Surface activation of the plasma systems involved with coagulation, fibrinolysis, and kinin formation and kinin generation involves factor XII (Hageman factor). This protein is a 76,000 dalton glycoprotein which circulates in plasma as an inactive form of a serine protease. A human liver cDNA clone for factor XII was used to screen a human genomic phage library. Two overlapping clones were isolated, AI-XII27 and AI-XII70, and contain the entire gene for human factor XII. The gene is 13.5 kb in length and consists of 14 exons and 12 introns. The transcriptional start site of the mRNA was determined using S1 mapping and primer extension analysis. The results indicate that the 5' untranslated end of the mRNA has a leader sequence of 47 bp and is not interrupted by an intron in the gene. DNA sequence analysis of the region upstream of the transcriptional start site does not contain TATA or CACGTG sequences, which are often found in other genes transcribed by RNA polymerase II. The positions of the introns in the coding sequence separate the protein into domains which are homologous to similar regions found in fibronectin and tissue-type plasminogen activator. Furthermore, wherever protein homologies are found, the positions of the introns in the triplet codon occur in the same reading frame as in the tissue-type plasminogen activator, urokinase plasminogen activator and factor XII genes. The intron/exon organization of the factor XII gene is different to the organization of other human genomic blood coagulation. In the present study, the organization of the entire gene for human factor XI is 25 kilobases in length. Overlapping regions of the gene have been subcloned and the gene for factor XI has been isolated from two independent phage libraries using a full length eDNA for factor XI as a hybridization probe. Overlapping recombinant phage containing the human factor XI gene have been isolated and characterized. Restriction mapping, Southern blotting and hybridization studies indicate that the entire gene for human factor XII is 25 kilobases in length. Overlapping regions of the gene have been subcloned and the DNA sequence of selective regions has been determined. These results show that the gene for factor XI is composed of 15 exons and 14 introns. Exon I codes for the 5' noncoding sequences and exon II codes for the signal peptide of 18 amino acid residues. The four tandem repeats that constitute the heavy chain of factor XIa are each encoded by two consecutive exons (exons III and IV, V and VI, VII and VIII, IX and X). The location of the introns and the junction type among these four tandem repeats are strictly conserved. Exon XII, XIII, XIV and XV code for the light chain of factor XIIa that participates in the contact activation of blood coagulation. In the present study, the organization of the gene for human factor XI has been isolated and characterized. Restriction mapping, Southern blotting and hybridization studies indicate that the entire gene for human factor XI is 25 kilobases in length. Overlapping regions of the gene have been subcloned and the DNA sequence of selective regions has been determined. These results show that the gene for factor XI is composed of 15 exons and 14 introns. Exon I codes for the 5' noncoding sequences and exon II codes for the signal peptide of 18 amino acid residues. The four tandem repeats that constitute the heavy chain of factor XIa are each encoded by two consecutive exons (exons III and IV, V and VI, VII and VIII, IX and X). The location of the introns and the junction type among these four tandem repeats are strictly conserved. Exon XII, XIII, XIV and XV code for the light chain of factor XIIa that participates in the contact activation of blood coagulation.

The specificity of serine protease inhibitors belonging to the serpin superfamily depends on the nature of the reactive center amino acid residues. For example, Met→Arg mutation at the reactive center P1 residue (position 358) alters the specificity of α-antitrypsin (AT) from the Met-specific enzyme neutrophil elastase to the Arg-specific protease thrombin, plasma kallikrein (K) and activated Factor XII (AT) fragment (XIIa). To obtain an inhibitor species which would inhibit K and XIIa but not thrombin, we now have produced site-directed mutants of cloned AT cDNA an AT variant having Arg at P1 and Ala at P2. This modification at P2 was made because C1 inhibitor, the major inhibitor of K and XIIa, also has Ala at P2. In purified systems, AT Ala 358 Arg 358 inactivated thrombin, K and XIIa with 2nd-order rate constants of 1.1, 21.8 and 0.6 μM⁻¹ min⁻¹. Whereas values of 8.5, 4.2 and 2.1 μM⁻¹ min⁻¹ were found with AT Arg 358. Thus, when compared to AT Arg 358, AT Ala 358 Arg 358 was 5.2 times more efficient for inhibiting K but 7.7 times less efficient for inhibiting thrombin. In vivo, AT Ala 358 Arg 358 (0.7 mg i.v.) did not modify the thrombin time of male Wistar rats while a 2-fold prolongation was seen with 0.7 mg AT Arg 358. However, AT Ala 358 Arg 358 (0.7 mg i.v.) partially prevented the kinin-mediated circulatory collapse induced by XIIa (0.1 μg i.v. since 1944) treated with this double mutant had a blood pressure fall of 14±3 (mean±SD) mmHg while control animals (n=8) receiving saline or AT Arg 358-Ala 358 (0.7 mg i.v.) did not show a decrease in blood pressure (p<0.05, Mann Whitney U test). AT Ala 358 Arg 358 has therapeutic potential for disease states with activation of the plasma kinin-forming system such as angioedema attacks or septic shock.