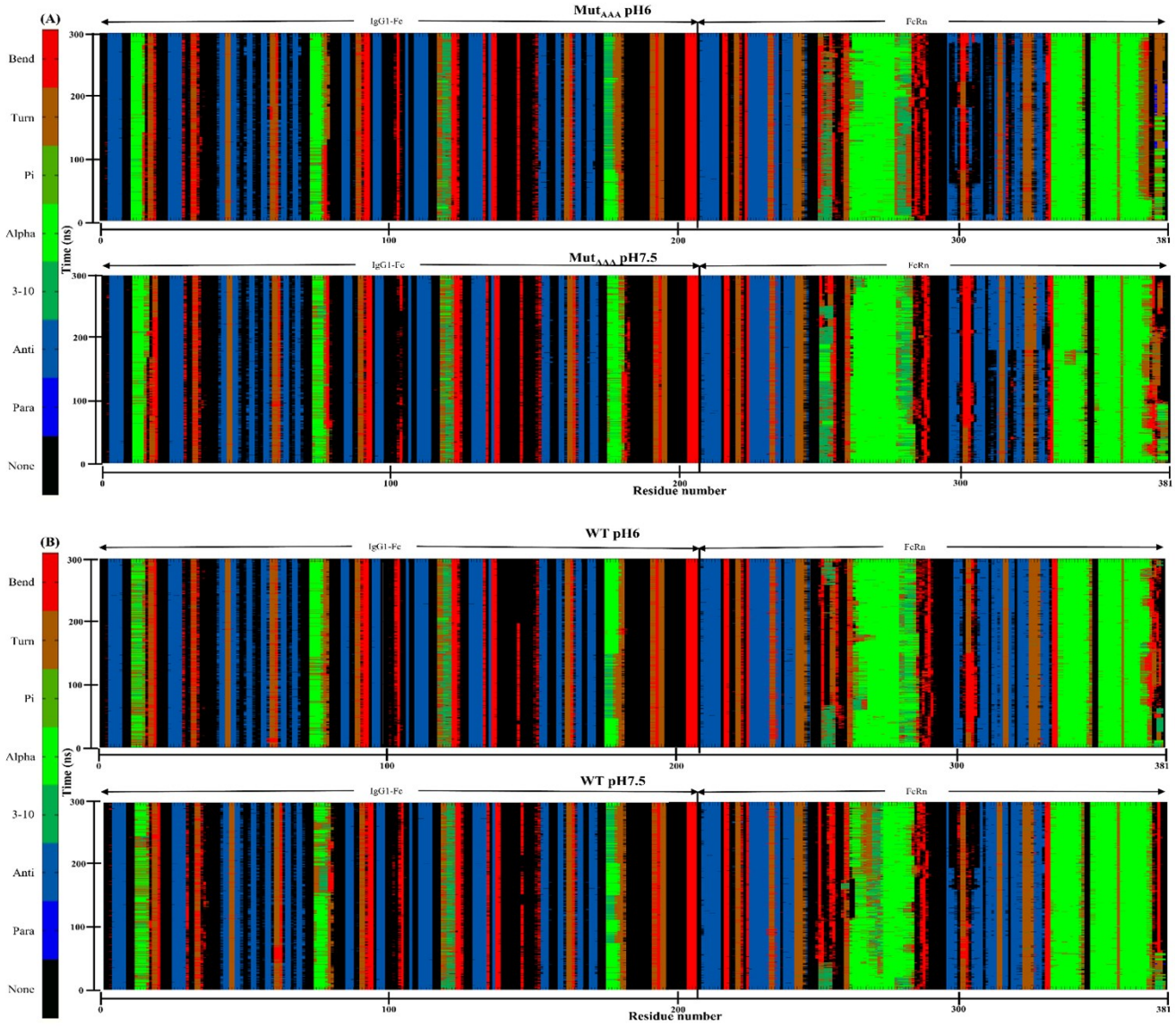



**Figure S4.** The secondary structure variation defined by DSSP program for IgG1-Fc variant (A) $Mut_{AAA}$, (B) WT, (C) $Mut_{YTE}$ and (D) $Mut_{M4}$ complexed with FcRn.

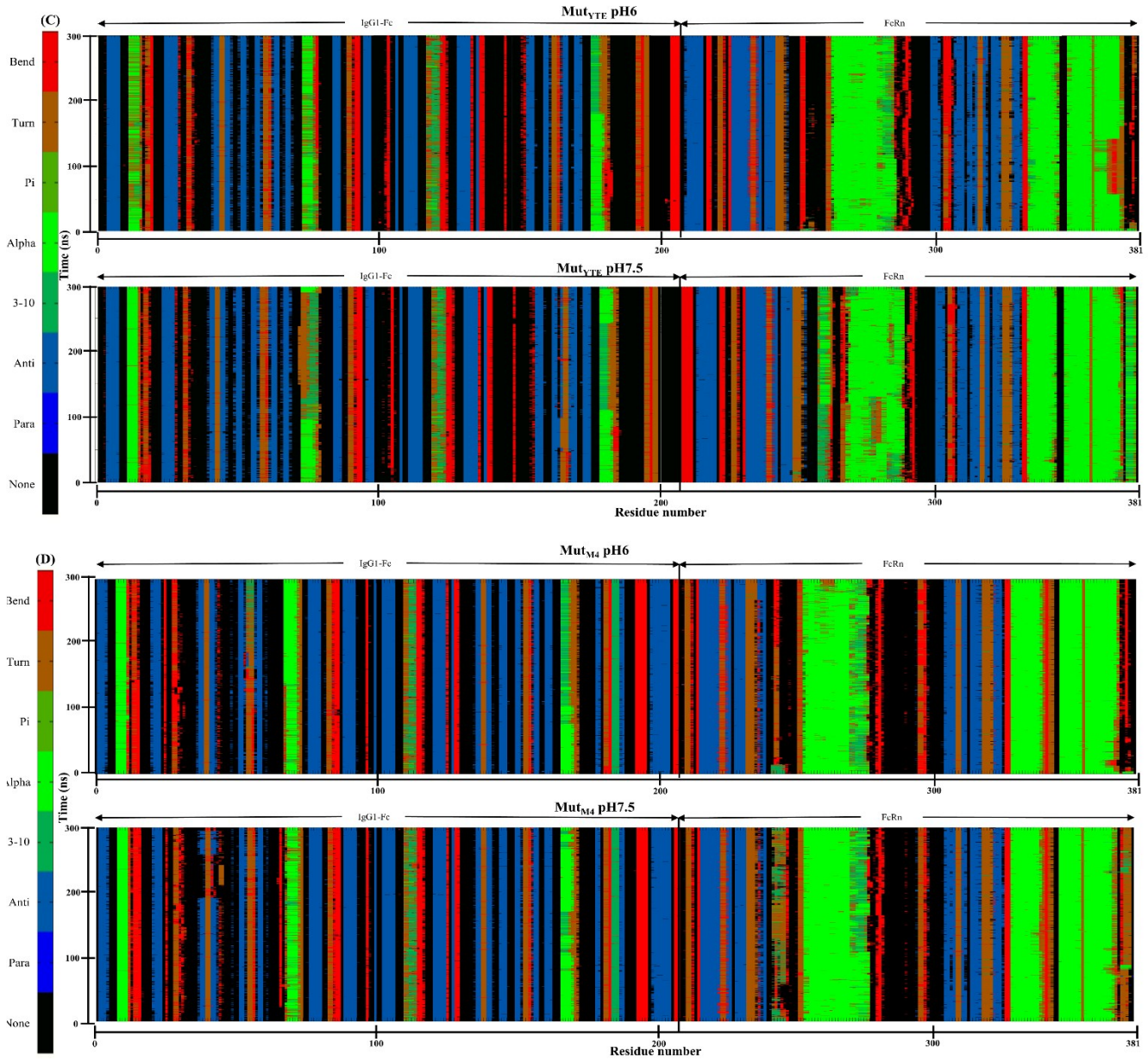
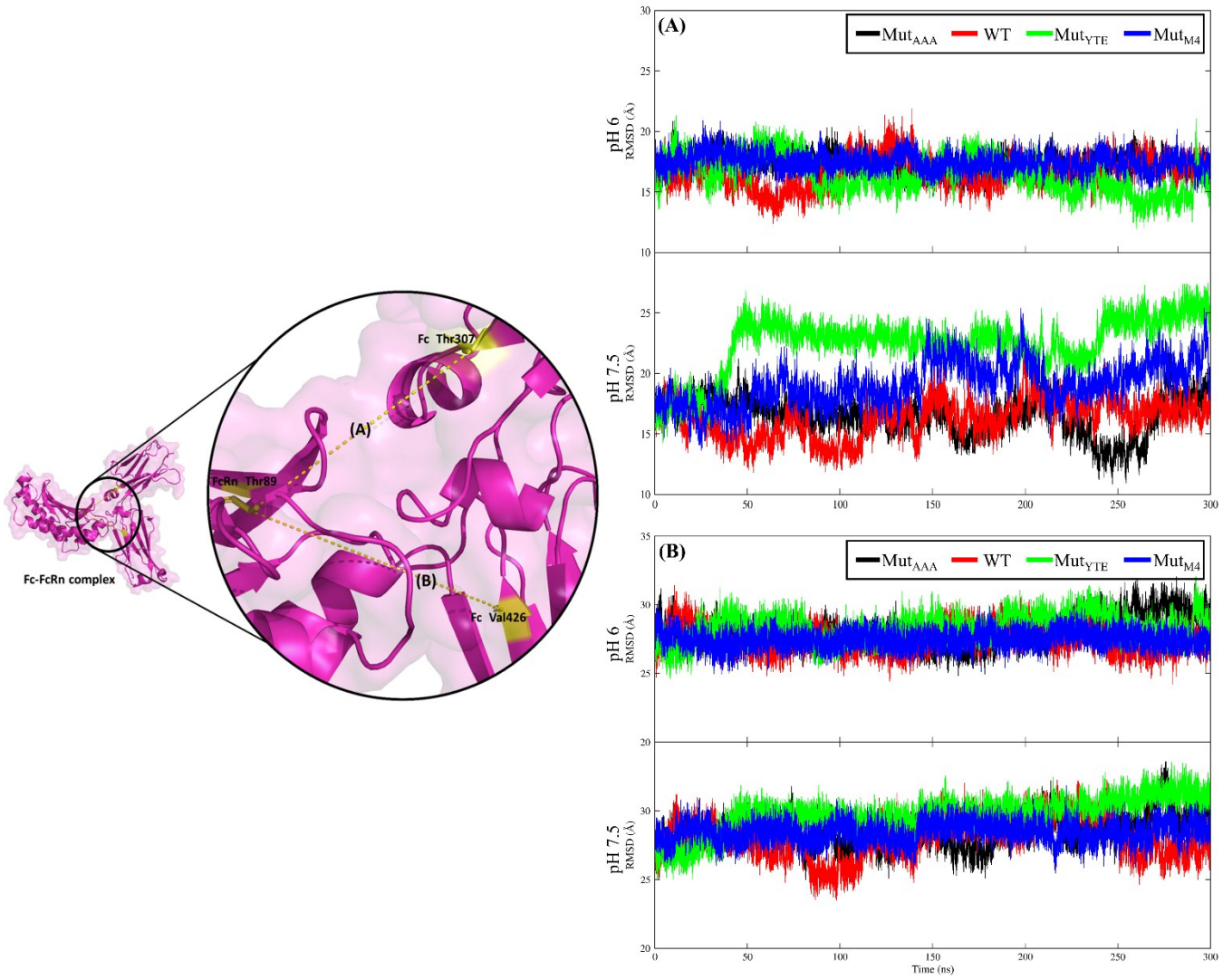
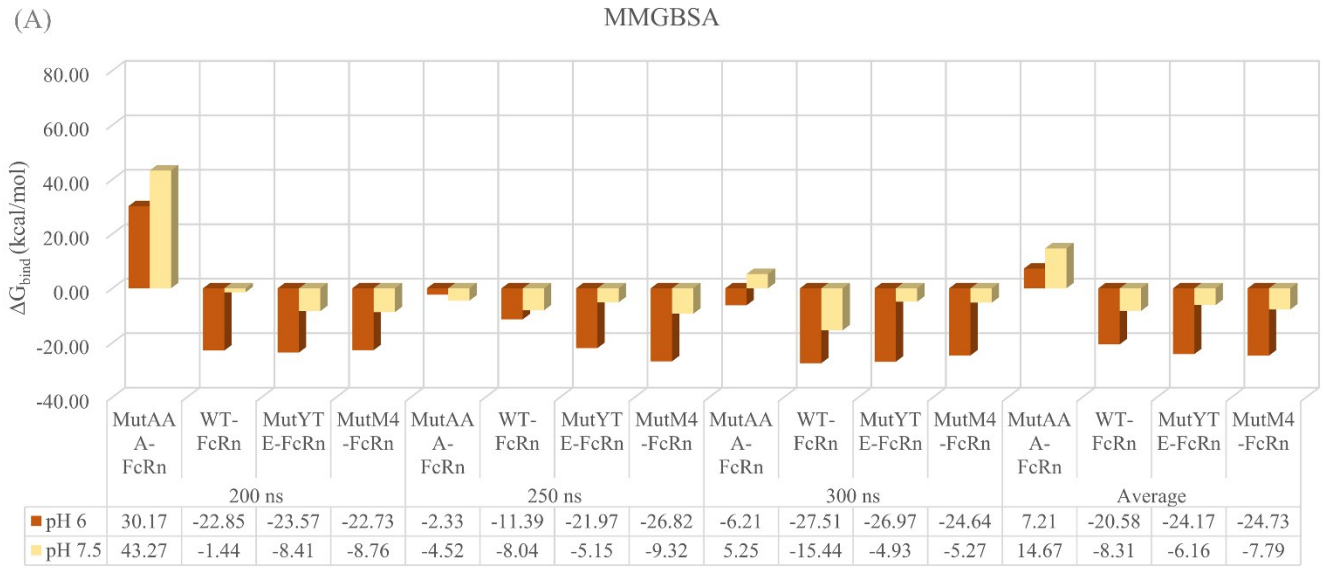


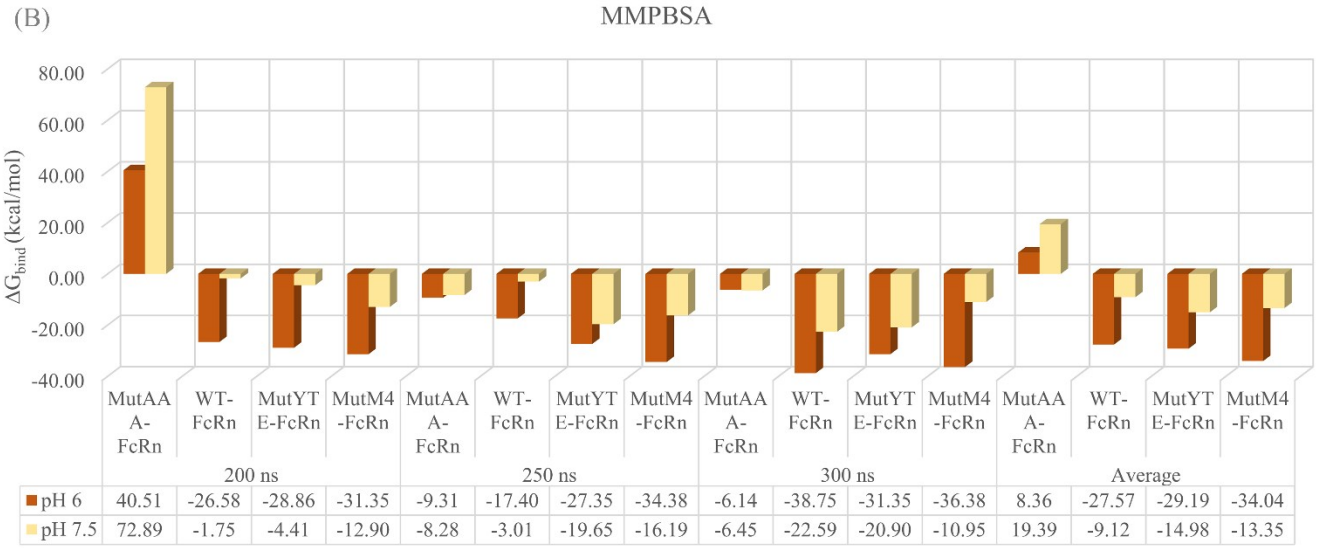

**Figure S4.** continued




**Supplementary Figure S5.** Left side of the picture showed the Fc-FcRn complex (pink ribbon presentation) with the three residues (colored yellow) used for distance measurement between Fc and FcRn. Distance between (A) FcRn Thr89 and Fc Thr307 and, (B) FcRn Thr89 and Fc Val426 from constant pH molecular dynamics simulation at pH 6.0 and 7.5 with the function of time for all Fc-variants ($Mut_{AAA}$, WT, $Mut_{YTE}$ and $Mut_{M4}$). Complex figure was prepared using Pymol (DeLano, 2003) and graph were plotted using Grace plotting tool (Turner & Stambulchik, 1998).




| | MutAAA-FcRn | WT-FcRn | MutYTE-FcRn | MutM4-FcRn | MutAAA-FcRn | WT-FcRn | MutYTE-FcRn | MutM4-FcRn | MutAAA-FcRn | WT-FcRn | MutYTE-FcRn | MutM4-FcRn | MutAAA-FcRn | WT-FcRn | MutYTE-FcRn | MutM4-FcRn |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 200 ns | | | | 250 ns | | | | 300 ns | | | | Average | | | |
| pH 6 | 30.17 | -22.85 | -23.57 | -22.73 | -2.33 | -11.39 | -21.97 | -26.82 | -6.21 | -27.51 | -26.97 | -24.64 | 7.21 | -20.58 | -24.17 | -24.73 |
| pH 7.5 | 43.27 | -1.44 | -8.41 | -8.76 | -4.52 | -8.04 | -5.15 | -9.32 | 5.25 | -15.44 | -4.93 | -5.27 | 14.67 | -8.31 | -6.16 | -7.79 |




| | MutAAA-FcRn | WT-FcRn | MutYTE-FcRn | MutM4-FcRn | MutAAA-FcRn | WT-FcRn | MutYTE-FcRn | MutM4-FcRn | MutAAA-FcRn | WT-FcRn | MutYTE-FcRn | MutM4-FcRn | MutAAA-FcRn | WT-FcRn | MutYTE-FcRn | MutM4-FcRn |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 200 ns | | | | 250 ns | | | | 300 ns | | | | Average | | | |
| pH 6 | 40.51 | -26.58 | -28.86 | -31.35 | -9.31 | -17.40 | -27.35 | -34.38 | -6.14 | -38.75 | -31.35 | -36.38 | 8.36 | -27.57 | -29.19 | -34.04 |
| pH 7.5 | 72.89 | -1.75 | -4.41 | -12.90 | -8.28 | -3.01 | -19.65 | -16.19 | -6.45 | -22.59 | -20.90 | -10.95 | 19.39 | -9.12 | -14.98 | -13.35 |

**Figure S6.** The binding free energy calculated using (A) MMGBSA and (B) MMPBSA approach.

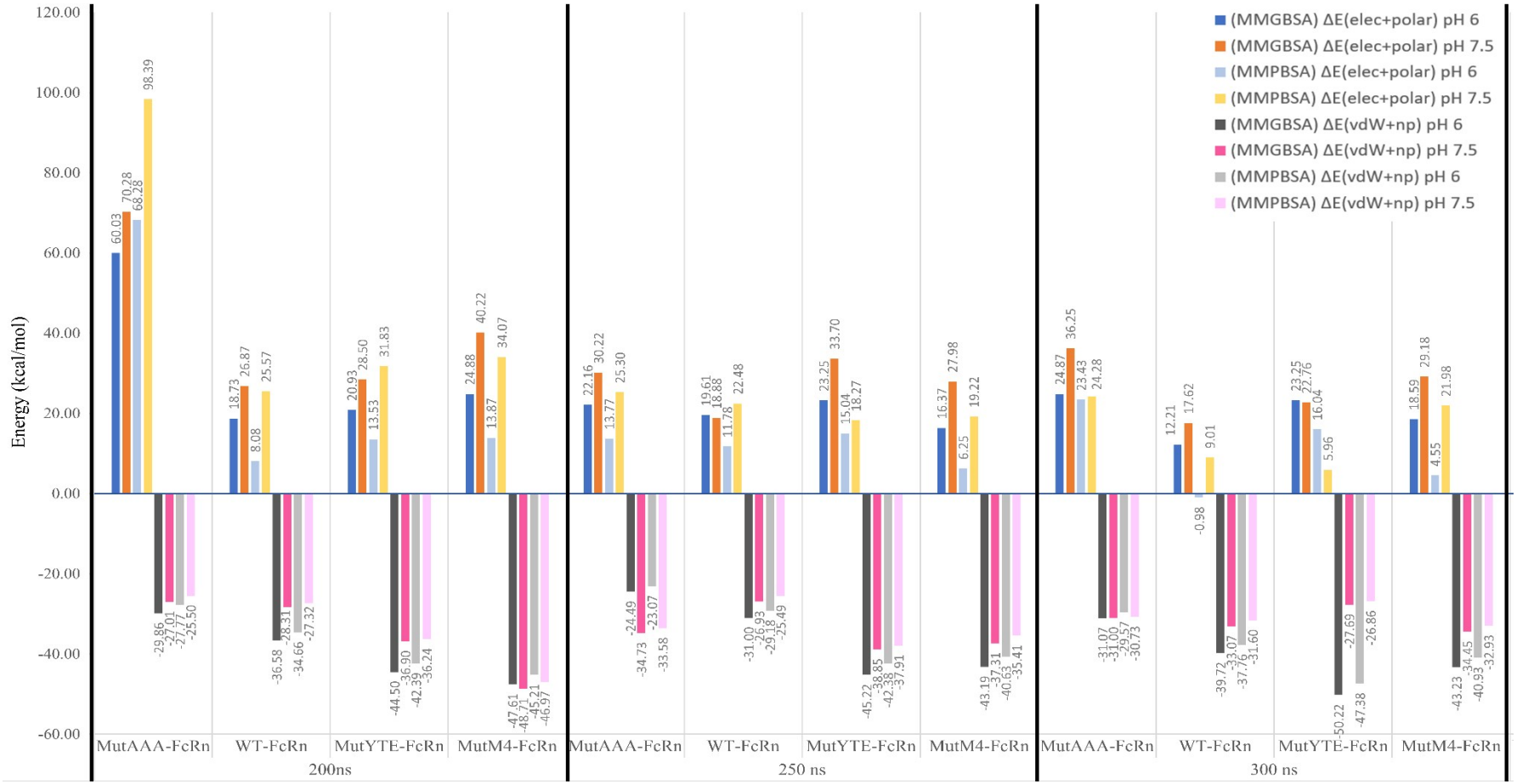



**Figure S7.** The hydrophilic ($\Delta E_{elec+polar}$) and hydrophobic ($\Delta E_{vdW+np}$) interaction in Fc-FcRn complex using MMGBSA and MMPBSA approach.

## Supplementary Table

**Supplementary Table S1.** Fc-FcRn MM-GBSA pair-wise decomposition binding free energy (kcal/mol) calculation averaged at (200 ns, 250 ns and 300 ns, respectively). Only $\Delta G_{Bind}$ less than -1.5 kcal/mol are listed here.

| **pH 6.0** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
|---|---|---|---|---|---|---|---|---|
| $Mut_{AAA}$ | Leu251 | -3.01(0.76) | -1.23(0.73) | 2.98(0.73) | -0.42(0.06) | 1.76(1.03) | -3.43(0.58) | -1.68(0.84) |
| | Met252 | -2.83(0.61) | -3.20(2.24) | 2.95(1.87) | -0.27(0.07) | -0.25(2.91) | -3.10(0.48) | -3.35(1.28) |
| | Ser254 | -2.70(1.56) | -11.19(3.05) | 9.36(1.94) | -0.74(0.08) | -1.84(3.53) | -3.44(1.16) | -5.27(2.01) |
| | Leu309 | -1.51(0.43) | -4.35(1.13) | 3.27(0.85) | -0.28(0.09) | -1.08(1.40) | -1.80(0.37) | -2.88(0.76) |
| | Gln311 | -3.42(1.27) | -8.71(3.64) | 8.58(2.39) | -0.73(0.09) | -0.13(4.26) | -4.14(0.96) | -4.27(1.94) |
| | His433 | -1.35(0.74) | -30.39(7.84) | 30.19(7.35) | -0.22(0.07) | -0.2(10.74) | -1.57(0.57) | -1.78(1.26) |
| FcRn | Tyr88 | -1.67(0.55) | -0.94(1.10) | 1.24(0.79) | -0.18(0.05) | 0.30(1.33) | -1.86(0.43) | -1.55(0.63) |
| | Phe117 | -2.53(0.51) | -0.02(0.51) | 0.77(0.47) | -0.31(0.08) | 0.74(0.69) | -2.85(0.42) | -2.11(0.64) |
| | Trp131 | -5.32(0.80) | -1.64(0.87) | 3.72(0.87) | -0.86(0.09) | 2.07(1.23) | -6.18(0.64) | -4.11(0.89) |
| | Pro132 | -3.77(0.87) | 0.20(0.92) | 0.34(0.73) | -0.72(0.09) | 0.55(1.17) | -4.49(0.68) | -3.95(0.83) |
| **pH 7.5** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
| | Leu251 | -3.07(0.72) | 0.72(0.96) | 1.01(0.81) | -0.45(0.07) | 1.73(1.25) | -3.52(0.55) | -1.79(0.83) |
| | Ser254 | -2.69(1.39) | -6.12(3.19) | 7.28(2.50) | -0.61(0.14) | 1.16(4.02) | -3.30(1.09) | -2.15(1.48) |
| | Leu309 | -1.68(0.71) | -2.59(1.15) | 2.23(0.88) | -0.36(0.11) | -0.36(1.43) | -2.04(0.58) | -2.39(0.99) |
| | Asn434 | -1.98(1.05) | -6.01(2.21) | 6.22(1.77) | -0.43(0.10) | 0.21(2.81) | -2.41(0.81) | -2.20(1.25) |
| FcRn | Trp131 | -6.36(1.18) | -1.99(1.24) | 3.97(0.97) | -1.05(0.15) | 1.98(1.56) | -7.41(0.94) | -5.43(1.24) |
| | Pro132 | -3.00(0.70) | -0.43(0.69) | 0.62(0.61) | -0.55(0.10) | 0.19(0.91) | -3.55(0.56) | -3.36(0.72) |

**Supplementary Table S1.** contimued

| **pH 6.0** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
|---|---|---|---|---|---|---|---|---|
| WT | Met252 | -3.11(0.72) | -6.19(1.33) | 4.69(0.94) | -0.26(0.10) | -1.51(1.60) | -3.37(0.58) | -4.88(1.24) |
| | Ile253 | -6.92(1.24) | -7.69(2.20) | 6.52(1.48) | -1.08(0.09) | -1.16(2.60) | -8.00(0.95) | -9.16(1.81) |
| | Ser254 | -1.38(2.05) | -15.61(3.11) | 11.18(1.76) | -0.62(0.09) | -4.43(3.44) | -2.00(1.51) | -6.44(1.58) |
| | Leu309 | -1.55(0.46) | -5.84(1.47) | 4.76(0.93) | -0.26(0.07) | -1.09(1.70) | -1.81(0.37) | -2.90(1.30) |
| | His310 | -1.20(1.48) | -57.36(7.45) | 56.59(6.22) | -0.18(0.08) | -0.77(9.67) | -1.38(1.10) | -2.15(2.00) |
| | Asn434 | -4.58(1.18) | -8.46(3.00) | 10.51(2.45) | -0.76(0.09) | 2.05(3.85) | -5.34(0.90) | -3.29(1.77) |
| | His435 | -3.09(1.44) | -49.45(7.54) | 50.14(6.29) | -0.47(0.07) | 0.69(9.78) | -3.55(1.07) | -2.86(1.93) |
| FcRn | Asn113 | -2.52(1.13) | -5.79(3.71) | 6.37(2.88) | -0.53(0.15) | 0.58(4.66) | -3.05(0.91) | -2.47(1.96) |
| | Glu115 | -3.19(1.50) | -92.31(6.36) | 93.19(5.26) | -0.86(0.08) | 0.88(8.21) | -4.04(1.12) | -3.16(3.23) |
| | Asp130 | -2.69(1.66) | -94.90(1.71) | 95.62(1.29) | -0.59(0.09) | 0.72(1.14) | -3.28(1.24) | -2.56(3.09) |
| | Trp131 | -6.71(1.22) | -1.48(2.32) | 1.55(1.74) | -0.75(0.15) | 0.07(2.87) | -7.47(0.97) | -7.39(1.78) |
| | Pro132 | -4.73(0.86) | 2.64(0.72) | -2.22(0.63) | -0.70(0.09) | 0.42(0.95) | -5.42(0.67) | -5.00(0.83) |
| | Glu133 | -1.65(1.78) | -89.92(5.18) | 86.17(4.39) | -0.43(0.08) | -3.75(6.76) | -2.09(1.31) | -5.84(2.27) |
| | Leu135 | -1.72(0.52) | 1.76(0.51) | -1.34(0.45) | -0.38(0.10) | 0.42(0.68) | -2.10(0.44) | -1.68(0.64) |
| **pH 7.5** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
| WT | Met252 | -1.84(0.59) | -2.80(1.99) | 1.82(1.76) | -0.15(0.09) | -0.98(2.65) | -1.99(0.47) | -2.96(0.91) |
| | Ile253 | -4.87(1.40) | -3.53(2.33) | 3.42(1.59) | -0.97(0.14) | -0.11(2.78) | -5.84(1.09) | -5.94(1.35) |
| | Ser254 | -1.18(1.15) | -9.09(2.27) | 6.60(1.69) | -0.44(0.09) | -2.49(2.81) | -1.62(0.88) | -4.11(1.21) |
| | Leu309 | -1.54(0.72) | -5.16(1.33) | 4.37(0.86) | -0.26(0.13) | -0.79(1.55) | -1.81(0.60) | -2.60(1.35) |
| | Asn434 | -3.99(1.20) | -9.46(2.58) | 10.54(1.98) | -0.69(0.08) | 1.08(3.22) | -4.68(0.91) | -3.60(1.25) |
| FcRn | Glu115 | -2.64(1.66) | -88.66(8.12) | 89.4(6.15) | -0.79(0.11) | 0.74(10.09) | -3.43(1.26) | -2.70(3.84) |
| | Trp131 | -7.70(1.16) | -4.07(2.67) | 5.57(1.95) | -0.88(0.13) | 1.50(3.27) | -8.58(0.91) | -7.08(1.69) |
| | Pro132 | -3.95(0.84) | 0.93(0.75) | -0.7(0.68) | -0.63(0.09) | 0.22(1.02) | -4.57(0.66) | -4.35(0.79) |

**Supplementary Table S1.** contimued

| pH 6.0 | | $\Delta E_{vdW}$ ($SD_{error}$) | $\Delta E_{elec}$ ($SD_{error}$) | $\Delta G_{polar}$ ($SD_{error}$) | $\Delta G_{np}$ ($SD_{error}$) | $\Delta E_{elec+polar}$ ($SD_{error}$) | $\Delta E_{vdW+np}$ ($SD_{error}$) | $\Delta G_{Bind}$ ($SD_{error}$) |
|---|---|---|---|---|---|---|---|---|
| $Mut_{YTE}$ | Tyr252 | -2.56(0.97) | -4.63(1.47) | 4.03(1.41) | -0.31(0.14) | -0.60(2.04) | -2.87(0.78) | -3.47(1.51) |
| | Ile253 | -6.01(1.24) | -7.34(2.93) | 6.27(1.32) | -0.92(0.10) | -1.07(3.00) | -6.93(0.95) | -8.00(2.03) |
| | Thr254 | -4.30(1.71) | -5.20(5.78) | 6.06(2.55) | -0.92(0.09) | 0.85(5.89) | -5.22(1.27) | -4.37(4.00) |
| | Leu309 | -1.50(0.46) | -1.61(0.85) | 1.71(0.80) | -0.19(0.08) | 0.10(1.16) | -1.69(0.38) | -1.59(0.59) |
| | Gln311 | -2.50(0.90) | -4.79(3.22) | 5.61(2.54) | -0.43(0.07) | 0.81(4.08) | -2.93(0.68) | -2.12(1.25) |
| | His433 | -0.99(0.59) | -34.6(8.72) | 33.67(8.22) | -0.13(0.06) | -0.94(11.97) | -1.12(0.46) | -2.06(0.97) |
| | Asn434 | -3.40(1.09) | -8.33(1.92) | 9.61(1.67) | -0.57(0.12) | 1.29(2.54) | -3.97(0.85) | -2.68(1.18) |
| | His435 | -2.80(1.23) | -54.25(5.21) | 53.09(4.63) | -0.44(0.06) | -1.17(6.95) | -3.24(0.91) | -4.41(1.59) |
| FcRn | Leu112 | -2.56(0.60) | -4.01(0.84) | 4.65(0.89) | -0.19(0.04) | 0.64(1.22) | -2.75(0.46) | -2.11(0.77) |
| | Asn113 | -4.33(1.21) | -13.83(5.31) | 14.21(3.42) | -0.89(0.08) | 0.37(6.17) | -5.23(0.91) | -4.85(2.53) |
| | Glu115 | -3.06(1.22) | -64.29(6.73) | 65.24(5.79) | -0.52(0.07) | 0.95(8.86) | -3.59(0.91) | -2.64(1.83) |
| | Asp130 | -2.36(1.58) | -93.01(8.72) | 91.31(7.55) | -0.66(0.09) | -1.70(11.51) | -3.02(1.18) | -4.72(2.69) |
| | Trp131 | -7.28(1.06) | -5.38(1.90) | 5.33(1.42) | -0.77(0.08) | -0.05(2.34) | -8.05(0.81) | -8.10(1.41) |
| | Pro132 | -3.44(0.86) | 0.57(0.57) | 0.11(0.54) | -0.61(0.11) | 0.68(0.79) | -4.06(0.68) | -3.37(0.89) |
| **pH 7.5** | | $\Delta E_{vdW}$ ($SD_{error}$) | $\Delta E_{elec}$ ($SD_{error}$) | $\Delta G_{polar}$ ($SD_{error}$) | $\Delta G_{np}$ ($SD_{error}$) | $\Delta E_{elec+polar}$ ($SD_{error}$) | $\Delta E_{vdW+np}$ ($SD_{error}$) | $\Delta G_{Bind}$ ($SD_{error}$) |
| $Mut_{YTE}$ | Tyr252 | -3.35(0.81) | -6.14(0.94) | 4.58(0.90) | -0.26(0.05) | -1.57(1.30) | -3.61(0.61) | -5.18(1.37) |
| | Ile253 | -4.45(1.28) | -6.95(1.56) | 5.77(1.08) | -0.74(0.12) | -1.18(1.86) | -5.19(0.99) | -6.36(1.56) |
| | Thr254 | -1.16(1.59) | -13.47(3.55) | 8.55(1.95) | -0.50(0.11) | -4.92(3.89) | -1.66(1.20) | -6.58(2.10) |
| | Asn434 | -5.33(1.22) | -8.59(2.11) | 10.5(1.67) | -0.75(0.07) | 1.91(2.67) | -6.08(0.91) | -4.17(1.51) |
| | His435 | -3.28(1.39) | -47.39(7.03) | 49.07(6.78) | -0.48(0.06) | 1.68(9.77) | -3.76(1.03) | -2.08(2.15) |
| FcRn | Trp131 | -7.49(1.08) | -1.86(1.83) | 4.16(1.54) | -0.79(0.11) | 2.30(2.39) | -8.29(0.84) | -5.99(1.57) |
| | Pro132 | -4.90(0.79) | 1.44(0.54) | -1.57(0.53) | -0.68(0.06) | -0.14(0.76) | -5.58(0.60) | -5.71(0.86) |
| | Glu133 | -2.15(1.81) | -80.39(6.97) | 78.33(5.09) | -0.53(0.06) | -2.06(8.53) | -2.68(1.32) | -4.74(3.25) |
| | Leu135 | -2.15(0.52) | 2.09(0.43) | -1.46(0.39) | -0.45(0.08) | 0.63(0.58) | -2.59(0.43) | -1.96(0.57) |

**Supplementary Table S1.** contimued

| **pH 6.0** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
|---|---|---|---|---|---|---|---|---|
| $Mut_{M4}$ | Tyr252 | -3.54(0.69) | -5.52(1.05) | 2.88(0.99) | -0.27(0.05) | -2.64(1.44) | -3.81(0.52) | -6.44(1.35) |
| | Ile253 | -6.72(1.25) | -3.64(2.46) | 2.26(1.57) | -0.93(0.07) | -1.38(2.85) | -7.66(0.93) | -9.04(1.89) |
| | Phe254 | -5.40(1.35) | -6.20(1.74) | 6.50(1.23) | -1.12(0.11) | 0.30(2.10) | -6.52(1.03) | -6.22(1.29) |
| | Leu309 | -1.50(0.33) | -6.42(0.98) | 4.12(0.67) | -0.17(0.05) | -2.29(1.17) | -1.67(0.27) | -3.96(1.09) |
| | His310 | -0.60(1.65) | -60.26(6.80) | 56.35(5.20) | -0.16(0.05) | -3.91(8.49) | -0.77(1.20) | -4.67(1.93) |
| | Gln311 | -2.62(1.19) | -10.03(3.08) | 9.73(1.96) | -0.51(0.08) | -0.29(3.56) | -3.13(0.90) | -3.42(1.71) |
| | Asn434 | -5.01(1.15) | -10.38(2.42) | 13.08(1.83) | -0.83(0.09) | 2.69(3.00) | -5.85(0.88) | -3.16(1.51) |
| | His435 | -3.28(1.58) | -58.94(6.49) | 58.28(5.33) | -0.37(0.06) | -0.66(8.36) | -3.65(1.16) | -4.31(1.82) |
| | Tyr436 | -1.79(0.54) | 0.47(0.38) | 0.00(0.44) | -0.26(0.06) | 0.46(0.58) | -2.05(0.43) | -1.58(0.52) |
| FcRn | Leu112 | -2.01(0.59) | -1.39(0.52) | 2.00(0.69) | -0.19(0.06) | 0.61(0.85) | -2.20(0.46) | -1.59(0.53) |
| | Glu115 | -3.06(1.63) | -110.45(8.48) | 109.01(6.97) | -0.97(0.07) | -1.44(10.93) | -4.03(1.20) | -5.47(3.25) |
| | Glu116 | -1.24(0.81) | -63.76(4.72) | 63.64(4.60) | -0.23(0.05) | -0.12(6.59) | -1.47(0.61) | -1.59(0.87) |
| | Trp131 | -10.05(1.05) | -5.21(2.29) | 4.59(1.26) | -1.07(0.08) | -0.62(2.51) | -11.11(0.80) | -11.73(2.22) |
| | Pro132 | -5.06(0.75) | 2.69(0.62) | -2.53(0.60) | -0.68(0.07) | 0.16(0.86) | -5.74(0.58) | -5.58(0.88) |
| | Leu135 | -2.22(0.63) | 1.84(0.64) | -1.47(0.57) | -0.45(0.10) | 0.36(0.85) | -2.67(0.52) | -2.31(0.69) |
| **pH 7.5** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
| $Mut_{M4}$ | Tyr252 | -3.67(0.74) | -5.45(1.18) | 3.84(0.97) | -0.30(0.05) | -1.61(1.52) | -3.97(0.56) | -5.58(1.37) |
| | Ile253 | -5.68(1.36) | -5.28(1.78) | 4.11(1.23) | -0.94(0.15) | -1.17(2.13) | -6.62(1.07) | -7.79(1.80) |
| | Phe254 | -5.73(1.25) | -8.17(3.14) | 7.94(1.96) | -1.20(0.11) | -0.23(3.60) | -6.92(0.96) | -7.15(1.95) |
| | Asn434 | -5.20(1.12) | -8.94(2.66) | 11.80(1.98) | -0.86(0.08) | 2.87(3.28) | -6.06(0.85) | -3.19(1.55) |
| | His435 | -2.94(1.53) | -45.91(10.10) | 47.13(9.27) | -0.40(0.09) | 1.22(13.69) | -3.34(1.14) | -2.11(1.40) |
| FcRn | Trp131 | -8.46(1.37) | -4.80(2.25) | 4.43(1.09) | -0.92(0.10) | -0.37(2.37) | -9.39(1.04) | -9.76(2.30) |
| | Pro132 | -4.86(0.84) | 2.58(0.62) | -2.77(0.61) | -0.67(0.07) | -0.20(0.87) | -5.53(0.64) | -5.73(0.88) |
| | Leu135 | -2.21(0.54) | 2.41(0.60) | -1.90(0.51) | -0.46(0.07) | 0.50(0.79) | -2.67(0.43) | -2.16(0.59) |

**Supplementary Table S2.** Fc-FcRn MM-PBSA pair-wise decomposition binding free energy (kcal/mol) calculation averaged at (200 ns, 250 ns and 300 ns, respectively). Only $\Delta G_{Bind}$ less than -1.5 kcal/mol are listed here.

| **pH 6.0** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
|---|---|---|---|---|---|---|---|---|
| $Mut_{AAA}$ | Met252 | -2.83(0.61) | -3.20(2.24) | 2.85(1.66) | 0.00(0.00) | -0.35(2.76) | -2.83(0.43) | -3.18(1.25) |
| | Ser254 | -2.70(1.56) | -11.19(3.05) | 9.05(1.98) | 0.00(0.00) | -2.14(3.56) | -2.70(1.11) | -4.84(2.12) |
| | Leu309 | -1.51(0.43) | -4.35(1.13) | 3.29(0.80) | 0.00(0.00) | -1.06(1.36) | -1.51(0.31) | -2.58(0.75) |
| | Gln311 | -3.42(1.27) | -8.71(3.64) | 7.75(2.21) | 0.00(0.00) | -0.95(4.14) | -3.42(0.90) | -4.37(1.99) |
| | His433 | -1.04(0.82) | -24.88(5.16) | 24.17(4.55) | 0.00(0.00) | -0.72(6.86) | -1.04(0.58) | -1.76(1.96) |
| FcRn | Phe117 | -2.53(0.51) | -0.02(0.51) | 0.91(0.60) | 0.00(0.00) | 0.89(0.78) | -2.53(0.36) | -1.64(0.60) |
| | Trp131 | -5.32(0.80) | -1.64(0.87) | 3.67(0.98) | 0.00(0.00) | 2.02(1.31) | -5.32(0.57) | -3.30(1.00) |
| | Pro132 | -3.77(0.87) | 0.20(0.92) | 0.38(0.71) | 0.00(0.00) | 0.58(1.15) | -3.77(0.61) | -3.20(0.81) |
| **pH 7.5** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
| $Mut_{AAA}$ | Ser254 | -2.69(1.39) | -6.12(3.19) | 7.10(2.69) | 0.00(0.00) | 0.98(4.16) | -2.69(0.99) | -1.71(1.46) |
| | Thr256 | -1.12(0.66) | -3.56(3.13) | 3.16(2.54) | 0.00(0.00) | -0.39(4.01) | -1.12(0.47) | -1.51(1.68) |
| | Leu309 | -1.68(0.71) | -2.59(1.15) | 1.79(0.86) | 0.00(0.00) | -0.80(1.43) | -1.68(0.50) | -2.47(0.96) |
| | Asn434 | -1.98(1.05) | -6.01(2.21) | 6.04(1.74) | 0.00(0.00) | 0.03(2.79) | -1.98(0.74) | -1.95(1.32) |
| FcRn | Trp131 | -6.36(1.18) | -1.99(1.24) | 4.40(1.14) | 0.00(0.00) | 2.40(1.68) | -6.36(0.83) | -3.96(1.31) |
| | Pro132 | -3.00(0.70) | -0.43(0.69) | 0.59(0.57) | 0.00(0.00) | 0.16(0.89) | -3.00(0.49) | -2.84(0.77) |

**Supplementary Table S2.** contimued

| **pH 6.0** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
|---|---|---|---|---|---|---|---|---|
| WT | Met252 | -3.11(0.72) | -6.19(1.33) | 4.37(0.82) | 0.00(0.00) | -1.82(1.52) | -3.11(0.51) | -4.93(1.26) |
| | Ile253 | -6.92(1.24) | -7.69(2.20) | 6.43(1.48) | 0.00(0.00) | -1.26(2.60) | -6.92(0.88) | -8.18(1.96) |
| | Ser254 | -1.38(2.05) | -15.61(3.11) | 9.87(1.80) | 0.00(0.00) | -5.74(3.47) | -1.38(1.45) | -7.12(1.69) |
| | Leu309 | -1.55(0.46) | -5.84(1.47) | 4.79(0.78) | 0.00(0.00) | -1.05(1.59) | -1.55(0.33) | -2.60(1.22) |
| | His310 | -1.09(1.22) | -51.48(5.85) | 48.52(4.35) | 0.00(0.00) | -2.96(7.21) | -1.09(0.86) | -4.05(4.27) |
| | His433 | -0.69(0.49) | -25.30(8.95) | 24.18(7.86) | 0.00(0.00) | -1.12(11.89) | -0.69(0.35) | -1.81(1.72) |
| | Asn434 | -4.58(1.18) | -8.46(3.00) | 10.61(2.33) | 0.00(0.00) | 2.14(3.76) | -4.58(0.84) | -2.44(1.87) |
| | His435 | -3.09(1.44) | -49.45(7.54) | 50.19(5.70) | 0.00(0.00) | 0.74(9.36) | -3.09(1.02) | -2.35(3.62) |
| FcRn | Asn113 | -2.52(1.13) | -5.79(3.71) | 5.74(3.06) | 0.00(0.00) | -0.05(4.78) | -2.52(0.80) | -2.57(2.15) |
| | Trp131 | -6.71(1.22) | -1.48(2.32) | 4.44(1.94) | 0.00(0.00) | 2.96(3.01) | -6.71(0.86) | -3.75(1.81) |
| | Pro132 | -4.73(0.86) | 2.64(0.72) | -2.21(0.57) | 0.00(0.00) | 0.43(0.91) | -4.73(0.61) | -4.29(0.85) |
| | Glu133 | -1.65(1.78) | -89.92(5.18) | 87.87(4.95) | 0.00(0.00) | -2.06(7.16) | -1.65(1.26) | -3.71(2.99) |
| | Leu135 | -1.72(0.52) | 1.76(0.51) | -1.69(0.47) | 0.00(0.00) | 0.06(0.70) | -1.72(0.37) | -1.65(0.60) |
| **pH 7.5** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
| WT | Met252 | -1.84(0.03) | -2.80(1.99) | 1.97(1.54) | 0.00(0.00) | -0.83(2.50) | -1.84(0.02) | -2.66(1.00) |
| | Ile253 | -4.87(1.25) | -3.53(2.33) | 3.15(1.67) | 0.00(0.00) | -0.38(2.83) | -4.87(-0.88) | -5.24(1.64) |
| | Ser254 | -1.18(0.96) | -9.09(2.27) | 5.98(1.76) | 0.00(0.00) | -3.11(2.85) | -1.18(0.68) | -4.29(1.20) |
| | Gln311 | -2.06(0.87) | -5.66(4.36) | 5.50(3.32) | 0.00(0.00) | -0.16(5.42) | -2.06(-0.62) | -2.22(2.18) |
| | Asn434 | -3.99(1.42) | -9.46(2.58) | 11.01(1.85) | 0.00(0.00) | 1.56(3.13) | -3.99(-1.01) | -2.43(1.43) |
| FcRn | Trp131 | -7.70(3.82) | -4.07(2.67) | 8.78(1.96) | 0.00(0.00) | 4.71(3.27) | -7.70(-2.70) | -2.99(2.08) |
| | Pro132 | -3.95(1.16) | 0.93(0.75) | -0.53(0.58) | 0.00(0.00) | 0.39(0.94) | -3.95(-0.82) | -3.55(0.78) |

**Supplementary Table S2.** contimued

| **pH 6.0** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
|---|---|---|---|---|---|---|---|---|
| $Mut_{YTE}$ | Tyr252 | -2.56(0.97) | -4.63(1.47) | 3.16(1.53) | 0.00(0.00) | -1.47(2.12) | -2.56(0.69) | -4.03(1.72) |
| | Ile253 | -6.01(1.24) | -7.34(2.93) | 6.32(1.25) | 0.00(0.00) | -1.02(2.95) | -6.01(0.88) | -7.03(2.42) |
| | Thr254 | -4.30(1.71) | -5.20(5.78) | 6.39(2.51) | 0.00(0.00) | 1.19(5.86) | -4.30(1.21) | -3.11(4.26) |
| | Gln311 | -2.50(0.90) | -4.79(3.22) | 4.92(2.37) | 0.00(0.00) | 0.13(3.96) | -2.50(0.64) | -2.36(1.76) |
| | His433 | -0.99(0.59) | -34.60(8.72) | 32.22(7.38) | 0.00(0.00) | -2.38(11.38) | -0.99(0.42) | -3.38(1.66) |
| | His435 | -2.80(1.23) | -54.25(5.21) | 52.50(4.68) | 0.00(0.00) | -1.75(6.99) | -2.80(0.87) | -4.55(2.81) |
| FcRn | Leu112 | -2.56(0.60) | -4.01(0.84) | 4.89(0.92) | 0.00(0.00) | 0.88(1.25) | -2.56(0.43) | -1.68(0.92) |
| | Asn113 | -4.33(1.21) | -13.83(5.31) | 13.59(3.55) | 0.00(0.00) | -0.24(6.27) | -4.33(0.86) | -4.57(2.58) |
| | Glu115 | -3.06(1.22) | -64.29(6.73) | 65.60(5.32) | 0.00(0.00) | 1.31(8.52) | -3.06(0.86) | -1.75(3.60) |
| | Asp130 | -2.36(1.58) | -93.01(8.72) | 92.49(7.34) | 0.00(0.00) | -0.53(11.36) | -2.36(1.11) | -2.89(3.11) |
| | Trp131 | -7.28(1.06) | -5.38(1.90) | 8.14(1.38) | 0.00(0.00) | 2.76(2.32) | -7.28(0.75) | -4.52(1.66) |
| | Pro132 | -3.44(0.86) | 0.57(0.57) | -0.22(0.48) | 0.00(0.00) | 0.36(0.74) | -3.44(0.61) | -3.09(0.85) |
| **pH 7.5** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
| $Mut_{YTE}$ | Tyr252 | -3.35(0.81) | -6.14(0.94) | 5.30(0.92) | 0.00(0.00) | -0.84(1.31) | -3.35(0.57) | -4.19(1.42) |
| | Ile253 | -4.45(1.28) | -6.95(1.56) | 4.54(0.92) | 0.00(0.00) | -2.41(1.75) | -4.45(0.90) | -6.86(1.48) |
| | Thr254 | -1.16(1.59) | -13.47(3.55) | 7.17(2.06) | 0.00(0.00) | -6.30(3.97) | -1.16(1.12) | -7.46(2.14) |
| FcRn | Trp131 | -7.49(1.08) | -1.86(1.83) | 5.81(1.68) | 0.00(0.00) | 3.94(2.48) | -7.49(0.76) | -3.55(1.64) |
| | Pro132 | -4.90(0.79) | 1.44(0.54) | -1.28(0.48) | 0.00(0.00) | 0.16(0.72) | -4.90(0.56) | -4.74(0.84) |
| | Leu135 | -2.15(0.52) | 2.09(0.43) | -1.77(0.38) | 0.00(0.00) | 0.32(0.58) | -2.15(0.37) | -1.82(0.55) |

**Supplementary Table S2.** contimued

| **pH 6.0** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
|---|---|---|---|---|---|---|---|---|
| $Mut_{M4}$ | Tyr252 | -3.54(0.69) | -5.52(1.05) | 3.95(0.81) | 0.00(0.00) | -1.57(1.32) | -3.54(0.49) | -5.11(1.17) |
| | Ile253 | -6.72(1.25) | -3.64(2.46) | 2.00(1.70) | 0.00(0.00) | -1.64(2.94) | -6.72(0.88) | -8.36(2.05) |
| | Phe254 | -5.40(1.35) | -6.20(1.74) | 5.43(1.19) | 0.00(0.00) | -0.76(2.07) | -5.40(0.95) | -6.16(1.45) |
| | Leu309 | -1.50(0.33) | -6.42(0.98) | 4.52(0.63) | 0.00(0.00) | -1.90(1.14) | -1.50(0.23) | -3.41(0.78) |
| | His310 | -0.60(1.65) | -60.26(6.80) | 51.64(4.60) | 0.00(0.00) | -8.62(8.06) | -0.60(1.17) | -9.22(3.54) |
| | Gln311 | -2.62(1.19) | -10.03(3.08) | 7.47(1.65) | 0.00(0.00) | -2.56(3.35) | -2.62(0.84) | -5.18(1.91) |
| | Asn434 | -5.01(1.15) | -10.38(2.42) | 13.78(1.84) | 0.00(0.00) | 3.39(3.01) | -5.01(0.81) | -1.62(1.79) |
| | His435 | -3.28(1.58) | -58.94(6.49) | 58.09(4.96) | 0.00(0.00) | -0.85(8.10) | -3.28(1.12) | -4.13(3.86) |
| FcRn | Glu115 | -3.06(1.63) | -110.45(8.48) | 111.23(6.57) | 0.00(0.00) | 0.78(10.64) | -3.06(1.15) | -2.28(3.71) |
| | Trp131 | -3.10(1.05) | -5.21(2.29) | 6.97(1.14) | 0.00(0.00) | 1.76(2.42) | -3.10(0.75) | -8.29(2.14) |
| | Pro132 | -5.06(0.75) | 2.69(0.62) | -2.68(0.51) | 0.00(0.00) | 0.01(0.80) | -5.06(0.53) | -5.05(0.83) |
| **pH 7.5** | | **$\Delta E_{vdW}$ ($SD_{error}$)** | **$\Delta E_{elec}$ ($SD_{error}$)** | **$\Delta G_{polar}$ ($SD_{error}$)** | **$\Delta G_{np}$ ($SD_{error}$)** | **$\Delta E_{elec+polar}$ ($SD_{error}$)** | **$\Delta E_{vdW+np}$ ($SD_{error}$)** | **$\Delta G_{Bind}$ ($SD_{error}$)** |
| $Mut_{M4}$ | Tyr252 | -3.67(0.74) | -5.45(1.18) | 3.87(1.28) | 0.00(0.00) | -1.58(1.74) | -3.67(0.53) | -5.25(1.44) |
| | Ile253 | -5.68(1.36) | -5.28(1.78) | 2.98(1.17) | 0.00(0.00) | -2.29(2.08) | -5.68(0.96) | -7.97(1.77) |
| | Phe254 | -5.73(1.25) | -8.17(3.14) | 7.32(1.95) | 0.00(0.00) | -0.86(3.60) | -5.73(0.88) | -6.58(1.87) |
| | Asn434 | -5.20(1.12) | -8.94(2.66) | 12.58(1.84) | 0.00(0.00) | 3.64(3.18) | -5.20(0.79) | -1.56(1.89) |
| FcRn | Trp131 | -8.46(1.37) | -4.80(2.25) | 6.22(1.23) | 0.00(0.00) | 1.42(2.46) | -8.46(0.97) | -7.05(2.19) |
| | Pro132 | -4.86(0.84) | 2.58(0.62) | -2.55(0.48) | 0.00(0.00) | 0.03(0.78) | -4.86(0.60) | -4.83(0.86) |
| | Leu135 | -2.21(0.54) | 2.41(0.60) | -2.12(0.52) | 0.00(0.00) | 0.29(0.79) | -2.21(0.38) | -1.92(0.57) |

**Table S3.** Intermolecule interactions of MD representative structures for IgG1-Fc variant complexed with FcRn. ***Bold** residues are involved in hydrogen bonding.

**$Mut_{AAA}$ Hydrophilic Interaction**

| pH 6 | | | pH 7.5 | | |
|---|---|---|---|---|---|
| **IgG1-Fc** | **FcRn** | **distance (Å)** | **IgG1-Fc** | **FcRn** | **distance (Å)** |
| Gln311 .A.OE1 | Glu116 .B.H | 1.8 | ***Asn434 .A.H** | ***Asp130 .B.O** | **2.0** |
| ***Gln311 .A.H** | ***Glu115 .B.OE1** | **1.9** | Thr256 .A.OG1 | Lys85 .B.HE3 | 2.3 |
| Thr250 .A.O | Trp131 .B.HZ3 | 2.2 | Ser254 .A.O | Lys85 .B.HB2 | 2.5 |
| Leu251 .A.O | Pro132 .B.HD2 | 2.4 | Leu309 .A.HD22 | Asn113 .B.ND2 | 2.6 |
| Asn434 .A.OD1 | Pro132 .B.HA | 2.7 | Gln311 .A.OE1 | Asn113 .B.HB3 | 2.7 |
| **Ser254 .A.HG** | **Glu133 .B.OE1** | **3.0** | Gln311 .A.HG2 | Asn113 .B.O | 2.8 |
| | | | Gln311 .A.HG2 | Leu112 .B.O | 2.8 |
| | | | Asn434 .A.OD1 | Pro132 .B.HB3 | 2.8 |

**$Mut_{AAA}$ Hydrophobic Interaction**

| pH 6 | | | pH 7.5 | | |
|---|---|---|---|---|---|
| **IgG1-Fc** | **FcRn** | **distance (Å)** | **IgG1-Fc** | **FcRn** | **distance (Å)** |
| Leu251 .A | Trp131 .B | 2.1 | His433 .A | Asp130 .B | 1.9 |
| Gln311 .A | Trp131 .B | 2.2 | Leu251 .A | Pro132 .B | 2.2 |
| Met252 .A | Glu133 .B | 2.2 | Leu314 .A | Glu115 .B | 2.2 |
| Leu309 .A | Glu115 .B | 2.4 | Leu251 .A | Trp131 .B | 2.3 |
| Leu314 .A | Trp131 .B | 2.6 | Glu430 .A | Trp131 .B | 2.3 |
| Leu251 .A | Pro132 .B | 3.5 | Leu251 .A | Trp131 .B | 2.8 |
| | | | Leu251 .A | Pro132 .B | 3.0 |
| | | | Arg255 .A | Lys85 .B | 3.1 |
| | | | Met428 .A | Trp131 .B | 3.1 |
| | | | Thr256 .A | Lys85 .B | 3.3 |

**WT Hydrophilic Interaction**

| pH 6 | | | pH 7.5 | | |
|---|---|---|---|---|---|
| **IgG1-Fc** | **FcRn** | **distance (Å)** | **IgG1-Fc** | **FcRn** | **distance (Å)** |
| ***His310 .A.HD1** | ***Glu115 .B.OE2** | **1.1** | Asn434 .A.HA | Asp130 .B.O | 2.3 |
| ***Ser254 .A.HG1** | ***Glu133 .B.OE1** | **1.2** | Leu251 .A.O | Pro132 .B.HD3 | 2.6 |
| Ser254 .A.O | Tyr88 .B.HH | 1.7 | ***Ser254 .A.H** | **Glu133 .B.OE1** | **2.7** |
| ***Ile253 .A.O** | ***Asn113 .B.HD22** | **1.9** | Ser254 .A.O | Tyr88 .B.HE2 | 2.8 |
| Leu251 .A.O | Trp131 .B.HD1 | 2.5 | Asn434 .A.O | Trp131 .B.HA | 2.8 |
| Leu309 .A.HB3 | Glu115 .B.OE2 | 2.8 | | | |
| Ile253 .A.HD11 | Trp131 .B.NE1 | 2.9 | | | |

**WT Hydrophobic Interaction**

| pH 6 | | | pH 7.5 | | |
|---|---|---|---|---|---|
| **IgG1-Fc** | **FcRn** | **distance (Å)** | **IgG1-Fc** | **FcRn** | **distance (Å)** |
| Gln311 .A | Glu115 .B | 1.3 | His310 .A | Glu115 .B | 1.2 |
| Asn434 .A | Asp130 .B | 1.6 | Ile253 .A | Glu133 .B | 1.6 |
| Ile253 .A | Glu133 .B | 1.6 | Ser254 .A | Leu82 .B | 2.0 |
| Met252 .A | Glu133 .B | 1.9 | Ile253 .A | Phe117 .B | 2.2 |
| Thr256 .A | Asn113 .B | 1.9 | Ile253 .A | Glu115 .B | 2.3 |
| Asn434 .A | Gly129 .B | 2.0 | Leu251 .A | Trp131 .B | 2.3 |
| His433 .A | Asp130 .B | 2.1 | Met428 .A | Pro132 .B | 2.3 |
| Met252 .A | Pro132 .B | 2.1 | Asn434 .A | Leu135 .B | 2.7 |
| Ser254 .A | Leu82 .B | 2.1 | Ile253 .A | Trp131 .B | 2.7 |
| Asn434 .A | Leu135 .B | 2.2 | His435 .A | Trp131 .B | 3.0 |
| His435 .A | Asp130 .B | 2.2 | His435 .A | Asp130 .B | 3.1 |
| Tyr436 .A | Pro132 .B | 2.4 | Met252 .A | Pro132 .B | 3.1 |
| Ile253 .A | Leu112 .B | 2.7 | Tyr436 .A | Pro132 .B | 3.1 |
| Asn434 .A | Trp131 .B | 2.9 | | | |
| Ile253 .A | Phe117 .B | 2.9 | | | |
| Asn434 .A | Pro132 .B | 3.4 | | | |
| His435 .A | Trp131 .B | 3.6 | | | |

**Table S3.** continued

**$Mut_{YTE}$ Hydrophilic Interaction**

| pH 6 | | | pH 7.5 | | |
|---|---|---|---|---|---|
| **IgG1-Fc** | **FcRn** | **distance (Å)** | **IgG1-Fc** | **FcRn** | **distance (Å)** |
| ***His435 .A.HD1** | ***Asp130 .B.O** | **1.9** | Ile253 .A.N | Glu133 .B.HE21 | 2.1 |
| ***Thr254 .A.OG1** | ***Glu133 .B.HE11** | **1.9** | Asn434 .A.O | Pro132 .B.HA | 2.3 |
| ***His310 .A.ND1** | ***Glu115 .B.HE12** | **2.3** | Leu251 .A.O | Pro132 .B.HD2 | 2.5 |
| Asn434 .A.O | Pro132 .B.HD3 | 2.4 | His435 .A.H | Asp130 .B.O | 2.8 |
| Leu251 .A.O | Trp131 .B.HD1 | 2.6 | | | |
| Leu432 .A.O | Asp130 .B.HD11 | 2.8 | | | |

**$Mut_{YTE}$ Hydrophobic Interaction**

| pH 6 | | | pH 7.5 | | |
|---|---|---|---|---|---|
| **IgG1-Fc** | **FcRn** | **distance (Å)** | **IgG1-Fc** | **FcRn** | **distance (Å)** |
| His433 .A | Asp130 .B | 1.5 | Thr254 .A | Glu133 .B | 2.0 |
| Ile253 .A | Leu112 .B | 2.1 | His435 .A | Pro132 .B | 2.0 |
| Leu309 .A | Glu115 .B | 2.2 | Thr254 .A | Leu82 .B | 2.1 |
| Thr254 .A | Leu112 .B | 2.3 | Tyr436 .A | Leu135 .B | 2.3 |
| Tyr252 .A | Glu133 .B | 2.3 | Asn434 .A | Asp130 .B | 2.7 |
| Gln311 .A | Glu115 .B | 2.4 | His435 .A | Trp131 .B | 2.9 |
| Ile253 .A | Phe117 .B | 2.8 | Asn434 .A | Pro132 .B | 3.6 |
| Thr254 .A | Gly84 .B | 2.9 | | | |
| Thr254 .A | Leu112 .B | 2.9 | | | |
| Leu251 .A | Pro132 .B | 3.1 | | | |
| Asn434 .A | Trp131 .B | 3.1 | | | |
| Tyr436 .A | Pro132 .B | 3.1 | | | |
| Ile253 .A | Glu133 .B | 3.4 | | | |
| His435 .A | Trp131 .B | 3.6 | | | |

**$Mut_{M4}$ Hydrophilic Interaction**

| pH 6 | | | pH 7.5 | | |
|---|---|---|---|---|---|
| **IgG1-Fc** | **FcRn** | **distance (Å)** | **IgG1-Fc** | **FcRn** | **distance (Å)** |
| ***His310 .A.HD1** | ***Glu115 .B.OE1** | **1.1** | Ile253 .A.H | Glu133 .B.OE2 | 2.0 |
| ***His435 .A.HD1** | ***Asp130 .B.O** | **1.3** | Asn434 .A.O | Pro132 .B.HG3 | 2.1 |
| ***Ile253 .A.H** | ***Glu133 .B.OE1** | **1.3** | Leu251 .A.O | Pro132 .B.HD2 | 2.4 |
| ***Phe254 .A.H** | ***Glu133 .B.OE2** | **1.7** | Thr250 .A.O | Trp131 .B.HZ3 | 2.5 |
| ***Gln311 .A.HE22** | ***Glu116 .B.O** | **1.9** | Asn434 .A.HB3 | Trp131 .B.O | 2.6 |
| Leu251 .A.O | Pro132 .B.HD3 | 2.3 | | | |
| Thr250 .A.O | Trp131 .B.HZ3 | 2.4 | | | |
| Asn434 .A.OD1 | Leu135 .B.HD21 | 2.6 | | | |
| Asn434 .A.HB3 | Trp131 .B.O | 2.8 | | | |

**$Mut_{M4}$ Hydrophobic Interaction**

| pH 6 | | | pH 7.5 | | |
|---|---|---|---|---|---|
| **IgG1-Fc** | **FcRn** | **distance (Å)** | **IgG1-Fc** | **FcRn** | **distance (Å)** |
| Gln311 .A | Glu115 .B | 1.1 | Gln311 .A | Glu115 .B | 1.3 |
| Tyr252 .A | Pro132 .B | 1.9 | Tyr252 .A | Glu133 .B | 1.4 |
| Gln311 .A | Trp131 .B | 2.0 | His433 .A | Gln124 .B | 1.5 |
| Ile253 .A | Phe117 .B | 2.2 | His435 .A | Asp130 .B | 1.9 |
| Phe254 .A | Leu112 .B | 2.3 | Phe254 .A | Leu82 .B | 2.1 |
| Tyr436 .A | Pro132 .B | 2.4 | Ile253 .A | Trp131 .B | 2.5 |
| His435 .A | Trp131 .B | 2.6 | Tyr436 .A | Leu135 .B | 2.6 |
| Phe254 .A | Tyr88 .B | 2.6 | Tyr252 .A | Pro132 .B | 2.8 |
| Ile253 .A | Trp131 .B | 2.9 | Phe254 .A | Tyr88 .B | 2.9 |
| Tyr436 .A | Leu135 .B | 2.9 | | | |
| Ile253 .A | Glu115 .B | 3.1 | | | |
| Asn434 .A | Trp131 .B | 3.2 | | | |