Haemophilia B: database of point mutations and short additions and deletions — second edition

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The data base below lists known point mutations and short deletions and additions in the factor IX gene, which cause the bleeding disorder haemophilia B or Christmas disease (for reviews, see Brownlee 1988, Giannelli 1989, Thompson 1990). Mutations result in defective clotting factor IX—a 415 amino-acid-long glycoprotein normally present in plasma and an essential component of the middle phase of the intrinsic clotting cascade. The disease is a rare, inherited, X-linked recessive disorder affecting 1 in about 30,000 males and only very rarely females.

The purpose of this database is to update last year's one (Giannelli et al, 1990) by collecting in an accessible, summary form, molecular data on the causative mutations of haemophilia B patients worldwide. It is not intended to replace primary publications although it does contain a significant amount of unpublished work. Because haemophilia B is a disease with a relatively high *de novo* mutation rate, it has been thought for many years that a wide spectrum of mutations covering many parts of the gene would cause disease. This database amply demonstrates this, but also highlights nucleotides where there are mutation hotspots, because we have included not only molecularly *unique* mutations, but also *repeat* observations of the same mutation.

Because of the vast rate of increase in knowledge in this field since the first point mutation, 'Chapel Hill', was named and characterized in 1983 (Noyes et al, 1983), there has been controversy as to how to name a large number of patients in an anonymous way suitable for publication, and indeed a variety of differing conventions have been favoured by different investigators (see main Table). In an attempt to simplify the present situation, we introduce here a simple numerical nomenclature which we refer to as a Patient Identity Number, or PIN number. Thus, in this database, patients have PIN numbers ranging from 1 to 388. We hope that this new system will be accepted by all workers in this field and that the definitive PIN number now assigned to a given patient or pedigree will coexist with the existing nomenclature (if any) contained within the original reference.

The factor IX gene lies on the long arm of the X chromosome at Xq27 and its entire sequence of 33 kb is known (Yoshitake et al, 1985). It contains 8 exons (a–h) encoding 6 major domains of factor IX. These are: (1) exon a—a hydrophobic *signal* peptide which targets the protein for secretion from the hepatocyte into the blood stream. (2) exons b and c—a propeptide and *gla* domain,—the latter containing 12 γ-carboxyglutamyl residues. This post-translational modification is required for the correct folding and calcium binding of factor IX. (3) exon d—a *type B, or first epidermal growth factor-like domain*, which shows homology to epidermal growth factor (EGF) and, in addition, contains conserved carboxylate residues including a β-hydroxyaspartate at amino acid 64. This domain binds an additional Ca^{2+} with high affinity (Handford et al, 1990). (4) exon e—a *type A, or second epidermal growth factor-like (EGF) domain* which lacks the conserved carboxylate residues of the EGF type B domain. (5) exon f—an *activation* domain, within which factor XIa cleaves twice, converting factor IX to IXa; (6) exons g and h—the *serine protease or catalytic domain*, responsible for the proteolysis of factor X to Xa. This region is homologous to other well studied serine proteases (e.g. chymotrypsin) and it is thought likely that his (221), asp (269) and ser (365), all participate in the classical catalytic mechanism.

Factor IX is initially synthesised in the liver as a precursor molecule, either 46, 41 or 39 amino acids (it is not known which, although 39 is probable (Pang et al, 1990)) longer at its N-terminus than the 415-long mature factor IX found in plasma.

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Processing steps occur in the hepatocyte prior to secretion and sequentially remove the hydrophobic signal peptide and the propeptide. In addition to the γ-carboxylation of the 12 N-terminal glutamyl residues carried out by a vitamin K-dependent carboxylase, and the partial β-hydroxylation of aspartate 64, N-linked carbohydrate side chains are added at residues 157 and 167 and at least an O-linked carbohydrate at serine 53.

There are 397 entries in this second edition of the database compared with 221 last year (Giannelli et al, 1990). Besides point mutants, it includes 40 short (defined as less than 20 nucleotides) deletions or additions or both, made up from 31 deletions, 6 additions and 3 examples involving both additions and deletions. There are also 9 double mutations, 8 inhibitor patients and 1 female haemophiliac, presumably caused by non-random X-inactivation. The list excludes 29 patients with partial or complete gene deletions or more complex rearrangements (Thompson, 1990). Of the 388 patients studied (see Summary Table), 206 are unique molecular events, the remainder being repeats. As is well known, many (and here, 132 or 72%) of these repeats occur at CG doublets and involve a CG → TG or CA change. As discussed before (Giannelli et al, 1990), such mutants are believed to be genuine 'hotspots' for mutation (although the independent origin of identical mutations has not been demonstrated in every case), because of methylation of cytosine to 5′ methylcytosine. This modified cytosine is amongst the more unstable residues in DNA and deaminates giving rise to thymine, in either the coding or non-coding strand of the gene. For example, nucleotide 31,008 is represented 19 times in the database and 6 other mutations involving nucleotides within CG doublets are reported 10 times or more. We calculate from the database that 39% (or 151 of the total of 388 mutations) occur at CG doublets. The remaining 28% repeat mutations do not involve CG mutations, but these cases generally occur twice or three times only in the database. They may, in some cases, represent genuine independent mutations. However, we suspect a majority are the same 'founder' mutation in related pedigrees. An exception to the 'rule' that multiple repeat mutations are confined to CG doublets are the 19 reported mutants at nucleotide 31,311. Thompson et al (1990) have proposed from a haplotype analysis that these represent a single 'founder' mutant which, for unknown reasons, has become, atypically, widely distributed.

There is probably some explanation other than chance for the few, atypical, cases where CG mutants are rare, occurring only once, twice or three times (e.g. nucleotides 17,761, −6 and 6,461, respectively). We propose that non-methylation or partial methylation of the cytosine in the CG doublet could explain the 17,761 and −6 observations, whilst the low frequency of mutations at 6,461 might be due to the extremely mild nature of the disease (~30% clotting activity) caused by this particular mutation (R→Q at amino acid 29) resulting in an under-reporting of this mutation.

The distribution of mutants according to protein domains and control regions within the gene (see Summary Table) shows that mutations have been detected in all categories listed except the poly(A) site. Missense mutations within individual protein domains give valuable information as to the essential nature of specific amino acids and are a significant aid to structural studies of domains (e.g. see Handford et al, 1990). Similarly, promoter mutations are invaluable in studying gene regulation (e.g. Crossley & Brownlee, 1990).

The only other specific group of inherited diseases with a comparable number of characterized mutations as in haemophilia B are the haemoglobinopathies. They are caused mostly by point mutations in the α or β-globin locus, and over 150 molecularly unique mutations are known (Winslow & Anderson, 1983). In addition, there are more than 50 non-deletion mutations causing α- or β-thalassaemia, affecting the globin genes (Thein & Weatherall, 1988).

The data base was compiled from separate lists updating the previous year's list prepared by coordinators for the different countries as follows:- Giannelli and Green representing the UK, Sweden and Iceland (70 new entries); High and Sommer representing USA (58 new entries); Lillicrap representing Canada (11 new entries); Ludwig and Olek representing Germany (29 new entries); Reitsma representing The Netherlands (no new entries); Goossens representing France (1 new entry); Yoshioka representing Japan (1 new entry); and Brownlee, the rest of the world (7 new entries) and central coordinator. We plan to update this data base annually. New data or notification of errors or omissions should be sent to the individual country coordinators by 31st December 1991. This database is available from individual country coordinators on floppy discs written in Wordperfect 5.1 on an IBM PS2 computer. We hope to generate a new-style database by 1992 which will be held on the EMBL DataLibrary file server in Heidelberg, Germany, in a form which can be retrieved directly from them by electronic mail.

ACKNOWLEDGEMENT

We thank Barbara Paxman for acting as coordinating secretary.

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Summary Table derived from main database

Location[1]	Exon	Nucleotide number[3]	Number of mutants[2]	Unique molecular events[2]
Signal peptide (−46 to −18)	a	30–116	1	1
Propeptide (−17 to −1)	b	6,326–6,375	28	4
Gla	b	6,376–6,489	32	22
(1 to 46)	c	6,678–6,701		
EGF (1st)	d	10,392–10,505	31	18
(47 to 84)				
EGF (2nd)	e	17,669–17,797	13	12
(85 to 127)				
activation	f	20,363–20,565	47	22
(128 to 195)				
catalytic	g	30,039–30,153	196	98
(196 to 415)	h	30,822–31,372		
Subtotal			*348*	*177*
Promoter			12	8
Donor splice sites			17	13
Acceptor splice sites			7	6
Cryptic splice[4]			4	2
Poly(A) site			0	0
Totals			**388**	**206**

[1] Amino acid numbers used (Anson et al, 1984)
[2] Excluding normal variants within double mutants
[3] For numbering, see Yoshitake et al (1985)
[4] These are possible new splice sites within exons

Characterized Point Mutations and Short Deletions/Additions in patients with Haemophilia B (Christmas disease)

Patient[7]	Clotting (normal =100%)	Antigen (normal =100%)	Nucleotide[1,3,8] position & mutation	Amino acid[1] change	Comments[3]	Reference	Patient Identity Number[10]
HB5, Japan	<1	<1	-793, G→A	None	Double (see 20,551), N	Matsushita et al (1990)	1
Leyden 1	<1→60	<1→60	-20, T→A	None	Promoter	Reitsma et al (1988)	2
Datteln	<1→36[5]	<1→36[5]	-20, T→A	None	Promoter	Ludwig et al	3
High Wycombe	13-70[5]		-6, G→A[4]	None	Promoter	Crossley et al (1990)	4
Leyden, USA	10	13	-6, G→A[4]	None	Promoter	Hirosawa et al (1990)	5
Toulouse	1→30[5]	1→30[5]	-6, G→C	None	Promoter	Gispert et al (1989)	6
Toronto 20	3		-5, A→T	None	Promoter	Picketts et al	7
Leyden, NZ	1-32[5]		8, T→C	None	Promoter	Royle et al (1990)	8
Leyden 2	<1→60	<1→60	13, A→G	None	Promoter	Reitsma et al (1989)	9
HB13	32		13, A→G	None	Promoter	Koeberl et al (1989)	10
Norwich	3-35[5]		13, A→G	None	Promoter	Crossley et al (1989)	11
Leyden 3	<1→60	<1→60	13, Δ1	None	Promoter	Reitsma et al (1989)	12
Aachen	<1		13, A→C	None	Promoter, C/EBP-binding site	Ludwig et al	13
Riegelsberg	<1	<1	37, G→A[4]	-44, R→H	Double (see 31,084), N	Ludwig et al	14

UK 22	2	<1	79, T→A	-30, I→N	Signal peptide	Green, Montandon et al	15
UK 36		<1	111-120, Δ10	-19	Frameshift, Donor splice (a)	Green, Montandon et al	16
Recklinghausen	<1	<1	114, Ins AT	-18	Frameshift	Ludwig et al	17
Malmö 33	3	2	122, G→A		Donor splice (a)	Green, Montandon et al	18
Boxtel	4	36	6,364, C→T[4]	-4, R→W		Reitsma et al	19
Heiden	<1		6,364, C→T[4]	-4, R→W		Ludwig et al	20
Lienen	<1	40	6,364, C→T[4]	-4, R→W		Ludwig et al	21
Malmö 6	<1	26-34	6,364, C→T[4]	-4, R→W		Green et al (1989)	22
Malmö 19	2-3	36	6,364, C→T[4]	-4, R→W		Green et al (1990)	23
Malmö 20	2	27	6,364, C→T[4]	-4, R→W		Green et al (1990)	24
Malmö 40	1	30	6,364, C→T[4]	-4, R→W		Green et al (1990)	25
UK 130	2		6,364, C→T[4]	-4, R→W		Green, Montandon et al	26
UK 134	<1		6,364, C→T[4]	-4, R→W		Green, Montandon et al	27
UK 129	4		6,364, C→T[4]	-4, R→W		Green, Montandon et al	28
Bendorf	<1		6,365, G→T	-4, R→L		Ludwig et al	29
Beuten	<1	45	6,365, G→T	-4, R→L		Ludwig et al	30
Gleiwitz	<1	49	6,365, G→T	-4, R→L		Ludwig et al	31
Kingston 1 (HB55)	<1	27	6,365, G→T	-4, R→L		Koeberl et al (1990a)	32
Oxford 3	<1	89	6,365, G→A[4]	-4, R→Q		Bentley et al (1986)	33

San Dimas	<1	98	6,365, G→A[4]	-4, R→Q	Abnormal carboxylation; circulates with propeptide	Ware et al (1989)	34
HB56	<1		6,365, G→A[4]	-4, R→Q		Bottema et al (1990a)	35
Dortmund	<1		6,365, G→A[4]	-4, R→Q		Ludwig et al	36
Hong Kong 2	4	93	6,365, G→A[4]	-4, R→Q		Chan et al (1990)	37
Hong Kong 3	1	82	6,365, G→A[4]	-4, R→Q		Chan et al (1990)	38
Kawachinagano	<1	46	6,365 G→A[4]	-4, R→Q		Sugimoto et al (1989)	39
Kingston 2	<1		6,365, G→A[4]	-4, R→Q		Koeberl et al (1990a)	40
Münster	<1		6,365, G→A[4]	-4, R→Q		Ludwig et al	41
Strasbourg II	<1	40	6,365, G→A[4]	-4, R→Q		de la Salle	42
Troed-y-Rhiw	4	80	6,365, G→A[4]	-4, R→Q		Liddell et al (1989a)	43
UK 3	1	48	6,365, G→A[4]	-4, R→Q		Green et al (1989)	44
UK 4	1	45	6,365, G→A[4]	-4, R→Q		Green et al (1989)	45
Cambridge	<1	80	6,375, G→C/T[2]	-1, R→S	Abnormal carboxylation; circulates with propeptide	Diuguid et al (1986)	46
London, Ont 1 (HB54)	6		6,379, A→G	2, N→D		Koeberl et al (1990a)	47
UK 12	<1		6,392, Δ1	6	Frameshift, Inhibitor	Green et al (1989)	48
Oxford b2	5	5	6,395, A→C	7, E→A	Gla	Winship & Dragon (1991)	49
Malmö 8	<1	<0.1	6,398-9, Δ2	8	Frameshift	Green et al (1991a)	50
UK 84	14	118	6,400, T→A	9, F→I		Green, Montandon et al	51

Bonn 2	<1	<1	6,402-6, Δ5	9	Frameshift, Inhibitor	Ludwig et al	52
Oxford b3	<1	0.2	6,406, C→T	11, Q→Stop		Winship & Dragon (1991)	53
Hong Kong 1	3	97	6,410, G→C	12, G→A		Chan et al (1990)	54
Mühlheim/Ruhr	4	4	6,416-17, Δ2	14	Frameshift, somatic mosaic?	Ludwig et al	55
Heessen	<1		6,427, T→C	18, C→R		Ludwig et al	56
Zutphen	<1	100	6,427, T→C	18, C→R		Reitsma et al	57
UK 115	<1	19	6,443, G→A	23, C→Y		Green, Montandon, et al	58
Rheidt	2	32	6,449, T→C	25, F→S		Ludwig et al	59
Seattle 3	<1	30	6,454, G→A	27, E→K	Gla	Chen et al (1989b)	60
Chongqing	<1	3	6,455, A→T	27, E→V	Gla	Wang et al (1990b)	61
HB28	<1	<1	6,460, C→T[4]	29, R→Stop		Koeberl et al (1990b)	62
HB61	<1	7	6,460, C→T[4]	29, R→Stop		Koeberl et al (1990b)	63
Malmö 4	<1	<0.1	6,460, C→T[4]	29, R→Stop	Inhibitor	Green et al (1989)	64
UK 14	<1	2	6,460, C→T[4]	29, R→Stop		Montandon et al (1989)	65
UK 24	1		6,460, C→T[4]	29, R→Stop		Green et al (1990)	66
Unnamed	<1	<1	6,460, C→T[4]	29, R→Stop		Ludwig et al	67
UK 69	<1		6,460, C→T[4]	29, R→Stop		Green et al (1991b)	68
UK 55	<1	<1	6,460, C→T[4]	29, R→Stop		Green et al (1991b)	69
Toronto 17 (HB58)	37		6,461, G→A[4]	29, R→Q		Koeberl et al (1990a)	70

HB2	30		6,461, G→A[4]	29, R→Q	Double (see 30,134)	Koeberl et al (1989)	71
Unnamed	20	70	6,461, G→A[4]	29, R→Q	Double (see 30,134)	Chen et al (1991)	72
Malmö 9	<1	<0.1	6,466, Δ1	31	Frameshift	Green et al (1991a)	73
HB9	4		6,474, A→C	33, E→D	Gla	Koeberl et al (1989)	74
UK 10	<1	12	6,484-6, Δ3	37, ΔR	In frame	Green et al (1989)	75
Unnamed	<1		6,488, C→G	38, T→R		Ludwig et al	76
Ursem	1	<1	6,491-4 or 6,492-5, Δ4		Double (see 31,103), Donor splice (b) probably causes disease	Poort et al (1990)	77
Unnamed	<1	<1	6,491-4 or 6,492-5, Δ4		Donor splice (b)	Chen & Thompson	78
UK 83	<1	1	6,491-4 or 6,492-5, Δ4		Donor splice (b)	Green, Montandon et al	79
HB74/77	1	1	6,495, T→C		Donor splice (b)	Bottema et al (1990c)	80
Malmö 10	<1	0.2	6,666-75, Δ10		Acceptor splice (c)	Green et al (1991a)	81
HB7, Japan	<1	<1	6,680-1, Δ2	39	Frameshift, Inhibitor	Matsushita et al (1990)	82
Hoogeveen	14	96	6,690, A→G	43, K→E		Reitsma et al	83
UK 25	<1	<1	6,702, G→A	43, D→N?	Donor splice (c)?	Green, Montandon et al	84
Oxford 2	0.5	0.4	6,704, T→G		Donor splice (c)	Winship (1986)	85
Pirmasens	<1	<1	6,704, T→C		Donor splice (c)	Ludwig et al	86
Toronto 16 (HB53)	3		10,391, G→A		Acceptor splice (d)	Koeberl et al (1990a)	87

Alabama	10	100	10,392, A→G	47, D→G		Davis et al (1987)	88
HB75	14	80	10,393, T→A	47, D→E		Bottema et al (1990c)	89
Oxford d3	1	90	10,393, T→A	47, D→E		Winship & Dragon (1991)	90
Malmö 27	19	108	10,395, G→T	48, G→V		Green et al (1991a)	91
UK 86			10,397-9, Δ3, Ins A	49	Frameshift	Green, Montandon et al	92
New London	<1	114	10,401, A→C	50, Q→P	Decreased XIa activation	Lozier et al (1990)	93
Hollywood	11	58	10,415, C→G	55, P→A		Spitzer et al (1990b)	94
UK 7	10-12	49	10,415, C→G	55, P→A		Green et al (1989)	95
Unnamed	10	<30	10,415, C→G	55, P→A		Chen et al (1991)	96
Malmö 21	12	52	10,415, C→T	55, P→S		Green et al (1991a)	97
Malmö 22	26		10,416, C→T	55, P→L		Green et al (1991a)	98
Basel	<1		10,418, T→C	56, C→R		Alkan et al (1991)	99
Kleve	<1	<1	10,419, G→C	56, C→S		Ludwig et al (1991)	100
Toronto 2 (HB32)	1	2	10,419, G→A	56, C→Y		Koeberl et al (1990a)	101
Durham	14		10,430, G→A[4]	60, G→S		Denton et al (1988)	102
Kingston 3 (HB57)	10	11	10,430, G→A[4]	60, G→S		Koeberl et al (1990a)	103
Lelystad	13	34	10,430, G→A[4]	60, G→S		Poort et al	104
Oud en Nieuw Gastel	12	31	10,430, G→A[4]	60, G→S		Poort et al (1989b)	105

Purmerend	17	22	10,430, G→A[4]	60, G→S		Poort et al	106
UK 27	10		10,430, G→A[4]	60, G→S		Green et al (1990)	107
Unnamed	11	19	10,430, G→A[4]	60, G→S		Chen et al (1989b)	108
Unnamed	17	30	10,430, G→A[4]	60, G→S		Chen et al (1989b)	109
Unnamed	10	18	10,430, G→A[4]	60, G→S		Chen et al (1991)	110
Unnamed	15	54	10,430, G→A[4]	60, G→S		Chen & Thompson	111
Oxford d2	10	28	10,430, G→A[4]	60, G→S		Winship & Dragon (1991)	112
Toronto 6 (HB37)	1	2	10,431, G→A	60, G→D		Koeberl et al (1990a)	113
Oxford d1	3	117	10,442, G→A	64, D→N	ß Hydroxyaspartate	Winship & Dragon (1991)	114
UK 6	8	87	10,443, A→G	64, D→G	β Hydroxyaspartate	Green et al (1989)	115
Trier	<1		10,458, A→G	69, Y→C		Ludwig et al	116
UK 67	6	12	10,479, G→T	76, G→V		Green, Montandon et al	117
UK 19			10,482, T→G	77, F→Y		Green, Montandon et al	118
UK 132			10,507-10, Δ4		Donor splice (d), normal carrier female	Green, Montandon et al	119
Toronto 8 (HB39)	2	3	10,512, A→G		Double (see 30,864), Donor splice (d)	Koeberl et al (1990a)	120
HB6	20		17,660-3, Δ 4		Acceptor splice (e)	Koeberl et al (1989)	121
Toronto 14 (HB48)	3	3	17,667, A→G		Acceptor splice (e)	Koeberl et al (1990a)	122
Malmö 11	<1	<1	17,668, G→C		Acceptor splice (e)	Green et al (1991a)	123

Seattle 2	<1	<1	17,669, Δ1	85	Frameshift	Schach et al (1987)	124
Königswinter	<1		17,678, G→C	88, C→S		Ludwig et al	125
Fukuoka	2	66	17,689, A→C[2]	92, N→H		Suehiro et al (1989a)	126
Edmonton 1	<1		17,700, C→A	95, C→Stop		Tam et al	127
Hamilton 1 (HB45)	<1		17,710, T→C	99, C→R		Koeberl et al (1990a)	128
UK 50	<1	<1	17,727, Ins TT	105	Frameshift	Green, Montandon et al	129
Malmö 35	21	14	17,736, G→A	107, None	cryptic splice?	Green et al (1991a)	130
Malmö 42	20	24	17,736, G→A	107, None	cryptic splice?	Green et al (1991a)	131
Malmö 37	15	24	17,736, G→A	107, None	cryptic splice?	Green et al (1991a)	132
Unnamed	20	120	17,738, T→C	107, V→A		Chen et al (1991)	133
Leamington	13		17,756, G→C	114, G→A		Ritchie et al (1989)	134
Oxford e1	5	4	17,756, G→C	114, G→A		Winship & Dragon (1991)	135
Nastetten	<1		17,759, A→G	115, Y→C		Ludwig et al	136
Malmö 7	<1	<0.1	17,761, C→T[4]	116, R→Stop	Double (see 30,890)	Montandon et al (1990a)	137
UK 28	5	5	17,761, C→A	116, None	cryptic splice?	Green, Montandon et al	138
Würzburg	<1		17,764, Ins C	117	Frameshift	Ludwig et al	139
UK 9	<1	0.4	17,773, A→T	120, N→Y		Green et al (1989)	140
Nörtingen	<1		17,798, G→T		Donor splice (e)	Ludwig et al	141
Toronto 13 (HB44)	10		17,810, A→G		Donor splice (e)	Koeberl et al (1990a)	142

Toronto 15 (HB52)	10		17,810, A→G		Donor splice (e)	Koeberl et al (1990a)	143
UK 63			17,810, A→G		Donor splice (e)	Green, Montandon et al	144
Dakar	<1	<1	20,374, T→C	132, C→R		Vidaud (1990)	145
Malmö 12	<1	<0.1	20,375, G→T	132, C→F		Green et al (1991a)	146
Malmö 44			20,398, Δ1	140	Frameshift	Green et al (1991a)	147
Albuquerque	1	30	20,413, C→T[4]	145, R→C	Decreased XIa activation	Toomey et al (1988)	148
Cardiff 1	<1	66	20,413, C→T[4]	145, R→C		Liddell et al (1989b)	149
UK 21	1		20,413, C→T[4]	145, R→C		Green et al (1990)	150
UK 23	2	43	20,413, C→T[4]	145, R→C		Green et al (1990)	151
Oxford f1	3	54	20,413, C→T[4]	145, R→C		Winship & Dragon (1991)	152
Chapel Hill	8	100	20,414, G→A[4]	145, R→H	Decreased XIa activation	Noyes et al (1983)	153
Chicago 2	7	160	20,414, G→A[4]	145, R→H	Decreased XIa activation	Diuguid et al (1989)	154
HB25	4		20,414, G→A[4]	145, R→H	Decreased XIa activation	Koeberl et al (1989)	155
Malmö 17	4-11	91	20,414, G→A[4]	145, R→H		Green et al (1990)	156
Malmö 23	7	148	20,414, G→A[4]	145, R→H		Green et al (1991a)	157
Malmö 32	5-8	115	20,414, G→A[4]	145, R→H		Green et al (1991a)	158
Malmö 36	7	110	20,414, G→A[4]	145, R→H		Green et al (1991a)	159
Malmö 38			20,414, G→A[4]	145, R→H		Green et al (1991a)	160
Nagoya-3	<1	60	20,414, G→A[4]	145, R→H		Hamaguchi et al (1990) Suehiro et al (1990)	161

HB76	6	100	20,414, G→A[4]	145, R→H		Bottema et al (1990c)	162
HB23	<1		20,466-78, Δ13	162	Frameshift	Koeberl et al (1989)	163
HB17	<1		20,497, C→T	173, Q→Stop		Koeberl et al (1989)	164
HB78	2	<1	20,501, Δ1	174	Frameshift	Bottema et al (1990c)	165
Malmö 13	<1	0.5	20,510, Δ1	177	Frameshift	Green et al (1991a)	166
Brest	<1	85	20,512, T→C	178, F→L	Double (see 20,518), N?	Vidaud	167
BM Nagoya	<1	100	20,518, C→T[2,4]	180, R→W	B_m	Suehiro et al (1989b)	168
Deventer	<1	130	20,518, C→T[4]	180, R→W	B_m	Bertina et al (1990)	169
Dernbach	<1	69	20,518, C→T[4]	180, R→W		Ludwig et al	170
Idaho	<1		20,518, C→T[4]	180, R→W		Demers et al (1990)	171
New York 2	<1	74	20,518, C→T[4]	180, R→W	B_m	Driscoll et al (1989b)	172
Dominican Rep.	<1	95	20,518, C→T[4]	180, R→W	B_m	Driscoll et al (1989b)	173
Brest	<1	85	20,518, C→G	180, R→G	Double (see 20,512)	Vidaud	167
Madrid	<1	90	20,518, C→G	180, R→G	B_m	Solera et al (1991)	174
Hilo	<1	120	20,519, G→A[4]	180, R→Q	B_m, decreased XIa activation	Huang et al (1989) Monroe et al (1989)	175
Hilo, Fr	<1	120	20,519, G→A[4]	180, R→Q	B_m[6]	Vidaud (1990)	176
Novara	<1	112	20,519, G→A[4]	180, R→Q	B_m	Bertina et al (1990)	177
Rheine 2	<1		20,519, G→A[4]	180, R→Q		Ludwig et al	178
Altenhunden	<1		20,519, G→A[4]	180, R→Q		Ludwig et al	179

HB79	3	100	20,519, G→A[4]	180, R→Q		Bottema et al (1990c)	180
Milano	<1	130	20,521, G→T	181, V→F	B_m	Bertina et al (1990)	181
Cardiff 2	15	132	20,524, G→C	182, V→L	B_m[6]	Taylor et al (1990)	182
Kashihara	<1	120	20,524, G→T	182, V→F	B_m[6]	Sakai et al (1989)	183
UK 54	<1	97	20,527-9, Δ3	183, ΔG	In frame	Green, Montandon et al	184
Bottrop 1	<1	92	20,531-3, Δ3	184, ΔG	In frame	Ludwig et al	185
HB5 Japan	<1	<1	20,551, C→T	191, Q→Stop	Inhibitor, Double (see -793)	Matsushita et al (1990)	1
Unnamed	<1	<1	20,552, A→T	191, Q→L		Chen et al (1991)	186
Malmö 5	<1	<0.1	20,561, G→A	194, W→Stop	Inhibitor	Green et al (1989)	187
UK 114			20,561, G→A	194, W→Stop	Normal carrier female	Green, Montandon et al	188
Unnamed	<1	<1	20,564, A→G	195, Q→R		Ludwig et al	189
Oxford 1	<0.5	0.3	20,566, G→T		Donor splice (f)	Rees et al (1985)	190
Rotenburg	<1	<1	20,566, G→A		Donor splice (f)	Ludwig et al	191
Toronto 19	<1	<1	30,070, G→C	206, C→S		Taylor et al (1990)	192
UK 43	<1		30,072, G→A	207, G→R		Green, Montandon et al	193
UK 37		1	30,076, G→A	208, G→D		Green, Montandon et al	194
Wültschkau	7		30,084, G→T	211, V→F		Ludwig et al	195
Unnamed	4		30,084, G→T	211, V→F		Chen et al (1991)	196
Bottrop 2	<1	<1	30,090, G→T	213, E→Stop		Ludwig et al	197

HB72	4	<1	30,096, T→C	215, W→R		Bottema et al (1990c)	198
Unnamed	<1	0.1	30,097, G→A	215, W→Stop		Chen et al (1991)	199
Unnamed	4		30,100, T→C	216, I→T		Chen et al (1991)	200
HB41	7		30,100, T→C	216, I→T		Koeberl et al (1990a)	201
Malmö 39	4	4	30,100, T→C	216, I→T		Green et al (1991a)	202
Toronto 5 (HB36)	<1	3	30,112, C→T	220, A→V		Koeberl et al (1990a)	203
Toronto 11 (HB49)	4		30,112, C→T	220, A→V		Koeberl et al (1990a)	204
HB24	1		30,119, T→G	222, C→W		Koeberl et al (1989)	205
HB2	30		30,134, T→C	None	Double (see 6,461), N	Koeberl et al (1989)	71
Unnamed	20	70	30,134, T→C	None	Double (see 6,461), N	Chen et al (1991)	72
HB1	12		30,150, G→A[4]	233, A→T		Koeberl et al (1989)	206
Malmö 28	22		30,150, G→A[4]	233, A→T		Green et al (1991a)	207
Malmö 29	5-22	12	30,150, G→A[4]	233, A→T		Green et al (1991a)	208
Malmö 30	8-15		30,150, G→A[4]	233, A→T		Green et al (1991a)	209
Malmö 31	11	15	30,150, G→A[4]	233, A→T		Green et al (1991a)	210
Opladen	10	13	30,150, G→A[4]	233, A→T		Ludwig et al	211
Edmonton 3	15		30,150, G→A[4]	233, A→T		Tam et al	212
Unnamed	10	11	30,150, G→A[4]	233, A→T		Chen et al (1991)	213
Unnamed	15	15	30,150, G→A[4]	233, A→T		Chen et al (1991)	214

Iceland 1	3	119	30,800, Ins A	None	Double (see 31,119), N	Green et al (1991b)	215
HB6, Japan	<1	<1	30,821, G→A		Inhibitor, Acceptor splice (h)	Matsushita et al (1990)	216
Unnamed	<1	<1	30,821, G→A		Acceptor splice (h)	Chen et al (1991)	217
Spijkenisse	2	74	30,854, G→A	245, E→K		Reitsma et al	218
Monschau	3	39	30,855, A→T	245, E→V		Ludwig et al	219
HB60	<1	<1	30,863, C→T[4]	248, R→Stop		Koeberl et al (1990a)	220
Malmö 3	<1	<0.1	30,863, C→T[4]	248, R→Stop	Inhibitor	Green et al (1989)	221
Malmö 14	<1	<0.1	30,863, C→T[4]	248, R→Stop		Green et al (1991a)	222
Malmö 15	<1	<0.1	30,863, C→T[4]	248, R→Stop		Green et al (1991a)	223
UK 26	<1	4	30,863, C→T[4]	248, R→Stop		Green et al (1990)	224
UK 47	<1		30,863, C→T[4]	248, R→Stop		Green et al (1991b)	225
Unnamed	<1	<1	30,863, C→T[4]	248, R→Stop		Wang et al (1990a)	226
Las Cruces	<1	<1	30,863, C→T[4]	248, R→Stop		Tarnower & Smith	227
Artesia	<1	<1	30,863, C→T[4]	248, R→Stop		Tarnower & Smith	228
Unnamed	<1	<1	30,863, C→T[4]	248, R→Stop		Ludwig et al	229
Seattle 4	3-4	3-4	30,864, G→A[4]	248, R→Q		Chen et al (1989b) Chen et al (1991)	230
Toronto 8 (HB39)	2	3	30,864, G→A[4]	248, R→Q	Double (see 10,512)	Koeberl et al (1990a)	120
Unnamed	1	1	30,864, G→A[4]	248, R→Q		Chen et al (1991)	231

Unnamed	4	4	30,864, G→A[4]	248, R→Q		Chen et al (1991)	232
Dreihacken	8		30,864, G→A[4]	248, R→Q		Ludwig et al	233
Leiria	<1	<1	30,875, C→T[4]	252, R→Stop		Siguret et al (1988)	234
Malmö 41	<1	6	30,875, C→T[4]	252, R→Stop		Green et al (1991a)	235
Portland	<1	<1	30,875, C→T[4]	252, R→Stop		Chen et al (1989a)	236
Toronto 18	3		30,875, C→T[4]	252, R→Stop		Taylor (1990)	237
Calgary 1	<1	<1	30,875, C→T[4]	252, R→Stop		Poon et al (1987)	238
Hong Kong 8	<1	<10	30,875, C→T[4]	252, R→Stop		Chan et al	239
UK 120	<1		30,875, C→T[4]	252, R→Stop		Green et al (1991b)	240
UK 16	13		30,876, G→T	252, R→L		Green, Montandon et al	241
Malmö 7	<1	<0.1	30,890, C→T	257, H→Y	Double (see 17,761), N	Montandon et al (1990a)	137
HB8	24		30,900, A→G	260, N→S		Koeberl et al (1989)	242
UK 88	7		30,924, A→G	268, H→R		Green, Montandon et al	243
UK 15	2	2	30,929, A→T	270, I→F		Green, Montandon et al	244
Beuren	<1	<1	30,930, T→C	270, I→T		Ludwig et al	245
Toronto 1 (HB31)	1	4	30,933, C→T	271, A→V		Koeberl et al (1990a)	246
UK 48			30,942, Δ1	274	Frameshift, normal carrier female	Green, Montandon et al	247
San Antonio	<1	14	30,945, T→C	275, L→P		Jagadeeswaran	248
Malmö 1	<1	<0.1	30,950-7, Δ 8	277	Frameshift, Inhibitor	Green et al (1989)	249

Zoeterwoude	13	13	30,956, T→A	279, L→I	Reitsma et al	250
Unnamed	<1	<1	30,981, C→T	287, P→L	Chen et al (1991)	251
Oxford h2	2	3	30,992, G→C	291, A→P	Winship & Dragon (1991)	252
UK 13	4-16		30,992, G→A	291, A→T	Montandon et al (1989)	253
UK 33	7	19	30,992, G→A	291, A→T	Green et al (1991b)	254
UK 41	9	11	30,992, G→A	291, A→T	Green et al (1991b)	255
Beberbeck	4	7	31,008, C→T[4]	296, T→M	Ludwig et al	256
B.Liebenzell	6	7	31,008, C→T[4]	296, T→M	Ludwig et al	257
HB19	<1		31,008, C→T[4]	296, T→M	Koeberl et al (1989)	258
Malmö 25	4	15	31,008, C→T[4]	296, T→M	Green et al (1990)	259
Neuhausen	4	9	31,008, C→T[4]	296, T→M	Ludwig et al	260
UK 32	6	5	31,008, C→T[4]	296, T→M	Green et al (1990)	261
Unnamed	2	6	31,008, C→T[4]	296, T→M	Chen et al (1991)	262
Unnamed	-	6	31,008, C→T[4]	296, T→M	Chen et al (1991)	263
Unnamed	4	10	31,008, C→T[4]	296, T→M	Chen et al (1991)	264
Unnamed	5	11	31,008, C→T[4]	296, T→M	Chen et al (1991)	265
Farmington	2	6	31,008, C→T[4]	296, T→M	Tarnower & Smith	266
HB70	1	23	31,008, C→T[4]	296, T→M	Ketterling et al (1991)	267
HB84	6	7	31,008, C→T[4]	296, T→M	Ketterling et al (1991)	268

HB85	5	7	31,008, C→T[4]	296, T→M		Ketterling et al (1991)	269
HB89	5	7	31,008, C→T[4]	296, T→M		Ketterling et al (1991)	270
Greensboro	9	8	31,008, C→T[4]	296, T→M		Rose and High	271
UK 49			31,008, C→T[4]	296, T→M		Green et al (1991b)	272
Glostrup h1			31,008, C→T[4]	296, T→M		Winship & Dragon (1991)	273
UK 73	5	10	31,008, C→T[4]	296, T→M		Green et al (1991b)	274
Malmö 18	<1	0.3	31,035, G→A	305, G→D		Green et al (1991a)	275
HB27	18	46	31,041, T→C	307, V→A		Bottema et al (1989a)	276
Unnamed	15	40	31,041, T→C	307, V→A		Chen et al (1991)	277
Malmö 26	3	4	31,041, T→G	307, V→G		Green et al (1991a)	278
UK 122	5		31,044, G→A	308, S→N		Green, Montandon et al	279
Emsdetten	<1		31,045, T→G	308, S→R		Ludwig et al	280
Oxford h3	<1	65	31,046, G→A	309, G→S		Winship & Dragon (1991)	281
Unnamed	<1	58	31,047, G→T	309, G→V		Thompson et al (1989)	282
Toronto 21	<1	86	31,049, T→C	310, W→R		Picketts et al	283
Unnamed	<1	<1	31,051, G→A	310, W→Stop		Wang et al (1990a)	284
Albuquerque 2	<1	<1	31,051, G→A	310, W→Stop		Tarnower & Smith	285
HB26	3		31,052, G→A	311, G→R		Koeberl et al (1989)	286
Amagasaki	<1	100	31,053, G→A	311, G→E	B_m[6]	Sakai et al (1990)	287

UK 137	<1	100	31,059, T→G	313, V→G		Green, Montandon et al	288
UK 11	<1	<2	31,059-60, Δ2	313	Frameshift	Green et al (1989)	289
Goldbach	<1		31,070, G→C	317, G→R		Ludwig et al	290
Toronto 7 (HB38)	<1	90	31,080, C→A	320, A→D		Koeberl et al (1990a)	291
Riegelsberg	<1	<1	31,084-90, Δ7	321	Frameshift, Double (see 37)	Ludwig et al	14
Oxford h5	4	4	31,103, G→T	328, V→F		Winship (1990)	292
Ursem	1	<1	31,103, G→A	328, V→I	Double (see 6,491-4), N	Poort et al (1990)	77
UK 90	7		31,110, T→C	330, L→P		Green, Montandon et al	293
Ratingen 2	<1	<1	31,110-12, $\Delta 3^{9}$	331, ΔV	In frame	Ludwig et al	294
Oxford h1	7	96	31,113, T→C	331, V→A		Winship & Dragon (1991)	295
Brünov	4		31,115, G→T	332, D→Y		Ludwig et al	296
HB29	<1	<1	31,118, C→T^{4}	333, R→Stop		Koeberl et al (1990b)	297
HB30	<1	1	31,118, C→T^{4}	333, R→Stop		Koeberl et al (1990b)	298
UK 34	6		31,118, C→T^{4}	333, R→Stop	Female	Montandon et al (1990b)	299
Unnamed	<1	1	31,118, C→T^{4}	333, R→Stop		Chen et al (1991)	300
Unnamed	<1	<1	31,118, C→T^{4}	333, R→Stop		Ludwig et al	301
Unnamed	<1	<1	31,118, C→T^{4}	333, R→Stop		Ludwig et al	302
Unnamed	<1	<1	31,118, C→T^{4}	333, R→Stop		Ludwig et al	303
HB83	13	70	31,118, C→G	333, R→G		Bottema et al (1990c)	304

UK 2	<1	135	31,119, G→A[4]	333, R→Q		Tsang et al (1988)	305
Heerde	1	122	31,119, G→A[4]	333, R→Q		Poort et al (1989a)	306
Iceland 1	3	119	31,119, G→A[4]	333, R→Q	Double (see 30,800)	Green et al (1991b)	215
UK 5	1-2	75	31,119, G→A[4]	333, R→Q		Green et al (1989)	307
UK 18	1	130	31,119, G→A[4]	333, R→Q		Green et al (1990)	308
Unnamed	2	32	31,119, G→A[4]	333, R→Q		Wang et al (1990a)	309
Toronto 22	<1	87	31,119, G→A[4]	333, R→Q		Picketts et al	310
Unnamed	2	38	31,119, G→A[4]	333, R→Q		Chen et al (1991)	311
Köln	2	60	31,119, G→A[4]	333, R→Q		Ludwig et al	312
Düsseldorf	4	86	31,119, G→A[4]	333, R→Q		Ludwig et al	313
Fellhammer	2	88	31,119, G→A[4]	333, R→Q		Ludwig et al	314
Bor	4	93	31,119, G→A[4]	333, R→Q		Ludwig et al	315
Hong Kong 6	9	100	31,122, C→A	334, A→D		Chan et al (1990)	316
UK 8	2	2	31,127, T→C	336, C→R		Green et al (1989)	317
Unnamed	<1	5	31,127, T→C	336, C→R		Chen et al (1991)	318
Malmö 24	<1	<1	31,128, G→A	336, C→Y		Green et al (1991a)	319
Bonn 1	<1	<1	31,133, C→T[4]	338, R→Stop		Ludwig et al (1989)	320
New York (?)	<1	<1	31,133, C→T[4]	338, R→Stop		Driscoll et al (1989a)	321
UK 20	2	<1	31,133, C→T[4]	338, R→Stop		Green et al (1990)	322

UK 31	<1		31,133, C→T[4]	338, R→Stop		Green et al (1990)	323
Unnamed	<1	<1	31,133, C→T[4]	338, R→Stop		Freedenberg et al (1989)	324
Edmonton 2	<1	<1	31,133, C→T[4]	338, R→Stop		Tam et al	325
Calgary 2	<1	<1	31,133, C→T[4]	338, R→Stop		Poon et al (1987)	326
Samli	<1	<1	31,149-51, Δ3 31,158-62, Δ5 31,158, Ins G	343	Frameshift	Ludwig et al	327
Gladbeck	4	87	31,151, A→T	344, I→F		Ludwig et al	328
Unnamed	<1	<1	31,157, 8 or 9 Ins AA	346	Frameshift	Chen & Thompson	329
Unnamed	3	103	31,163, A→G	348, M→V		Chen et al (1991)	330
Offenbach	<1		31,166 or 7, Δ1	349	Frameshift	Ludwig et al	331
Kingston 4	35	45	31,170, G→C	350, C→S	Somatic mosaic	Taylor et al (1991)	332
UK 17	<1	<1	31,170, G→A	350, C→Y		Green, Montandon et al	333
Unnamed	2	130	31,200, C→T	360, S→L		Chen et al (1991)	334
Eagle Rock	1-5	100	31,209, G→T	363, G→V		Bajaj et al (1990)	335
UK 35	2	53	31,209, G→A	363, G→E		Green, Montandon et al	336
Mechtal	<1	100	31,211, G→C	364, D→H		Ludwig et al	337
HB80	2	95	31,211, G→C	364, D→H		Bottema et al (1990c)	338
UK 30	2		31,211, G→A	364, D→N	B_m	Green, Montandon et al	339
Unnamed	<1	130	31,212, A→T	364, D→V		Chen et al (1991)	340

Varel	<1	89	31,213-14, TA→CG	365, S→G	Active site, Inhibitor, silent mutation at aa364	Ludwig et al (1988)	341
Schmallenberg	<1		31,215, G→T	365, S→I	Active site	Ludwig et al	342
Toronto 4 (HB35)	1	90	31,216, T→A	365, S→R	Active site	Koeberl et al (1990a)	343
Unnamed	<1	14	31,220, G→A	367, G→R		Chen et al (1991)	344
Bergamo	<1	156	31,223, C→A	368, P→T	B_m	Bertina et al (1990)	345
HB73	<1	<1	31,227, A→G	369, H→R		Bottema et al (1990c)	346
Malmö 16	15	13	31,248, C→A	376, T→N		Green et al (1991a)	347
Unnamed	<1	<1	31,253, T→C	378, F→L		Chen et al (1991)	348
Brantford	5		31,258, A→C	379, L→F		Tam et al	349
Hong Kong 5	7	<10	31,260, C→G	380, T→S		Chan et al (1990)	350
UK 76	<1	1	31,260, C→T	380, T→I		Green, Montandon et al	351
Hong Kong 4	<1	<10	31,261, Δ1	380	Frameshift	Chan et al (1990)	352
Mainz	<1	<1	31,287, G→A	389, C→Y		Ludwig et al	353
UK 42	4	7	31,287, G→A	389, C→Y		Green, Montandon et al	354
Lake Elsinore	<1	100	31,290, C→T	390, A→V	B_m	Spitzer et al (1988)	355
Niigata	1-4	140	31,290, C→T	390, A→V	B_m	Sugimoto et al (1988)	356
Albuquerque 3	2	48	31,290, C→T	390, A→V		Tarnower & Smith	357
Unnamed	2	30	31,290, C→A	390, A→E		Wang et al (1990a) Chen et al (1991)	358

Angers	<1	90	31,307, G→A	396, G→R	B_m^6	Attree et al (1989)	359
Angers	<1	110	31,307, G→A	396, G→R	B_m^6	Vidaud et al (1988)	360
UK 29	<1		31,307-20, Δ14	396	Frameshift	Green, Montandon et al	361
HB11,12,14, 16,18	<1-6		31,311, T→C	397, I→T		Koeberl et al (1989)	362
Long Beach	<1	100	31,311, T→C	397, I→T		Ware et al (1988)	363
Los Angeles	<1	100	31,311, T→C	397, I→T		Spitzer et al (1990a)	364
Toronto 3 (HB34)	2	55	31,311, T→C	397, I→T		Bottema et al (1990b)	365
Toronto 9 (HB40)	2	65	31,311, T→C	397, I→T		Bottema et al (1990b)	366
Toronto 10 (HB46)	1	73	31,311, T→C	397, I→T		Bottema et al (1990b)	367
Toronto 12 (HB50)	4	61	31,311, T→C	397, I→T		Bottema et al (1990b)	368
Vancouver	3	62	31,311, T→C	397, I→T		Geddes et al (1989)	369
Vancouver, Fr	2	62	31,311, T→C	397, I→T	B_m^6	Attree et al (1989)	370
Vancouver, Fr	3	70	31,311, T→C	397, I→T	B_m^6	Attree et al (1989)	371
Vancouver, Fr	4	52	31,311, T→C	397, I→T	B_m^6	Attree et al (1989)	372
Unnamed	1	45	31,311, T→C	397, I→T		Thompson et al (1990)	373
Unnamed	3	64	31,311, T→C	397, I→T		Thompson et al (1990)	374
Unnamed	2	75	31,311, T→C	397, I→T		Thompson et al (1990)	375
Unnamed	5	96	31,311, T→C	397, I→T		Thompson et al (1990)	376
Unnamed	4	56	31,311, T→C	397, I→T		Chen et al (1991)	377

Unnamed	4	88	31,311, T→C	397, I→T		Chen et al (1991)	378
HB67	<1		31,311, T→C	397, I→T		Bottema et al (1990b)	379
HB69	3	54	31,311, T→C	397, I→T		Bottema et al (1990b)	380
HB43	8		31,326, C→T	402, S→F		Koeberl et al (1990)	381
Lincoln Park	3	9	31,327-8, Δ2 Ins AAGGTACCAA	402	Frameshift	Rao et al (1990)	382
Unnamed	4		31,331, T→C	404, Y→H		Ludwig et al	383
HB20	1		31,340, T→C	407, W→R		Koeberl et al (1989)	384
UK 53	<1	<1	31,342, G→A	407, W→Stop		Green, Montandon et al	385
Oxford h4	<1	0.2	31,344 or 5, Δ1	408	Frameshift	Winship & Dragon (1991)	386
HB62	<1		31,346, Ins GATT	408	Frameshift	Bottema et al (1989b)	387
Bordeaux	<1	<1	31,352, A→T	411, K→Stop		Attree et al (1989)	388

Footnotes:

1 For nucleotide numbering see Yoshitake et al (1985); for amino acid numbering Anson et al (1984).
2 Nucleotide change predicted from amino acid sequence.
3 The following comments or abbreviations are used:
  (i) Inhibitor - patients developing anti-factor IX antibodies in response to therapeutic factor IX.
  (ii) Frameshift - caused by the addition (symbol Ins) or deletion (symbol Δ) affecting nucleotides corresponding to the stated amino acid number and terminating at a new stop codon shortly after.
  (iii) Double - a double mutant, entered twice in the data base and cross-referenced.
  (iv) N - indicates the mutation, usually a double mutant, is probably a normal variant - not causing the disease.
  (v) the exon (a-h) immediately adjacent to donor or acceptor splice sites is noted.
  (vi) Gla refers to glutamic acid residues normally γ-carboxylated, and β-hydroxyaspartate to the single modified aspartate residue.
  (vii) B_m - patients with a prolonged bovine prothrombin time (Hougie & Twomey, 1967).
4 Indicates mutation of a CG to either TG or CA.
5 % varies with age, rising after puberty.
6 Bovine prothrombin time is moderately prolonged.
7 Patients are uniquely named, except for 'Vancouver,Fr' and 'Angers', where the authors have not distinguished different patients with the same mutation.
8 The position of insertions (Ins) corresponds to the first nucleotide of the inserted base. E.g. In Recklinghausen, 114, Ins AT, patient identity number = XX, the inserted dinucleotide AT occupies nucleotides 114 and 115 and displaces the residues normally found there, which now become residues 116 and 117.
9 Or, 31,111-3, or 31,112-4, or 31,113-5.
10 The PIN number is a patient identification number, introduced here as an aid to patient identification now and in the future. The PIN number is not intended to replace any existing nomenclature; rather, it will co-exist with it. Once a patient (and patients within the same pedigree) is given a PIN number, this will remain unaltered in updated, or new versions of this database.