Rule 4: $\beta = 4.2\%$, $\gamma = 91\%$, $\rho = 4.7$

IF (**Cysteine** is substituted by any other amino acids)
THEN (The substitution is intolerant)

Rule 5: $\beta = 6.6\%$, $\gamma = 95\%$, $\rho = 9.0$

WHEN (**Glycine** is substituted by any other amino acids)
IF (The evolutionary profile medium or highly prefers turns) $(6 \leq x_{24} \leq 7)$
THEN (The substitution is intolerant)

Rule 6: $\beta = 5.7\%$, $\gamma = 93\%$, $\rho = 6.1$

WHEN (Any amino acid is substituted by **Arginine**)
IF (The evolutionary profile is acidic AND the substituted amino acid has a medium to strongly negative change in hydrophobicity versus the evolutionary profile) $(1 \leq x_{20} \leq 3) \cap (1 \leq x_{39} \leq 2)$
THEN (The substitution is intolerant)