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Haemophilia A: database of nucleotide substitutions, deletions, insertions and rearrangements of the factor VIII gene, second edition

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ABSTRACT

A large number of different mutations in the factor VIII (*F8*) gene have been identified as a cause of haemophilia A. This compilation lists known single base-pair substitutions, deletions and insertions in the *F8* gene and reviews the status of the inversional events which account for a substantial proportion of mutations causing severe haemophilia A.

INTRODUCTION

Haemophilia A is an X-linked bleeding disorder affecting approximately 1 in 5000 males (reviewed by Green *et al.* 1991; Tuddenham and Cooper 1994; Hoyer 1994). It is caused by deleterious mutations in the factor VIII (*F8*) gene leading to deficiency of factor VIII, a co-factor for the activation of factor X by factor IXa. The *F8* gene comprises 26 exons spanning 186kb DNA (Gitschier *et al.* 1984; Toole *et al.* 1984) and encodes a 9kb mRNA.

A database of mutations in the *F8* gene, including single base-pair substitutions, deletions, insertions and rearrangements, was first published by Tuddenham *et al.* (1991). We present here an updated list of *F8* gene lesions. The major advances in our understanding of the molecular biology and genetics of haemophilia A are presented.

Inversions

The single most important advance in the last 3 years has been the elucidation of the molecular basis of the defects in about half of all patients with severe haemophilia A. Until recently, no mutations could be found in either the coding region or the splice junctions of the *F8* gene in ~40% of patients with the severe form of the disease (Higuchi *et al.* 1991b). The elucidation of this enigma came with the key finding that the screening of *F8* cDNA fragments for mutations was hampered by the impossibility of performing PCR amplification across the exon 22/23 boundary in these patients (Naylor *et al.* 1992;1993b). This was suggestive of a defect in intron 22 which is, at 32kb, the largest intron in the *F8* gene. A CpG island located within this intron, ~10kb 3′ to exon 22, is thought to act as a bidirectional promoter for two transcribed genes, termed *F8A* and *F8B* (Levinson *et al.* 1990;1992). The *F8A* gene lacks introns and is transcribed in the opposite direction to the *F8* gene. Two additional homologues of the *F8A* gene (termed the *A* genes), which are also transcribed, exist ~500kb upstream of the *F8* gene near the telomere (Levinson *et al.* 1990;1992). These genes are transcribed in the opposite direction to *F8A*.

It is now known that homologous intra-chromosomal recombination occurs between one or other of the upstream *A* genes and the *F8A* gene, generating inversions of the intervening *F8* gene sequence. Such inversions, which occur in ~40% of severe haemophiliacs, result in the separation of exons 1–22 from exons 23–26 by some 200–500kb DNA (Lakich *et al.* 1993; Naylor *et al.* 1993b). Millar *et al.* (1994) screened a total of 164 unrelated patients with severe haemophilia A for partial inversions of the *F8* gene. Inversions were found in 69 (42%) patients; most (90%) involved the distal rather than the proximal *A* gene. This unique mutational mechanism is therefore estimated to occur with a frequency of 7.2×10^{-6} per gene per gamete per generation. Although two patients with an inversion possessed inhibitors (antibodies) against factor VIII, possession of inhibitors did not appear to be associated disproportionately with inversion-type mutations (Millar *et al.* 1994).

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Goodeve *et al.* (1994) reported an inversion frequency of 48% in their study of 23 patients. Collins *et al.* (1994) and Ljung (1994) have reported inversion frequencies of 47% (85 patients) and 46% (41 patients) respectively. The frequencies of the proximal inversion of these three studies were 9%, 20% and 21% of the total number of inversions. Tizzano *et al.* (1994) reported an inversion frequency of 39% (92 patients); 36% of their patients with inversions developed inhibitor, a much higher proportion than that reported by Millar *et al.* (1994).

Point mutations

A total of 174 different single base-pair substitutions are listed in Table 1. Of these, 138 are missense mutations whilst 24 are nonsense mutations. An additional 12 mutations are thought to abolish correct mRNA splicing, either by removing a donor splice site (5) or an acceptor splice site (5) or possibly by activating a cryptic splice site (2). Some 25% of these single base-pair substitutions occur within CpG dinucleotides and are compatible with a mechanism of methylation-mediated deamination (i.e. C→T or G→A). Consistent with this dinucleotide being a hotspot for mutation (Cooper and Krawczak, 1993), examples of multiple mutation at CpG sites are frequent in the database.

Some 31 patients in the database possess inhibitors to exogenously given factor VIII; 27 of these (87%) possess nonsense mutations whereas 4 (13%) possess missense mutations. Intriguingly, two of the missense mutations (Arg 2209→Gln and Trp 2229→Cys) result in mild/moderate haemophilia A (3−7% FVIII:C). Inhibitors ca therefore still occur in patients with residual circulating factor VIII.

The clinical phenotype exhibited by haemophilia A patients with the same point mutation is not always the same. Examples of this phenomenon are to be found at codons 22, 162, 295, 326, 390, 412, 473, 479, 593, 704, 1680, 1689, 1922, 1941, 1997, 2150, 2159, 2209, 2304 and 2307. Among possible explanations are the influence of coinherited mutations/variants/polymorphisms, inter-laboratory differences in either assas or clinical assessment or the epistatic effects of other loci. Berg *et al.* (1994) have described a probable epistatic effect in a case of mild/moderate haemophilia A; coinheritance of both factor XI deficiency and haemophilia A was associated with a bleeding tendency that was more severe than that associated with either deficiency alone.

Deletions

A. Gross gene deletions. Some 78 different gross deletions of the *F8* gene have been reported in the literature (Table 2A). These range in size from 2 to >210kb. However, only a minority have been well mapped and only a few have had their breakpoints characterized. All but three are associated with a severe clinical phenotype. A substantial proportion (33%) are associated with the development of inhibitors.

B. Small deletions. A total of 39 different micro-deletions of the *F8* gene have been reported (Table 2B). These range in size from 1 to 23bp. A hotspot for deletions is evident between codons 339 and 341. The three different deletions reported at this location are consistent with a slipped mispairing mechanism; they span a double direct repeat (AATAATGAAGAA) sequence which matches the deletion hotspot consensus sequence of Cooper and Krawczak (1993). None of these patients is known to possess an inhibitor.

Insertions

No further examples of LINE element insertion into the *F8* gene (Kazazian *et al.* 1988) have been reported (Table 3). Dombroski *et al.* (1991) showed that the LINE element originally found in patient JH27 is an exact but truncated copy of a full-length LINE element found at chromosome 22q11.1−q11.2. The latter progenitor element (L1.2B) is one of four LINE elements at this location and has been designated LRE1 (L1 retrotransposable element 1). It appears to have occupied this position for at least 6 million years.

A total of 10 short insertions in the *F8* gene have been reported (Table 3); most involve the insertion of a single base-pair; often an A within a stretch of A residues. The 10bp insertion is a tandem duplication of existing sequence. The 1bp insertion at codon 1439 occurs in the same position as a 1bp deletion, within a stretch of 8A residues.

Estimation of the sex ratio of mutation frequencies

Haldane (1935) demonstrated that for any X-linked lethal disorder, assuming the mutation rate in males and females to be equal, the proportion of mutations occurring *de novo* will be one third. A lower proportion will, however, be found if the mutation rate is higher in males than in females or if the fitness of carrier females is somehow increased. Based upon the observed rarity of sporadic cases, Haldane (1947) concluded that the mutation rate in males could be as much as 10-fold higher than in females. The accuracy of Haldane's method is however, influenced markedly by reproductive fitness. Oldenburg *et al.* (1993) attempted to estimate the sex ratio of mutation frequencies when reproductive fitness was set at either 0.3 or 0.5. Haldane's approach yielded a male:female mutation ratio of 5.37 (95% confidence limits 2.2−13.0). Use of the equilibrium-independent indirect method of Rosendaal *et al.* (1990) gave a male: female mutation ratio of 3.4 (95% confidence limits); 1.2−8.8). Oldenburg *et al.* (1993) performed carrier detection analysis in 119 families with haemophilia A by RFLP analysis or by direct detection of the pathological lesion. Data on the mutational origin allowed direct estimation of the male:female mutation ratio as 15:1. These studies therefore point to a significantly higher mutation frequency in males than in females.

Further characterization of the *F8* gene

A considerable number of repetitive sequence elements have been located in the *F8* gene (Millar *et al.* 1993); some 30 Alu sequences are present in a total of 11 introns whilst three partial LINE elements are located within introns 13, 22 and 25.

Lynch *et al.* (1993) have reported evidence that a 1.2kb segment of the *F8* cDNA (spanning the A2 and A3 domains) acts as an inhibitor of mRNA accumulation and protein synthesis.

Indirect diagnosis of haemophilia A by linkage analysis

Although direct mutation analysis is now the method of choice for providing genetic counselling, carrier determination and antenatal diagnosis of haemophilia A, indirect diagnosis will continue to be used for various reasons. Firstly, only a minority of haemophilia treatment centres will be able to complete the mutation screening of their haemophilia A patients in the short term. Secondly, even if mutation screening can be performed, this is very time consuming as compared to linkage analysis. Moreover, many women at risk present only once they are pregnant, thus requiring urgent evaluation, and a high proportion

of these will be from families where the mutation has not yet been determined. Finally, in many families, all affected males have already died from AIDS or other complications of haemophilia. Although the prevalent inversion mutation can be detected in heterozygotes, other mutations, especially gross deletions would not be readily detectable in a surviving carrier daughter for example.

Intronic polymorphisms therefore continue to represent valuable genetic markers for linkage studies. Such markers have recently been reviewed, and methods of analysis summarised, in a joint publication of the World Health Organization and the World Federation of Haemophilia (Peake *et al.* 1993). Reviews by Broecker-Vriends *et al.* (1992) and Sommer (1987), may also be consulted. The most important recent advance in this area has been the discovery of two hypervariable dinucleotide tandem repeats in introns 13 and 22 of the *F8* gene (Lalloz *et al.* 1991). These can be analysed simultaneously (Lalloz *et al.* 1994) and can be determined rapidly and conveniently by automated laser scanning equipment (Schwaab *et al.* 1994). Up to 90% of females are informative (i.e. heterozygous) for at least one of the available intragenic markers. If other methods fail, antenatal diagnosis can be provided by fetal blood sampling at 18 weeks gestation. Preimplantation sex selection for female embryos has been successfully performed by biopsy of embryos at the 6 cell stage (Handyside *et al.* 1989). In principle, this could be applied to prevent Haemophilia A.

Mutation screening methods

The rapid increase in size of this database is due to the industry of many workers using the three rapid sensitive DNA screening methods that have been developed since 1987, all based on the polymerase chain reaction. These are the denaturing gradient gel electrophoresis (Fodde and Losekoot 1994), the chemical cleavage method (Cotton *et al.* 1988) and single stranded conformational polymorphism analysis (Hayashi and Yandell 1993). Various advantages and drawbacks of each method in terms of sensitivity, technical difficulty and reagent hazard can be debated and will determine local choice. Detailed protocols are given in Michaelides *et al.* (1994).

All three methods have been successfully applied to the *F8* gene by at least one group e.g. DGGE, Higuchi *et al.* (1991a,b); chemical cleavage, Naylor *et al.* (1992) and SSCP, Lin *et al.* (1993). These papers should be consulted for details of oligonucleotide primers required for the PCR amplification of individual exons of the *F8* gene, or, in the case of Naylor *et al.* (1992), the isolation and reverse transcription of ectopic mRNA transcripts from peripheral blood lymphocytes, and subsequent PCR amplification. This latter strategy has the added advantage of allowing the detection of missplicing events.

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Table 1. Single base substitutions found in the factor VIII gene of patients with haemophilia A

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 1	-19	ATG→ATA	Met→Ile	HP112	<1	?	Severe	No	Start codon
Exon 1	-5	CGA→TGA	Arg→Stop	2	<1	?	Severe	No	Signal peptide
Exon 1	-5	CGA→TGA	Arg→Stop	H541	<1	<1	Severe	No	Signal peptide
Exon 1	-5	CGA→TGA	Arg→Stop	GLA9	<1	?	Severe	?	Signal peptide
Exon 1	7	CTG→CGG	Leu→Arg	HP113	<1	?	Severe	No	
Exon 1	11	GAA→GTA	Glu→Val	H119	?	?	Mild	?	
Exon 1	11	GAA→GTA	Glu→Val	H119	?	?	Mild	No	
Exon 1	22	GGT→TGT	Gly→Cys	HP18	<1	?	Severe	No	
Exon 1	29	AGA→AAA	Arg→Cys	HP114	<1	?	Severe	No	-1 IVS1 acceptor splice site
Intron 2	-	cga→tga	-	H6	<1	?	Severe	No	Probably a neutral change ~300bp 3' to exon 2
Exon 2	56	GAT→GAA	Asp→Glu	GLA13	3	?	Moderate	No	
Exon 3	70	GGT→GAT	Gly→Asp	HP115	<1	?	Severe	No	-1 IVS2 donor splice site
Exon 3	73	GGT→GTT	Gly→Val	H48	?	?	Mild	?	
Exon 3	80	GTT→GAT	Val→Asp	HP116	<1	?	Severe	No	
Exon 3	85	GTC→GAC	Val→Asp	H99	?	?	Mild	?	
Exon 3	89	AAG→ACG	Lys→Thr	JH73	?	?	Mild	?	
Exon 3	91	ATG→GTG	Met→Val	JH71	?	?	Mild	?	
Exon 3	98	CTT→CGT	Leu→Arg	HP117	<1	?	Severe	No	
Exon 3	111	GGT→CGT	Gly→Arg	TWN18	<1	?	Severe	No	
Exon 3	113	GAA→GAC	Glu→Asp	HP118	<1	?	Severe	Yes	
Exon 4	114	TAT→TGT	Tyr→Cys	HP19	6.3	10.7	Mild	No	
Exon 4	116	GAT→GGT	Asp→Gly	HP119	<1	?	Severe	No	
Exon 4	118	ACC→ATC	Thr→Ile	HP20[a]	2.2	?	Moderate	No	
Exon 4	118	ACC→ATC	Thr→Ile	HP21[a]	2.0	10.7	Moderate	No	
Exon 4	139	CAG→TAG	Gln-Stop	HP140	<1	?	Severe	No	
Exon 4	145	GGT→GTT	Gly→Val	H91	?	?	Mild	?	
Exon 4	146	CCA→TCA	Pro→Ser	TWN106	<1	?	Severe	No	
Exon 4	156	TAC→TAA	Tyr→Stop	HP139	<1	?	Severe	No	

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 4	162	GTG→ATG	Val→Met	H72	?	?	Moderate	?	
Exon 4	162	GTG→ATG	Val→Met	H126	?	?	Mild	?	
Exon 4	162	GTG→ATG	Val→Met	HP25[b]	5.3	14.0	Mild	No	
Exon 4	162	GTG→ATG	Val→Met	HP26[b]	5.5	6.3	Mild	No	
Exon 4	162	GTG→ATG	Val→Met	HP24[c]	5.3	3.7	Mild	No	
Exon 4	162	GTG→ATG	Val→Met	HP22[c]	8.5	4.4	Mild	No	
Exon 4	162	GTG→ATG	Val→Met	H26	8	?	Moderate	No	
Exon 4	162	GTG→ATG	Val→Met	HP27	7.0	?	Mild	No	
Exon 4	162	GTG→ATG	Val→Met	H72	5	?	Mild	No	
Exon 4	162	GTG→ATG	Val→Met	HP23	5.3	6.0	Mild	No	
Exon 4	162	GTG→ATG	Val→Met	GLA5	9	?	Mild	No	
Exon 4	166	AAA→ACA	Lys→Thr	JH139	8	9.8	Mild	No	
Exon 4	170	TCA→TTA	Ser→Leu	LKC	3.5	8.7	Moderate	No	
Intron 4	-	cga→caa	-	JH17	5-10	41	Mild	No	Proposed to activate cryptic splice site ~1kb 3' to exon 4
Intron 4	-	ag/→gg/	-	Lisboa 1	1.7	1.3	Severe	No	-2 IVS4 acceptor splice site
Exon 5	203	GAT→GTT	Asp→Val	HP28	2.0	8.5	Moderate	No	
Exon 5	205	G/gt..ag/GG→T/ gt..ag/GG[2]	Gly→Trp	JH143	3.2	?	Moderate	?	-1 IVS5 donor splice site
Intron 5		ag/→gg/	-	2	<1	?	Severe	No	-2 IVS5 acceptor splice site
Intron 6	-	G/gta→G/gtg	-	GLA8	3	?	Moderate	No	+3 IVS6 donor splice site
Intron 6	-	ag/→ac/	-	JH105	?	?	Severe	?	-1 IVS6 acceptor splice site
Exon 7	247	GGA→GAA	Gly→Glu	HP139	10	?	Mild	No	
Exon 7	255	TGG→TGA	Trp→Stop	JH89	?	?	Severe	?	
Exon 7	259	GGA→AGA	Gly→Arg	HP120	<1	?	Severe	No	
Exon 7	266	GTG→GGG	Val→Gly	JH85	?	?	Mild	?	
Exon 7	272	GAA→GGA	Glu→Gly	JH20	2	3.5	Moderate	No	
Exon 7	272	GAA→AAA	Glu→Lys	19	6	?	Mild	?	
Exon 7	275	ACA→ATA	Thr→Ile	HP29[d]	4.8	20.2	Moderate	No	
Exon 7	275	ACA→ATA	Thr→Ile	HP30[d]	4.0	40.8	Moderate	No	

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 7	280	AAC→ATC	Asn→Ile	?	8-12	?	Mild	No	
Exon 7	282	CGC→CAC	Arg→His	JH86	<1	18	Severe	No	
Exon 7	282	CGC→CAC	Arg→His	OX28	<1	?	Severe	No	
Exon 7	282	CGC→CAC	Arg→His	JH88,JH106	?	?	Severe	?	
Exon 7	282	CGC→CTC	Arg→Leu		20	?	Mild	No	
Exon 7	282	CGC→CTC	Arg→Leu	HP121	<1	?	Severe	No	
Exon 7	282	CGC→CTC	Arg→Leu	HP122	<1	?	Severe	No	
Exon 7	289	TCG→TTG	Ser→Leu	JH152	37	106	?	?	
Exon 7	293	TTC→TCC	Phe→Ser	JH62	?	?	Mild	?	
Exon 7	295	ACT→GCT	Thr→Ala	HP32	9.5	11.6	Mild	No	
Exon 7	295	ACT→GCT	Thr→Ala	JH87	14-16	12.8	Moderate	No	
Exon 7	295	ACT→GCT	Thr→Ala	HP34[e]	7.0	5.0	Mild	No	
Exon 7	295	ACT→GCT	Thr→Ala	HP35[e]	21.5	17.9	Mild	No	
Exon 7	295	ACT→GCT	Thr→Ala	HP33[e]	10.5	8.3	Mild	No	
Exon 7	308	CTG→CCG	Leu→Pro	HP123	<1	?	Severe	No	
Exon 8	323	TAT→TAA	Tyr→Stop	TWN15,33	<1	?	Severe	No	
Exon 8	326	GTA→CTA	Val→Leu	H44	?	?	Severe	No	
Exon 8	326	GTA→CTA	Val→Leu	JH30	?	?	Moderate	?	
Exon 8	329	TGT→TAT	Cys→Tyr	H89	<1	?	Severe	?	
Exon 8	329	TGT→TAT	Cys→Tyr	H84	<1	?	Severe	No	
Exon 8	329	TGT→CGT	Cys→Arg	V107	?	?	Severe	No	
Exon 8	329	TGT→TCT	Cys→Ser	Lisboa 2	2.6	3.2	Moderate	No	
Exon 8	336	CGA→TGA	Arg→Stop	H4	0	?	Severe	?	Activated protein C cleavage site
Exon 8	336	CGA→TGA	Arg→Stop	H59	<1	<1	Severe	?	Activated protein C cleavage site
Exon 8	336	CGA→TGA	Arg→Stop	H19,J84,J88 J91,J138,J278	<1	<1	Severe	No	Activated protein C cleavage site
Exon 8	336	CGA→TGA	Arg→Stop	H59	<1	?	Severe	No	
Exon 8	372	CGC→CCC	Arg→Pro	HA824	3	?	Severe	No	Thrombin activation site

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 8	372	CGC→CAC	Arg→His	JH150	5	57	?	?	Thrombin activation site
Exon 8	372	CGC→CAC	Arg→His	A	6	130	Mild	No	Thrombin activation site
Exon 8	372	CGC→CAC	Arg→His	H453	3	?	Moderate	No	Thrombin activation site
Exon 8	372	CGC→CAC	Arg→His	JH35	5	325	Mild	No	Thrombin activation site
Exon 8	372	CGC→TGC	Arg→Cys	HA771	3	?	Severe	No	Thrombin activation site
Exon 8	372	CGC→TGC	Arg→Cys	J254	3	74	Moderate	No	Thrombin activation site
Exon 8	372	CGC→TGC	Arg→Cys	Okayama	3	80	Moderate	No	Thrombin activation site
Exon 8	372	CGC→TGC	Arg→Cys	HA862	<1	?	Severe	No	Thrombin activation site
Exon 8	372	CGC→TGC	Arg→Cys	HA1052	2	?	Severe	No	Thrombin activation site
Exon 8	373	TCA→TTA	Ser-Leu	BA	8	110	Mild	No	Thrombin activation site
Exon 8	373	TCA→TAA	Ser→Stop	MG	<1	<1	Severe	No	Thrombin activation site
Exon 8	373	TCA→CCA	Ser→Pro	SH	10	100	Mild	No	Thrombin activation site
Exon 8	386	ATT→AGT	Ile→Ser	TWN4	<1	?	Severe	No	
Exon 8	390	GAG→GGG	Glu→Gly	HP36	3.5	?	Moderate	No	
Exon 8	390	GAG→GGG	Glu→Gly	HP124	<1	?	Severe	No	
Exon 9	412	TTG→TTT	Leu→Phe	JH131	7	6.4	Mild	No	
Exon 9	412	TTG→TTT	Leu→Phe	HP37	5.0	?	Mild/Moderate	No	
Exon 9	425	AAA→AGA	Lys→Arg	JH74	<1	5	Severe	No	
Exon 9	427	CGA→TGA	Arg→Stop	HP126	<1	?	Severe	No	
Exon 9	427	CGA→TGA	Arg→Stop	H466	<1	<1	Severe	No	
Exon 9	427	CGA→TGA	Arg→Stop	HP125	<1	?	Severe	Yes	
Exon 9	431	TAC→AAC	Tyr→Asn	A211	4	?	Moderate	No	
Exon 10	469	GCA→GGA	Ala→Gly	HP38	2.3	45.3	Moderate	No	
Exon 10	473	TAT→CAT	Tyr→His	JH70	?	?	Mild	No	
Exon 10	473	TAT→TGT	Tyr→Cys	JH126,JH125	2.7/3.5	?	Moderate	No	
Exon 10	475	ATC→ACC	Ile→Thr	HP39[f]	5.5	8.8	Mild	No	
Exon 10	475	ATC→ACC	Ile→Thr	HP40[f]	7.0	6.9	Mild	No	
Exon 10	479	[C]GGA→AGA	Gly→Arg	OX16	2	?	Moderate	No	
Exon 10	479	[C]GGA→AGA	Gly→Arg	Porto1	17.8	31.6	Mild	No	

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 10	479	[C]GGA→AGA	Gly→Arg	140	10.0	?	Mild	No	
Exon 11	504	CTG→CTT	Leu→Leu	H140	?	?	Mild	?	Potential new acceptor site
Exon 11	504	CTG→CTT	Leu→Leu	JH101,JH18,JH19	?	?	Mild	No	Potential new acceptor site
Exon 11	525	GAT→AAT	Asp→Asn	MS	6	61	Moderate	No	
Exon 11	527	CGG→TGG	Arg→Trp	DG	15	126	Mild	No	
Exon 11	527	CGG→TGG	Arg→Trp	HP42	9.5	43.1	Mild	No	
Exon 11	527	CGG→TGG	Arg→Trp	HP41[g]	17.0	?	Mild	No	
Exon 11	527	CGG→TGG	Arg→Trp	HP43[g]	11.5	95.0	Mild	No	
Exon 11	527	CGG→TGG	Arg→Trp	HP44	23.0	>50.0	Mild	No	
Exon 11	527	CGG→TGG	Arg→Trp	JH122	?	?	?	?	
Exon 11	527	CGG→TGG	Arg→Trp	JB	10	100	Mild	No	
Exon 11	527	CGG→TGG	Arg→Trp	JH153	17	245	?	?	
Exon 11	527	CGG→TGG	Arg→Trp	JH94,JH95,JH96	14.5/18/ 17-18	>50/85/154	Mild	?	
Exon 11	531	CGC→GGC	Arg→Gly	JH144	9.2	?	Moderate	No	
Exon 11	531	CGC→TGC	Arg→Cys	H31	?	?	Moderate	?	
Exon 11	531	CGC→TGC	Arg→Cys	JH97,JH98	6.7/4.2	?	Moderate	?	
Exon 11	531	CGC→TGC	Arg→Cys	JH99	?	?	Moderate	?	
Exon 11	531	CGC→CAC	Arg→His	HP46	23.5	33.2	Mild	No	
Exon 11	531	CGC→CAC	Arg→His	HP45	32.0	>20.0	Mild	No	
Exon 11	531	CGC→TGC	Arg→Cys	HP47	6.5	8.3	Mild	No	
Exon 11	535	AGT→GGT	Ser→Gly	JH120,JH121	?	?	?	No	
Exon 11	535	AGT→GGT	Ser→Gly	H100	?	?	Mild	No	
Exon 11	542	GAT→GGT	Asp→Gly	JH63	<1	5	Severe	No	
Exon 11	557	GAA→TAA	Glu→Stop	VAA	<1%	?	Moderate	No	
Exon 11	**558**	**TCT→TTT**	**Ser→Phe**	**JH151**	**21**	**175**	**?**	**?**	
Exon 11	**565**	**CAG/gt→AAG/gt**	**Gln→Lys**	**JH123**	**?**	**?**	**Mild/Moderate**	**No**	**-3 IVS11 donor splice site**
Exon 11	**565**	**CAG/gt→AAG/gt**	**Gln→Lys**	**JH124**	**?**	**?**	**Moderate**	**No**	**-3 IVS11 donor splice site**
Exon 12	**566**	**ATA→ACA**	**Ile→Thr**	**FW**	**4**	**200**	**Moderate**	**No**	**New N-glycosylation site N564**

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 12	566	ATA→ACA	Ile→Thr	JH117	?	?	Severe	No	New N-glycosylation site N564
Exon 12	577	TCT→CCTTCT→CCT	Ser→Pro	JH114	?	?	?	?	
Exon 12	583	CGA→TGA	Arg→Stop	J34	<1	<1	Severe	No	
Exon 12	583	CGA→TGA	Arg→Stop	HP127	<1	?	Severe	No	
Exon 12	583	CGA→TGA	Arg→Stop	3	<1	?	Severe	No	
Exon 12	583	CGA→TGA	Arg→Stop	HP128	<1	?	Severe	No	
Exon 12	583	CGA→TGA	Arg→Stop	HP129	<1	?	Severe	No	
Exon 12	584	AGC→ATC	Ser→Ile	JH109	?	?	?	?	Loss N-glycosylation site N582
Exon 12	585	TGG→TGC	Trp→Cys	TWN64	<1	?	Severe	No	
Exon 12	586	TAC→TCC	Tyr→Ser	TWN68	<1	?	Severe	No	
Exon 12	593	CGC→TGC	Arg→Cys	V164	?	?	Moderate	?	
Exon 12	593	CGC→TGC	Arg→Cys	JH110,JH113	?	?	?	?	
Exon 12	593	CGC→TGC	Arg→Cys	JH82,JH83,JH84	?	?	Mild	No	
Exon 12	593	CGC→TGC	Arg→Cys	HP48	8.5	?	Mild	No	
Exon 12	593	CGC→TGC	Arg→Cys		15	?	Mild	No	
Exon 12	593	CGC→TGC	Arg→Cys	V158	?	?	Mild	?	
Exon 12	593	CGC→TGC	Arg→Cys	HA689	7	?	Moderate	?	
Exon 12	593	CGC→TGC	Arg→Cys	OX30	10	?	Mild	No	
Exon 12	612	AAC→AGC	Asn→Ser	JH111	?	?	?	?	
Intron 12	-	/gtgagt→gtgaat	-	JH107	?	?	Mild	?	+5 IVS 12 donor splice site
Intron 12	-	g→a at-37	-	H65	?	?	Moderate	?	Not proven to be pathological change
Exon 13	634	GTG→GCG	Val→Ala	JH156	5	138	Mild	No	
Exon 13	634	GTG→ATG	Val→Met	JH157	<1	175	Severe	No	
Exon 13	636	TAC→TAG	Tyr→Stop	HP130	<1	?	Severe	Yes	
Exon 13	636	TAC→TAG	Tyr→Stop	HP131	<1	?	Severe	No	
Exon 13	644	GCA→GTA	Ala→Val	JH136	14	25	Mild/Moderate	No	
Exon 13	658	TTC→CTC	Phe→Leu	HP49	5.1	50.5	Mild/Moderate	No	
Exon 14	698	CGG→TGG	Arg→Trp	H82	?	?	Mild	No	
Exon 14	701	GGC→GAC	Gly→Asp	GLA4	2	?	Moderate	Yes	Multicopper oxidase I site

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 14	704	[C]GCC→ACC	Ala→Thr	HP51	4.5	5.5	Moderate	No	
Exon 14	704	[C]GCC→ACC	Ala→Thr	JH78,JH79	?	?	Mild	No	
Exon 14	720	[C]GAG→AAG	Glu→Lys	HP53	12.5	>20.0	Mild	No	
Exon 14	720	[C]GAG→AAG	Glu→Lys	HP52	30.0	>20.0	Mild	No	
Exon 14	795	CGA→TGA	Arg→Stop	H518	<1	<1	Severe	No	
Exon 14	1038	GAG→AAG	Glu→Lys	JH132	2.4	10-20	Mild/Moderate	No	
Exon 14	1441	AAT→AAA	Asn→Lys	JH149	6	7	?	?	
Exon 14	1462	CTG→CCG	Leu→Pro	?	?	?	?	?	
Exon 14	1615	GAG→TAG	Glu→Stop	HA702	<1	?	Severe	No	
Exon 14	1680	TAT→TTT	Tyr→Phe	JH40	10	20	Mild	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	JH52	?	?	Mild	?	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP66[i]	6.0	10.1	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP69[i]	6.5	7.1	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP63	4.5	12.8	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP65	2.5	8.4	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP68	2.0	8.8	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP67	5.5	13.9	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP71[j]	5.0	9.5	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP54[j]	6.0	?	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP57[j]	8.5	?	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP70	5.5	14.4	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP64	4.0	5.4	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP56	?	?	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP55	2.8	?	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP62	2.5	?	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP58	4.5	6.4	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP60	4.0	14.6	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP61[k]	4.5	14.1	Moderate	No	Sulphated Tyr/vWF binding

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 14	1680	TAT→TTT	Tyr→Phe	HP72[k]	5.5	13.1	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT→TTT	Tyr→Phe	HP59	4.5	7.9	Moderate	No	Sulphated Tyr/vWF binding
Exon 14	1680	TAT-TTT	Tyr→Phe	W311	4	-	Moderate	No	
Exon 14	1680	TAT→TGT	Tyr→Cys	JH41	?	?	Severe	No	Sulphated Tyr/vWF binding
Exon 14	1686	CAG→TAG	Gln→Stop	JH36	<1	?	Severe	?	
Exon 14	1689	CGC→TGC	Arg→Cys	JH39	?	?	Moderate	No	Thrombin activation site
Exon 14	1689	CGC→TGC	Arg→Cys	HP14	<1	?	Severe	No	Thrombin activation site
Exon 14	1689	CGC→TGC	Arg→Cys	H10	0	96	Severe	No	Thrombin activation site
Exon 14	1689	CGC→TGC	Arg→Cys	JH38	5	211	Moderate	No	Thrombin activation site
Exon 14	1689	CGC→TGC	Arg→Cys	Hiroshima	4	178	Moderate	No	Thrombin activation site
Exon 14	1689	CGC→TGC	Arg→Cys	J242,J155,J403	4-5	100	Moderate	No	Thrombin activation site
Exon 14	1689	CGC→TGC	Arg→Cys	EF	5	100	Moderate	No	Thrombin activation site
Exon 14	1689	CGC→TGC	Arg→Cys	TWN43	<1	?	Severe	No	
Exon 14	1689	CGC→TGC	Arg→Cys	ARC5	2-5	87-220	Mild/Moderate	No	Thrombin activation site
Exon 14	1689	CGC→TGC	Arg→Cys	PB	<1	40	Severe	No	Thrombin activation site
Exon 14	1689	CGC→TGC	Arg→Cys	W381	12	?	Mild	No	
Exon 14	1689	CGC→CAC	Arg→His	HP15[l]	7	165	Mild	No	Thrombin activation site
Exon 14	1689	CGC→CAC	Arg→His	HP73[l]	11.0	100	Mild	No	Thrombin activation site
Exon 14	1696	CGA→TGA	Arg→Stop	J397	<1	?	Severe	Yes	Pattinson *et al* (1990a)
Exon 14	1696	CGA→TGA	Arg→Stop	OX23	<1		Severe	Yes	Naylor *et al* (1993b)
Exon 14	1696	CGA→GGA	Arg→Gly	4	17	?	Mild	No	
Exon 14	1698	CGC→TGC	Arg→Cys		<1	?	Severe	?	
Exon 14	1704	GAG→AAG	Glu-Lys	HA12	<1	?	Severe	No	
Exon 14	1709	TAT→TGT	Tyr→Cys	JH41	18	?	Moderate	No	
Intron 14		ag/GTA→ag/GTG		HP74	<1.0	<2.5	Severe	No	-3IVS 14 acceptor splice site
Exon 15	1750	GGA→AGA	Gly→Arg	HP77	22.0	23.5	Mild	No	
Exon 15	1750	GGA→AGA	Gly→Arg	HP75[m]	22.0	23.8	Mild	No	
Exon 15	1750	GGA→AGA	Gly→Arg	HP76[m]	21.0	24.5	Mild	No	
Exon 15	1750	GGA→AGA	Gly→Arg	HP78[m]	26.0	26.6	Mild	No	

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 15	1750	GGA→AGA	Gly→Arg	HP80	22.5	20.5	Mild	No	
Exon 15	1750	GGA→AGA	Gly→Arg	HP79	23.0	22.2	Mild	No	
Exon 15	1750	GGA→AGA	Gly→Arg	HP81	20.0	24.9	Mild	No	
Exon 15	1756	TTG→GTG	Leu→Val	HP83	5.0	1.5	Mild/Moderate	No	
Exon 15	1756	TTG→TTC	Leu→Phe	HP82	18.5	?	Mild	No	
Exon 15	1760	GGG→GAG	Gly→Glu	TWN72	<1	?	Severe	No	
Exon 15	1772	ATG→ACG	Met→Thr	JH116	<1	72	Severe	No	New N-glycosylation site N1770
Exon 16	1781	CGT→CAT	Arg→His	HP84	2.0	4.7	Moderate	No	
Exon 16	1781	CGT→CAT	Arg→His	HP86	2.5	?	Moderate	No	
Exon 16	1781	CGT→CAT	Arg→His	HP85	2.0	5.4	Moderate	No	
Exon 16	1781	CGT→CAT	Arg→His	JH128	?	?	Mild/Moderate	No	
Exon 16	1781	CGT→TGT	Arg→Cys	E	4-7	?	Mild	No	
Exon 16	1781	CGT→GGT	Arg→Gly	HP87	5.0	?	Mild/Moderate	No	
Exon 16	1784	TCC→TAC	Ser→Tyr	JH127	?	?	Severe	?	
Exon 16	1789	CTT→TTT	Leu→Phe	TWN100	7.2	?	Mild	No	
Exon 16	1789	CTT→TTT	Leu→Phe	H114	?	?	Mild	No	
Exon 16	1789	CTT→TTT	Leu→Phe	H107	?	?	Mild	?	
Exon 16	1796	CAG→TAG	Gln→Stop	TWN93	<1	?	Severe	Yes	Lin *et al* (1993)
Exon 16	1823	ATG→ATA	Met→Ile	TWN86	4.6	?	Moderate	No	
Exon 16	1825	CCC→TCCCCC→TCC	Pro→Ser	JH103^{n}	15	?	Moderate	No	
Exon 16	1825	CCC→TCC	Pro→Ser	HP88^{n}	12	18.1	Mild	No	
Exon 16	1826	ACT→CCT	Thr→Pro	JH102	?	?	Mild	No	
Exon 16	1827	AAA→TAA	Lys→Stop	TWN17	<1	?	Severe	Yes	Lin *et al* (1993)
Exon 16	1827	AAA→TAA	Lys→Stop	TWN13	<1	?	Severe	Yes	Lin *et al* (1993)
Exon 16	1834	GCC→GTC	Ala→Val	TWN44	18	?	Mild	No	
Exon 16	1834	GCC→ACC	Ala→Thr	GLA1	<1	?	Severe	No	May not be sole mutation
Exon 16	1843	CTG/gt→CTA/gt	Leu→Leu	JH104	9-18	?	Moderate	?	-1 IVS16 donor splice site
Exon 17	1846	GAT→AAT	Asp→Asn	HP133	<1	?	Severe	No	
Exon 17	1846	GAT→TAT	Asp→Tyr	HP132	<1	?	Severe	No	

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 17	1848	CAC→CGC	His→Arg	JH130	1-5	?	Mild/Moderate	No	
Exon 17	1848	CAC→CGC	His→Arg	HP89	1.5	20.1	Moderate	No	
Exon 17	1854	CCC→CGC	Pro→Arg	HP134	<1	?	Severe	No	
Exon 17	1869	AGA→ATA	Arg→Ile	GLA2	<1	?	Severe	No	
Exon 17	1874	CAG→TAG	Gln→Stop	OX3	<1	?	Severe	Yes	
Exon 17	1885	GAG→AAG	Glu→Lys	TWN66	<1	?	Severe	No	
Exon 18	1922	AAT→AGT	Asn→Ser	JH55	?	?	Severe	?	
Exon 18	1922	AAT→AGT	Asn→Ser	H87	?	?	Moderate	?	
Exon 18	1922	AAT→GAT	Asn→Asp	JH56	?	?	Moderate	?	
Exon 18	1922	AAT→GAT	Asn→Asp	JH51	<1	?	Severe	Yes	
Exon 18	1941	CGA→TGA	Arg→Stop	JH3	<1	?	Severe	No	
Exon 18	1941	CGA→TGA	Arg→Stop	6	<1	?	Severe	Yes	
Exon 18	1941	CGA→TGA	Arg→Stop	HP11	?	?	Severe	Yes	
Exon 18	1941	CGA→TGA	Arg→Stop	JH2	<1	?	Severe	Yes	
Exon 18	1941	CGA→TGA	Arg→Stop	JH44	?	?	Severe	Yes	
Exon 18	1941	CGA→TGA	Arg→Stop	RP296	<1	?	Severe	Yes	
Exon 18	1941	CGA→TGA	Arg→Stop	HA579	<1	?	Severe	Yes	
Exon 18	1941	CGA→TGA	Arg→Stop	JH45	?	?	Severe	?	
Exon 18	1941	CGA→TGA	Arg→Stop	WL	<1	<0.1	Severe	Yes	
Exon 18	1941	CGA→TGA	Arg→Stop	H4	<1	?	Severe	No	
Exon 18	1941	CGA→CAA	Arg→Gln	JH33	4-5	20	Mild	No	
Exon 18	1941	CGA→CAA	Arg→Gln	1286	?	?	Mild	No	
Exon 18	1941	CGA→CAA	Arg→Gln	OX15	2	?	Moderate	No	
Exon 18	1941	CGA→CAA	Arg→Gln	TWN46	17	?	Mild	No	
Exon 18	1941	CGA→CAA	Arg→Gln	TM	5	20	Moderate	No	
Exon 18	1941	CGA→CAA	Arg→Gln	321	3	?	Moderate	?	
Exon 18	1941	CGA→CTA	Arg→Leu	LB	7	?	Moderate	No	
Exon 18	1942	TGG→TAG	Trp→Stop	TWN65	<1	?	Severe	No	
Exon 18	1948	GGC→GAC	Gly→Asp	Porto2	7.4	48.7	Moderate	No	

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 18	1960	GGA→GTA	Gly→Val	HP90	6.0	?	Mild	No	
Exon 18	1961	CAT→TAT	His→Tyr	HP91	10.5	7.8	Mild	No	
Exon 18	1966	CGA→TGA	Arg→Stop	Montijo	1.4	9.1	Severe	Yes	
Exon 18	1966	CGA→TGA	Arg→Stop	8	<1	?	Severe	No	
Exon 18	1966	CGA→TGA	Arg→Stop	OX10	0	?	Severe	Yes	
Exon 18	1966	CGA→TGA	Arg→Stop	TWN91	<1	?	Severe	No	
Exon 18	1966	CGA→TGA	Arg→Stop	7	<1	?	Severe	Yes	
Exon 18	1966	CGA→TGA	Arg→Stop	TWN45	<1	?	Severe	No	
Exon 18	1987	GAA→TAA	Glu→Stop	OX33	<1		Severe	No	
Exon 19	1997	CGG→TGG	Arg→Trp	HP136	<1	?	Severe	No	
Exon 19	1997	CGG→TGG	Arg→Trp	JH137,JH138	3.4/2.6	?	Mild/Moderate	?	
Exon 19	2019	AAT→AGT	Asn→Ser	HP92	5.0	3.3	Mild/Moderate	No	
Exon 21	2046	TGG→CGG	Trp→Arg	H59	?	?	Moderate	No	
Exon 21	2069	TCT→TTT	Ser→Phe	HP93	<1.0	?	Severe	No	
Exon 22	2074	GAT→GGT	Asp→Gly	HP96	9.0	?	Mild	No	
Exon 22	2074	GAT→GGT	Asp→Gly	HP95	6.5	10.0	Mild	No	
Exon 22	2074	GAT→GGT	Asp→Gly	HP94	4.5	15.2	Mild	No	
Exon 22	2101	TTT→TTG	Phe→Leu	JH133^{o}	11	?	Mild/Moderate	No	
Exon 22	2101	TTT→TTG	Phe→Leu	HP97^{o}	7.0	5.3	Mild	No	
Exon 22	2105	TAT→TGT	Tyr→Cys	OX14	14	?	Mild	No	
Exon 22	2116	CGA→TGA	Arg→Stop	H208	<1	?	Severe	No	
Exon 22	2116	CGA→TGA	Arg→Stop	JH4, JH5	<1	?	Severe	No	
Exon 22	2116	CGA→TGA	Arg→Stop	TWN82,77	<1	?	Severe	No	
Exon 22	2116	CGA→TGA	Arg→Stop	9	<1	?	Severe	No	
Exon 22	2116	CGA→TGA	Arg→Stop	OX6	<1	?	Severe	No	
Exon 22	2116	CGA→TGA	Arg→Stop	HA360	<1	?	Severe	No	
Exon 22	2116	CGA→CCA	Arg→Pro	V99	<1	?	Severe	?	
Exon 22	2119	TCC→TAC	Ser→Tyr	JH134	5-8	?	Mild/Moderate	No	
Exon 22	2119	TCC→TAC	Ser→Tyr	HP98	3.5	9.2	Moderate	No	

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 23	2147	CGA→TGA	Arg→Stop	H377	<1	?	Severe	No	
Exon 23	2147	CGA→TGA	Arg→Stop	JH14	<1	?	Severe	Yes	
Exon 23	2147	CGA→TGA	Arg→Stop	V136	<1	?	Severe	?	
Exon 23	2147	CGA→TGA	Arg→Stop	JH60	?	?	Severe	?	
Exon 23	2147	CGA→TGA	Arg→Stop	PH	<1	<0.1	Severe	Yes	
Exon 23	2147	CGA→TGA	Arg→Stop	1281	<1	?	Severe	No	
Exon 23	2147	CGA→TGA	Arg→Stop	NK	1	<0.1	Severe	Yes	
Exon 23	2150	CGT→CAT	Arg→His	F	6	?	Mild	No	
Exon 23	2150	CGT→CAT	Arg→His	JH66,JH146	?	?	Mild/Moderate	No	
Exon 23	2150	CGT→CAT	Arg→His	JH57,JH58,JH59,JH65	5-7	?	Mild/Moderate	No	
Exon 23	2150	CGT→CAT	Arg→His	HP137	<1	?	Severe	No	
Exon 23	2150	CGT→CAT	Arg→His	H49	?	?	Mild	No	
Exon 23	2150	CGT→CAT	Arg→His	HP99	5	?	Moderate	No	
Exon 23	2150	CGT→CAT	Arg→His	H84	w	?	Mild	?	
Exon 23	**2150**	**CGT→CAT**	**Arg→His**	**HP100**	**3**	**?**	**Moderate**	**No**	
Exon 23	**2150**	**CGT→CAT**	**Arg→His**	**OX25**	**1-2**	**?**	**Moderate/Severe**	**No**	
Exon 22	**2153**	**CCA→CAA**	**Pro→Gln**	**HP101**	**3.0**	**5.6**	**Moderate**	**No**	
Exon 23	**2154**	**ACT→ATT**	**Thr→Ile**	**D**	**6**	**?**	**Mild**	**No**	
Exon 23	**2159**	**CGC→TGC**	**Arg→Cys**	**C**	**11-19**	**?**	**Mild**	**No**	
Exon 23	**2159**	**CGC→TGC**	**Arg→Cys**	**A**	**11-16**	**?**	**Mild**	**No**	
Exon 23	**2159**	**CGC→TGC**	**Arg→Cys**	**H138**	**10**	**?**	**Mild**	**No**	
Exon 23	**2159**	**CGC→TGC**	**Arg→Cys**	**JH154**	**10**	**6**	**?**	**No**	
Exon 23	**2159**	**CGC→TGC**	**Arg→Cys**	**RM**	**12**	**?**	**Mild**	**No**	
Exon 23	**2159**	**CGC→TGC**	**Arg→Cys**	**JH68**	**7.4**	**?**	**Moderate**	**?**	
Exon 23	**2159**	**CGC→TGC**	**Arg→Cys**	**H138**	**10**	**?**	**Mild**	**No**	
Exon 23	**2159**	**CGC→TGC**	**Arg→Cys**	**H52**	**?**	**?**	**Mild**	**No**	
Exon 23	**2159**	**CGC→TGC**	**Arg→Cys**	**B**	**9-12**	**?**	**Mild**	**No**	
Exon 23	**2159**	**CGC→TGC**	**Arg→Cys**	**HP102**	**11.0**	**15.4**	**Mild**	**No**	
Exon 23	**2159**	**CGC→TGC**	**Arg→Cys**	**HP104**	**6.0**	**8.6**	**Mild**	**No**	

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C $U.dl^{-1}$	FVIII:Ag $U.dl^{-1}$	Severity	Inhibitors	Comments
Exon 23	2159	CGC→TGC	Arg→Cys	HP103	14.5	15.7	Mild	No	
Exon 23	2159	CGC→TGC	Arg→Cys	OX13	12		Mild	No	
Exon 23	2159	CGC→CTC	Arg→Leu	HP105[P]	12.0	14.8	Mild	No	
Exon 23	2159	CGC→CTC	Arg→Leu	HP106[P]	25.0	?	Mild	No	
Exon 23	2159	CGC→CAC	Arg→His	HP107	22.0	11.9	Mild	No	
Exon 23	2163	CGC→CAC	Arg→His	JH67,JH61	?	?	Moderate	?	
Exon 23	2163	CGC→TGC	Arg→Cys	B	1	<10	Moderate	No	
Exon 23	2166	GTT→GCT	Leu→Ser	1308	<1	?	Severe	No	
Exon 24	2192	GCT→CCT	Ala→Pro	TWN7	1	?	Moderate	No	
Exon 24	2209	CGA→CAA	Arg→Gln	NO	3	?	Moderate	No	
Exon 24	2209	CGA→CAA	Arg→Gln	?	<1	?	Severe	?	
Exon 24	2209	CGA→CAA	Arg→Gln	JH34	3	?	Moderate	?	
Exon 24	2209	CGA→CAA	Arg→Gln	HA848	<1	?	Severe	No	
Exon 24	2209	CGA→CAA	Arg→Gln	HP16	7	130	Mild	Yes	
Exon 24	2209	CGA→CAA	Arg→Gln	HP17	<1	?	Severe	No	
Exon 24	2209	CGA→CAA	Arg→Gln	?	<1	?	Severe	No	
Exon 24	2209	CGA→CAA	Arg→Gln	JH50	?	?	Severe	No	
Exon 24	2209	CGA→CAA	Arg→Gln	JH18/JH19	<1	?	Severe	No	
Exon 24	2209	CGA→CAA	Arg→Gln	JH64	<1	4	Severe	No	
Exon 24	2209	CGA→CAA	Arg→Gln	H5	<1	?	Severe	No	
Exon 24	2209	CGA→CAA	Arg→Gln	785, 818	2-5	?	Moderate	No	
Exon 24	2209	CGA→CTA	Arg→Leu	H156	3	2.5	Moderate	No	
Exon 24	2209	CGA→TGA	Arg→Stop	HP12	?	?	Severe	No	
Exon 24	2209	CGA→TGA	Arg→Stop	H2	0	?	Severe	Yes	
Exon 24	2209	CGA→TGA	Arg→Stop	HP8	?	?	Severe	No	
Exon 24	2209	CGA→TGA	Arg→Stop	10	<1	?	Severe	No	
Exon 24	2209	CGA→TGA	Arg→Stop	HA735	<1	?	Severe	Yes	
Exon 24	2209	CGA→TGA	Arg→Stop	HP10	?	?	Severe	No	

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments
Exon 24	2209	CGA→TGA	Arg→Stop	JH46,JH47,JH93	?	?	Severe	?	
Exon 24	2209	CGA→TGA	Arg→Stop	JH16	<1	?	Severe	Yes	
Exon 24	2209	CGA→TGA	Arg→Stop	JH15	<1	?	Severe	Yes	
Exon 24	2209	CGA→TGA	Arg→Stop	HA735	<1	?	Severe	No	
Exon 24	2209	CGA→GGA	Arg→Gly	RP271	<1	?	Severe	No	
Exon 25	2223	ag/GTG→ag/ATG	Val→Met	?	?	?	?	?	+1 Intron 24 acceptor splice site
Exon 25	2229	TGG→TGT	Trp→Cys	OX1	3	?	Mild/Moderate	Yes (transient)	
Exon 25	2229	TGG→TGT	Trp→Cys	H143	?	?	Moderate	?	
Exon 25	2246	CAG→CGG	Gln→Arg	HP108	4.5	1.1	Moderate	No	
Exon 25	2246	CAG→CGG	Gln→Arg	HP109	4.0	<1.0	Moderate	No	
Exon 25	2270	CAG→TAG	Gln→Stop	HP138	<1	?	Severe	No	
Intron 25	-	caa→cga	-	H40	<1	?	Severe	No	Probably a neutral change ~1.9kb 5' to exon 26
Exon 26	2300	CCG→CTG	Pro→Leu	JH75	7.5	?	Mild	?	
Exon 26	2300	CCG→TCG	Pro-Ser	HA39	16	?	Mild	No	
Exon 26	2304	CGC→CAC	Arg→His	HP110	10.0	?	Mild	No	
Exon 26	2304	CGC→TGC	Arg→Cys	C	1	<10	Moderate	No	
Exon 26	2304	CGC→TGC	Arg→Cys	JH54	?	?	Mild	?	
Exon 26	2307	CGA→TGA	Arg→Stop	JH53	<1		Severe	?	
Exon 26	2307	CGA→TGA	Arg→Stop	1060	<1	?	Severe	No	
Exon 26	2307	CGA→TGA	Arg→Stop	H5	<1	?	Severe	No	
Exon 26	2307	CGA→TGA	Arg→Stop	RP469	<1	?	Severe	Yes	
Exon 26	2307	CGA→TGA	Arg→Stop	H22	0	?	Severe	No	
Exon 26	2307	CGA→TGA	Arg→Stop	JH49	<1	?	Severe	?	
Exon 26	2307	CGA→TGA	Arg→Stop	H5	<1	?	Severe	No	
Exon 26	2307	CGA→TGA	Arg→Stop	JH53	?	?	Severe	?	
Exon 26	2307	CGA→TGA	Arg→Stop	HP9	?	?	Severe	No	
Exon 26	2307	CGA→TGA	Arg→Stop	1060	<1	?	Severe	No	
Exon 26	2307	CGA→CAA	Arg→Gln	H6	2	?	Moderate	No	

Table 1. (*cont.*)

Exon/ Intron	Codon[1]	Nucleotide Change	Codon Change	Patient Identification	FVIII:C $U.dl^{-1}$	FVIII:Ag $U.dl^{-1}$	Severity	Inhibitors	Comments
Exon 26	2307	CGA→CAA	Arg→Gln	HA800	9	?	Mild	No	
Exon 26	2307	CGA→CAA	Arg→Gln	H104	10	6	Mild	No	
Exon 26	2307	CGA→CAA	Arg→Gln	H6	2	?	Moderate	No	
Exon 26	2307	CGA→CTA	Arg→Leu	JH48/JH32	<1	?	Severe	No	
Exon 26	2307	CGA→CTA	Arg→Leu	HP111	<1	?	Severe	?	
Exon 26	2307	CGA→CTA	Arg→Leu	HP13	?	?	Severe	No	
Exon 26	2307	CGA→CTA	Arg→Leu	JH32	2	4	Mild	No	
Exon 26	2307	CGA→CTA	Arg→Leu		?	?	Moderate	No	

[1]Codons numbered after scheme of Vehar *et al* (1984) i.e. starts at mature N-terminus and 19 signal peptide residues numbered negatively.
[a b c] etc. superscripts to patient identification indicate members of the same kindred.

Table 2. Deletions found in the factor VIII gene of patients with haemophilia A

A. Large deletions

Exon(s) deleted	Size of deletion (kb)	Patient/ Family	FVIII:C U.dl^{-1}	FVIII: U.dl^{-1}	Severity	Inhibitors	References
1–26	>210	?	?	?	Severe	No	Casarino *et al* (1986)
1–26	>210	H1	?	?	Severe	Yes	Casula *et al* (1990)
1–6	>55	H328	<1	?	Severe	Yes	Millar *et al* (1990)
1–5	>35	484	<1	?	Severe	No	Higuchi *et al* (1989)
1	?	1	<1	?	Severe	No	Reiner & Thompson (1992)
1	>2	JH13	<1	<1	Severe	No	Youssoufian *et al* (1988d)
1	>1	H309	<1	?	Severe	No	Millar *et al* (1990)
1	?	JH145	?	?	Severe	?	Higuchi *et al* (1991b)
Exon 1/ intron 1	13	HD7	<1	?	Severe	No	Schwaab *et al* (1993)
Intron 1*	7	1067	?	?	Severe	No	Levinson *et al* (1990)
2–4	?	TWN11	<1	?	Severe	Yes	Lin *et al* (1993)
2–3	9–12	JH21	<1	<1	Severe	No	Youssoufian *et al* (1988d) Cutting *et al* (1988) Woods-Samuels *et al* (1991)
3–13	60	JH22	<1	<1	Severe	Yes	Youssoufian *et al* (1988d) Cutting *et al* (1988)
3–5	11.7	H151	<1	?	Severe	No	Millar *et al* (1990)
3	1.7–2.0	656	<1	?	Severe	No	Higuchi *et al* (1988;1989)
4–25	133–145	JH23	<1	<1	Severe	No	Youssoufian *et al* (1988d) Cutting *et al* (1988)
4–10	?	TWN27,112	<1	?	Severe	Yes	Lin *et al* (1993)
5–13	57	H571	<1	?	Severe	Yes	Millar *et al* (1990)
5,6	?	?	?	?	Severe	?	Gitschier *et al* (1989)
5,6	2.5–10	2253	?	?	Severe	Yes	Levinson *et al* (1990)
5	2	H275	?	?	Severe	No	Broecker-Vriends *et al* (1990)
5 or 6	2	?	?	?	Severe	?	Broecker-Vriends *et al* (1988)
5,6	?	OX 26	<1	?	Severe	No	Naylor *et al* (1993a)
6	10	1059	?	?	Severe	No	Levinson *et al* (1990)
6	7	JH6	<1	<1	Severe	No	Youssoufian *et al* (1987b)
6	3–6	2213	?	?	Severe	No	Levinson *et al* (1990)
6	?	TWN108	<1	?	Severe	Yes	Lin *et al* (1993)
6	<6	HD8	<1	?	Severe	No	Schwaab *et al* (1993)
6	8–13	HD9	<1	?	Severe	No	Schwaab *et al* (1993)
7–22	110	H2	?	?	Severe	Yes	Casula *et al* (1990)
7–14	40–56	JH24	<1	<1	Severe	No	Youssoufian *et al* (1988d)
7–9	15–20	505	<1	?	Severe	Yes	Higuchi *et al* (1989)
10	4.8	149	<1	?	Severe	No	Krepelov *et al* (1992a)
11–22	60	JH1	?	?	Severe	Yes	Antonarakis *et al* (1985) Cutting *et al* (1988) Woods-Samuels *et al* (1991)
14–22	>36	H20	?	?	Severe	Yes	Nafa *et al* (1990)
14–22	?	?	?	?	Severe	Yes	Lillicrap (unpub. res.)
14–21	50	H229	<1	?	Severe	Yes	Millar *et al* (1990)
Intron 13/ exon 14	6.1	15[a]	<1	?	Severe	No	Krepelov *et al* (1992a)
Intron 13/ exon 14	6.1	311[a]	<1	?	Severe	Yes	Krepelov *et al* (1992a)
Intron 13/ exon 14	4.6	112	<1	?	Severe	Yes	Krepelov *et al* (1992a)
14	12–16	194/513	<1	?	Severe	Yes	Higuchi *et al* (1989)
14	6	?	<1	<0.1	Severe	Yes	Mikami *et al* (1988b)
14	2.3–3.0	580	<1	?	Severe	No	Higuchi *et al* (1989)
14	2.5	JH7	<1	<1	Severe	No	Youssoufian *et al* (1987b) Woods-Samuels *et al* (1991)
14	2.5	JH37	?	?	Severe	?	Woods-Samuels *et al* (1991)
15–22	~50	5	<1	?	Severe	Yes	Reiner & Thompson (1992)
15–22	>15	H157	<1	<1	Severe	No	Michaelides *et al* (unpub.res.)
15–22	>19	RP308	<1	?	Severe	Yes	Figuerido *et al* (unpub.res.)
15–21	?	JH141	?	?	Severe	?	Higuchi *et al* (1991b)
15–18	13	?	?	?	Severe	Yes	Camerino *et al* (1986) Bardoni *et al* (1988)
15	?	JH29	?	?	Severe	?	Antonarakis *et al* (unpub.res.)
16	>0.2	GLA11	1	?	Severe	No	Bidichandani *et al* (unpub.res.)

Table 2. (*cont.*)

A. Large deletions

Exon(s) deleted	Size of deletion (kb)	Patient/ Family	FVIII:C U.dl^{-1}	FVIII: U.dl^{-1}	Severity	Inhibitors	References
16–26	>95	?	<1	?	Severe	Yes	Figueiredo *et al* (1992)
Intron 15/ exon 16	0.304	HD10	<1	?	Severe	No	Schwaab *et al* (1993)
17–19	?	1	?	?	Severe	No	Wehnert *et al* (1989)
18,19+?	?	5	?	?	Severe	?	Grover *et al* (1987)
19	1.9	OX 27	<1	?	Severe	No	Naylor *et al* (1993a)
19–21	4.7	H58	<1	?	Severe	Yes	Millar *et al* (1990)
22	5.5	JH10	2–5	?	Moderate	No	Youssoufian *et al* (1987b)
Intron 22+	?	2	?	?	Severe	No	Wehnert *et al* (1989)
Intron 22+	?	3	?	?	Moderate	No	Wehnert *et al* (1989)
23–26	?	?	?	?	Severe	Yes	Din *et al* (1986)
23–26	?	HA664	?	?	Severe	Yes	Lavergne *et al* (1992)
23–25	>16	JH9	<1	<1	Severe	No	Youssoufian *et al* (1987b)
23–25	39	H96	<1	?	Severe	Yes	Gitschier *et al* (1985)
23–24	?	HA711	?	?	Moderate	No	Lavergne *et al* (1992)
24–25	>3.4	JH8	<1	<1	Severe	No	Youssoufian *et al* (1987b)
26	22	H51	<1	?	Severe	No	Gitschier *et al* (1985)
26	>18	277	<1	?	Severe	No	Higuchi *et al* (1989)
26	14	JH26	<1	<1	Severe	No	Youssoufian *et al* (1988d)
26	8.7	?	?	?	Severe	?	Bernardi *et al* (1989)
26	>2	H73	?	?	Severe	No	Nafa *et al* (1990)
26	>2	?	?	?	Severe	No	Youssoufian *et al* (1987c)
26	>2	H8	?	?	Severe	?	Bernardi *et al* (1989a)
26	?	JH12	?	?	Severe	?	Antonarakis *et al* (unpub.res.)
26	?	HA364	?	?	Severe	No	Lavergne *et al* (1992)
26	?	HA544	?	?	Severe	No	Lavergne *et al* (1992)
26	?	HA599	?	?	Severe	No	Lavergne *et al* (1992)
26	<10.5	RP620	<1	?	Severe	No	Figuerido *et al* (1994)
26	?	HD12	<1	?	Severe	No	Schwaab *et al* (1993)
part 26	?	HD11	<1	?	Severe	No	Schwaab *et al* (1993)

+Precise extent unknown but includes at least region indicated.
*Not proven to be cause of disease phenotype although segregates with disease allele.
[a]Patients related

B. Small deletions

Exon/ Intron	Codons	Size in bp (nucleotides deleted)	Patient/ Family	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments	References
Exon 1/ intron 1	14–29	86	RP451	<1	?	Severe	No	Includes IVS1 donor splice site	Figueiredo *et al* (1994)
Exon 2	48	2(AA)	TWN49	<1	?	Severe	No	Frameshift	Lin *et al* (1993)
Exon 2	50–51 (TTTG)	4(GTTT) or	HD12	<1	?	Severe	No	Frameshift	Seehafer *et al* (unpub.res.)
Exon 3/ intron 3	104–111	23	JH72	?	?	Severe	?	Includes IVS3 donor splice site	Higuchi *et al* (1991b)
Exon 3	103	2(GT)	HD13	<1	?	Severe	No	Frameshift	Seehafer *et al* (unpub.res.)
Exon 4	154–156	5(TACCT)	?	<1	?	Severe	?	Frameshift	Bidichandani *et al* (1994b)
Exon 6	210–2112	(AG)	TWN73	<1	?	Severe	No	Frameshift	Lin *et al* (1993)
Exon 7	264	1(T)	HD14	<1	?	Severe	No	Frameshift	Seehafer *et al* (unpub.res.)
Exon 7	283	1(G)	HD15	<1	?	Severe	?	Frameshift	Seehafer *et al* (unpub.res.)
Exon 8	339–342	9(AATAA TGAAGAA)	?	?	?	Severe	?	Deletes Asn Asn Glu Glu	Gitschier *et al* (unpub.res.)
Exon 8	339–342	9(AATAAT GAAGAA)	?	?	?	Severe	?	Deletes Asn Asn Glu Glu	Kazazian *et al* (unpub.res.)
Exon 8	340–341	4(AATG)	H23	?	?	Severe	No	Frameshift	Kogan & Gitschier (1990)
Exon 8	341	2(GA)	JH31	?	?	Severe	?	Frameshift	Antonarakis *et al* (unpub.res.)
Exon 8	381–382	2(TT)	HD16	<1	?	Severe	No	Frameshift	Seehafer *et al* (unpub.res.)
Exon 9	412	1(G)	TWN85	<1	?	Severe	No	Frameshift	Lin *et al* (1993)

Table 2. (*cont.*)

Exon/ Intron	Codons	Size in bp (nucleotides deleted)	Patient/ Family	FVIII:C U.dl^{-1}	FVIII:Ag U.dl^{-1}	Severity	Inhibitors	Comments	References
Exon 14	1194	1(A)	TWN107	<1	?	Severe	No	Frameshift	Lin *et al* (1993)
Exon 14	1212	1(C)	OX11	<1	?	Severe	No	Frameshift	Naylor *et al* (1993b)
Exon 14	1355–1356	4(TAGA)	TWN90	<1	?	Severe	No	Frameshift	Lin *et al* (1993)
Exon 14	1412–1414	5(CTCTT)	Guine Bisao	1.0	?	Severe	No	Frameshift	David *et al* (unpub.res.)
Exon 14	1422–5	4(AAGA)	OX21	<1	?	Severe	No	Frameshift	Naylor *et al* (1993b)
Exon 14	1439	1(A)	JH142	?	?	Severe	?	A8→A7, Frameshift	Antonarakis *et al* (unpub.res.)
Exon 14	1439	1(A)	OX32	<1	?	Severe	No	Frameshift	Naylor *et al* (1993b)
Exon 14	1535–6	2(GA)	JH80	?	?	Severe	?	Frameshift	Higuchi *et al* (1991b)
Exon 14	1601	1(C)	TWN63	<1	?	Severe	No	Frameshift	Lin *et al* (1993)
Exon 17	1880	1(C)	GLA6	<1	?	Severe	Yes	Frameshift (unpub.res.)	Bidichandani *et al*
Exon 18	1967–1968	1(A)	HD17	<1	?	Severe	No	Frameshift	Seehafer *et al* (unpub.res.)
Exon 18	1967–1968	1(A)	HD18	<1	?	Severe	No	Frameshift	Seehafer *et al* (unpub.res.)
Exon 19	1998	1(G) (First)	HD19	<1	?	Severe	Yes	Frameshift	Seehafer *et al* (unpub.res.)
Exon 23	2119	2	H148	?	?	?	?	Frameshift	Kazazian *et al* (unpub.res.)
Exon 23	2136	2(AA)	JH69	?	?	Severe	?	A4→A2, Frameshift	Antonarakis *et al* (unpub.res.)
Exon 24	2205	3(CTC)	JH90	?	?	Moderate	No	Deletes Pro 2205	Economou *et al* (1992)
Exon 24	2205	3(CTC)	JH91	?	?	Moderate	No	Deletes Pro 2205	Economou *et al* (1992)
Exon 24	2205	3(CTC)	TWN104	<1	?	Severe	No	Deletes Pro 2205	Lin *et al* (1993)
Exon 24	2214	1(G)	HD20	<1	?	Severe	No	Frameshift	Seehafer *et al* (unpub.res.)
Exon 25	2246	2(AG)	TWN23	<1	?	Severe	No	Frameshift	Lin *et al* (1993)
Exon 26	2285–2287	5(AAATC)	HD21	<1	?	Severe	No	Frameshift	Seehafer *et al* (unpub.res.)

Table 3. Insertions in the factor VIII gene causing haemophilia A

Exon	Nature of Insertion	Patient	FVIII:C	FVIII:Ag	Severity	Inhibitors	Reference
2	10bp (TTCCATTCAA at codon 38)	TWN3,80, 52,96	<1	?	Severe	?	Lin *et al* (1993)
11	1bp (G at codon 513)	JH100	?	?	Severe	?	Economou *et al* (unpub.res.)
12	3bp (ATC at codon 613)	H775	<1	?	Severe	No	Lavergne *et al* (unpub.res.)
13	1bp (A at codon 669)	HP50	<1	?	Severe	No	Seehafer *et al* (unpub.res.)
14	3.8 Kb LINE element	JH27	?	?	Severe	?	Kazazian *et al* (1988)
14	2.1 Kb LINE element	JH28	?	?	Severe	Yes	Kazazian *et al* (1988)
14	2bp (AA at codon 1324)	TWN94	<1	?	Severe	?	Lin *et al* (1993)
14	1bp (A at codon 961)	OX19	<1		Severe	No	Naylor *et al* (1993b)
14	1bp (TCA→TCAA at codon 1395)	JH77	<1	?	Severe	?	Higuchi *et al* (1991b)
14	1bp (A in stretch of 8 A residues at codons 1439–1441)	JH81	<1	?	Severe	?	Higuchi *et al* (1991b)
14	1bp (A in stretch of 8 A residues at codons 1439–1441)	Porto3	1.4	1.0	Severe	No	David *et al* (1994)
14	1bp (A at codon 1590)	TWN60	<1	?	Severe	?	Lin *et al* (1993)
17	1bp (T at codon 1855)	HP	<1	?	Severe	No	Schwaab *et al* (unpub.res.)
17	1bp (A in stretch of 4 A residues in codon 1888)	JH129	?	?	Severe	?	Higuchi *et al* (1991b)

Table 4. Haemophilia A — Mutations June 1994

Different point mutations					
Exon	Missense	Nonsense	Splicing Deletions	Small	Insertions
1	5	1	–	1	–
2	1	–	1	2	1
3	9	–	–	2	–
4	8	2	1	1	–
5	1	–	2	–	–
6	-	–	1	1	–
7	12	1	1	2	–
8	11	3	–	5	–
9	3	1	–	1	–
10	5	–	–	1	–
11	10	1	1	–	1
12	7	1	1	–	1
13	4	1	–	1	1
14	14	4	–	12	8
15	5	–	1	–	–
16	11	2	1	–	–
17	6	1	–	1	1
18	7	4	–	2	–
19	2	–	–	1	–
20	–	–	–	–	–
21	2	–	–	–	–
22	5	1	–	–	–
23	9	1	–	2	–
24	4	1	–	4	–
25	3	1	–	1	–
26	6	1	–	1	–
LARGE DELETIONS 81					