[Means for Solving the Problems]

The present inventors conducted dedicated studies to generate antibody constant regions that are improved through alternation of their amino acid sequences and have improved physicochemical properties (stability and homogeneity), immunogenicity, and safety, and pharmacokinetics. As a result, the present inventors successfully improved antibody constant region to have increased stability under acid conditions, reduced heterogeneity originated from disulfide bonds in the hinge region, reduced heterogeneity originated from the H-chain C terminus, and increased stability at high concentrations, as well as discovered novel constant region sequences having reduced Fcγ receptor-binding activity, while minimizing the generation of novel T-cell epitope peptides.

The present invention relates to antibody constant regions that are superior in terms of safety, immunogenicity risk, physicochemical properties (stability and homogeneity), and pharmacokinetics a through improvement by amino acid alteration; antibodies comprising such antibody constant region; pharmaceutical compositions comprising such antibody; and methods for producing them. More specifically, in a first aspect, the present invention provides an IgG2 constant region in which His at position 147 (position 268 in the EU numbering system), Arg at position 234 (position 355 in the EU numbering system), and/or Gln at position 298 (position 419 in the EU numbering system) in the amino acid sequence of SEQ ID NO: 2 have been substituted with Gln, Gln and Glu, respectively.

In a second aspect, the present invention provides an IgG2 constant region in which Cys at position 14 (position 131 in the EU numbering system), Arg at position 16 (position 133 in the EU numbering system), Cys at position 102 (position 219 in the EU numbering system), Glu at position 20 (position 137 in the EU numbering system), Ser at position 21 (position 138 in the EU numbering system), His at position 147 (position 268 in the EU numbering system), Arg at position 234 (position 355 in the EU numbering system), and Gln at position 298 (position 419 in the EU numbering system) in the amino acid sequence of SEQ ID NO: 2 have been substituted with Ser, Lys, Ser, Gly, Gly, Gln, Gln and Glu, respectively.

In a third aspect, the present invention provides an IgG2 constant region in which Cys at position 14 (position 131 in the EU numbering system), Arg at position 16 (position 133 in the EU numbering system), Cys at position 102 (position 219 in the EU numbering system), Glu at position 20 (position 137 in the EU numbering system), Ser at position 21 (position 138 in the EU numbering system), His at position 147 (position 268 in the EU numbering system), Arg at position 234 (position 355 in the EU numbering system), Gln at position 298 (position 419 in the EU numbering system), and Asn at position 313 (position 434 in the EU numbering system) in the amino acid sequence of SEQ ID NO: 2 have been substituted with Ser, Lys, Ser, Gly, Gly, Gln, Gln, Glu and Ala, respectively.

In a fourth aspect, the present invention provides a human antibody constant region comprising the amino acid sequence of SEQ ID NO: 36.

In a fifth aspect, the present invention provides an antibody comprising the constant region as defined herein.

In a sixth aspect, the present invention provides an anti-IL-6 receptor antibody comprising the constant region as defined herein.

In a seventh aspect, the present invention provides a pharmaceutical composition comprising the constant region as defined herein.

Also disclosed herein is:~~the present invention provides:~~

[1] a human antibody constant region of any one of:

(a) a human antibody constant region that comprises deletions of both Gly at position 329 (position 446 in the EU numbering system, see sequences of proteins of immunological interest, NIH Publication No.91-3242) and Lys at position 330 (position 447 in the EU numbering system) in the amino acid sequence of SEQ ID NO: 1;

(b) a human antibody constant region that comprises deletions of both Gly at position 325 (position 446 in the EU numbering system) and Lys at position 326 (position 447 in the EU numbering system) in the amino acid sequence of SEQ ID NO: 2; and

(c) a human antibody constant region that comprises deletions of both Gly at position 326 (position 446 in the EU numbering system) and Lys at position 327 (position 447 in the EU numbering system) in the amino acid sequence of SEQ ID NO: 3;

[2] an IgG2 constant region in which the amino acids at positions 209 (position 330 in the EU numbering system), 210 (position 331 in the EU numbering system), and 218 (position 339 in the EU numbering system) in the amino acid sequence of SEQ ID NO: 2 have been substituted with other amino acids;

[3] an IgG2 constant region in which the amino acid at position 276 (position 397 in the EU numbering system) in the amino acid sequence of SEQ ID NO: 2 has been substituted with another amino acid;

[4] an IgG2 constant region in which the amino acids at positions 14 (position 131 in the EU numbering system), 102 (position 219 in the EU numbering system), and/or 16 (position 133 in the EU numbering system) in the amino acid sequence of SEQ ID NO: 2 have been substituted