Haemophilia B: database of point mutations and short additions and deletions, fifth edition, 1994

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ABSTRACT

The fifth edition of the haemophilia B database lists in easily accessible form all known factor IX mutations due to small changes (base substitutions and short additions and/or deletions of <30bp) identified in haemophilia B patients. The 1,142 patient entries are ordered by the nucleotide number of their mutation. Where known, details are given on: factor IX activity, factor IX antigen in circulation, and origin of mutation. References to published mutations are given and the laboratories generating the data are indicated.

The data base below lists known point mutations and short deletions and additions in the factor IX gene, causing the bleeding disorder haemophilia B or Christmas disease (for reviews, see Roberts, 1993; Tuddenham & Giannelli, 1994)) These mutations result in a defective clotting factor IX — a glycoprotein of 415 amino acid residues normally present in plasma and an essential component of the clotting cascade. The disease is an X-linked inherited 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.*, 1993) 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 It is not intended to replace primary publications although it does contain a significant amount of unpublished work. We have continued our database numbering system (Giannelli *et al.* (1991) giving all patients a unique Patient Identity Number (PIN or ID number). As in previous years, we have included *repeat* observations of the same mutation, as well as molecularly *unique* mutations, but in order to keep the main table to a manageable size we have deleted from the table all the repeats of molecular events. Such events are entered in the table only once but the FIX:C and FIX:Ag entries show the average of the factor IX values associated with these mutations.

The comments relevant to each group of mutations are summarised and a full list of references and PIN numbers is given. The central coordinators will keep the data relative to the excluded mutations in a separate file that will be available on request.

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.*, 1991). (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, and VIIa plus tissue factor, cleave 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. Processing steps occur in the hepatocyte prior to secretion and

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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 an O-linked carbohydrate at least at serine 53 and 61 (Hase *et al.*, 1988; Nishimura *et al.*, 1992).

There are 1,142 patient entries in this fifth edition of the database compared with 807 patients last year (Giannelli *et al.*, 1993). Besides point mutants, it includes 97 short (defined as less than 30 nucleotides) deletions or additions or both, made up from 72 deletions, 20 additions and 5 examples involving both additions and deletions. There are also 16 double mutations, 1 triple mutation, 13 inhibitor patients, 2 somatic mosaics and 18 females (either affected or nonsymptomatic carriers). The list excludes the 29 patients with partial or complete gene deletions or more complex rearrangements (Thompson, 1990) and others observed since (Ketterling *et al.*, 1994; Saad *et al.*, 1994). Of the 1,142 patients studied, 476 show unique molecular events probably causing the disease, while the remainder are repeats. As is well known, many of these repeats occur at CG doublets and involve a CG→TG or CA change. As discussed before (Giannelli *et al.*, 1991), such mutants are believed to be genuine 'hotspots' for mutation. However it is now becoming clear that the high number of repeat observations at some CG doublets (*e.g.* 63 examples at 31,008) are caused, at least in part, by a founder effect. A founder effect is now well established (Thompson *et al.*, 1990; Bottema *et al.*, 1990b) for a mutation at a residue other than CGs (*e.g.* 31 examples at nucleotide 31,311) and there are many examples in the database of mutations repeating 2, 3 or occasionally 4 times. Probably many but not all of these will have a common origin.

We have continued to include information in the comments section, on new (or de novo) mutations where known. In addition, we note whether the mutation occurred in the mother or in the maternal grandfather or grandmother. Two coordinators have also included the age of the parent of the child carrying, or affected by, the mutant gene. Because not all coordinators list new mutations, and such data is incomplete, this database cannot be usefully analysed for the frequency of such new mutations.

The distribution of mutants according to protein domains and control regions within the gene shows that mutations have been detected in all regions except the poly(A) site. Remarkably, there are now 14 molecularly unique mutants occurring within a short region of the promoter, and these are invaluable in studying gene regulation (Crossley *et al.*, 1992; Picketts *et al.*, 1993; Reijnen *et al.*, 1993). Missense mutations within exons give valuable information as to the importance of particular amino acid residues. The present list contains 291 different amino acid substitutions (probably detrimental). Seventy-eight residues of factor IX show two or more amino acid substitutions. These include the active site serine (amino acid 365), and the proposed active site aspartate (amino acid 269), but none is yet known for the proposed active site histidine at amino acid 221. Mutations at 9 of the 12 γ carboxylglutamyl residues have now been detected, confirming their critical role for the function of factor IX. Amino acid substitutions have also been found at 21 of the 22 cysteines of circulating factor IX and therefore mutations have been found that compromise each one of the disulphide bridges of the mature protein, thus confirming the importance of such structures. This year 222 missense mutations were added, of which 55 are new.

The third (1992) edition of this data base (Giannelli *et al.* 1992) is now available from the EMBL file server. It can be obtained by sending the command GET HAEMB.DAT to NETSERV@EMBL-HEIDELBERG.DE (Internet address). A documentation file introducing the format used, which differs from this present data base because of restrictions imposed in transmitting data by electronic mail, is obtained by sending GET HAEMB.DOC to the same address. The format used in the 1991 File Server version of the data base is somewhat related to that used for the familiar EMBL nucleic acid sequence data base and should allow easy computer searching for particular features. The new entries in this 1993 edition of the data base will be available by the end of 1994, while this year's will be reformatted and transferred to the EMBL file server during 1994/5.

The data base was compiled by the central coordinators (Giannelli and Green) from separate lists updating the previous year's list prepared by coordinators for the different countries. This year these were as follows: Giannelli and Green representing the UK, Sweden and Iceland; Sommer representing USA; Lillicrap representing Canada; Ludwig and Schwaab representing Germany; Reitsma representing The Netherlands; Goossens representing France; and Brownlee, the rest of the world. New data or notification of errors or omissions should be sent to the individual country coordinators. This database, including all repeated mutations, is available from individual country coordinators on floppy discs written in Wordperfect 5.1 on an IBM PS2 computer.

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Table 1. 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
Brandenburg	<1	<1	-26, G→C	None	Promoter, L-F-A1/HNF4- binding site, ARE	Ludwig et al	395
Unnamed	<1→10	<1→10	-21, T→G	None	Promoter, HNF4	Crossley et al (1992)	812
(footnote 11)	<1→60 ⁵	<1→60	-20, T→A	None	Promoter, L-F-A1/HNF4- binding site	Reijnen et al (1993)	2 cases: Refs(93,121) PINs(2,3)
Marseille	7→20 ⁵		-20, T→C	None	Promoter, de novo in MGF	Ghanem et al (1993)	396
(footnote 11)	13→70 ⁵		-6, G→A ⁴	None	Promoter	10 cases: Refs(16,29,48,64,104,113,129 140,148) PINs(4,5,577-8,813-8)	
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
(footnote 11)	7		-5, A→G	None	Promoter	2 cases: Ref(129) PINs(579-80)	
Bangkok	5		6, 7 or 8, Δ1	None	Promoter	Hall et al (1992)	581
(footnote 11)	<1→37 ⁵		6, T→A	None	Promoter	2 cases: Refs(45,102) PINs(397,819)	
Leyden, NZ	1→32 ⁵		8, T→C	None	Promoter, C/EBP binding site, de novo in mother	Royle et al (1990)	8
(footnote 11)	<1→60 ⁵	<1→60 ⁵	13, A→G	None	Promoter	6 cases: Refs(26-7,48,75,122,130) PINs(9-11,398,820-1)	
Leyden 3	<1→60 ⁵	<1→60 ⁵	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 (1992a)	14
Calgary 4	<1	<1	48, A→T	-40, I→F	Double (see 31,133), N	Poon & Sinclair	399
B61	<1	<1	48, A→T	-40, I→F	N? only change found	Deutz-Terlouw et al	822
YungLing	<6	<1	58, Δ1	-37	Frameshift	Lin et al	823
UK 22	2	<1	79, T→A	-30, I→N	Signal peptide	Green et al (1993)	15
(footnote 11)	<1		89, Δ1	-27	Frameshift	2 cases: Refs(81,172) PINs(582,824)	
HB130	20		111, T→C	-19, C→R	Signal peptide	Bottema et al (1991b)	400
UK 36		<1	111-120, Δ10	-19	Frameshift, Donor splice (a)	Saad et al (1994)	16
Meaux	<1		112, Δ1	-19	Frameshift	Ghanem et al (1993)	401
DK 27	<5	<10	113, T→G	-19, C→W	Signal peptide	Nielsen et al	825
Recklinghausen	<1	<1	114, Ins AT	-18	Frameshift	Ludwig et al	17
UK 277	1		116, A→G	-18, none	Donor splice (a)?	Saad et al (1994)	826
HB64	<1	2	117, G→A	-17, V→I	Donor splice (a)?	Bottema et al (1991a)	402
UK 245	<1		117, G→C	-17, V→L	Donor splice (a)?	Saad, Rowley et al	827
(footnote 11)	2		118, G→T		Donor splice (a)	2 cases: Refs(129-30) PINs(828-9)	
Malmö 33	3	2	122, G→A		Donor splice (a), de novo in MGF	Green et al (1991b)	18
HB135			6,320, T→G		Acceptor splice (b)	Bottema et al (1991b)	403
UK 70	<1		6,325, G→A		Acceptor splice (b)	Saad et al (1994)	404
Spain	<1		6,325, G→T		Acceptor splice (b)	Ghanem et al (1993)	405
Nice	<1		6,325,Δ2,Ins A		Acceptor splice (b)	Costes et al	830
(footnote 11)	2	32	6,364, C→T ⁴	-4, R→W		17 cases: Refs(14,48,52-4,74,86, 123,129) PINs(19-28,406-8,583-5,831)	
(footnote 11)	<1	43	6,365, G→T	-4, R→L		8 cases: Refs(48,74,76,176) PINs(29-32,409-10,832-3)	
(footnote 11)	<1	54	6,365, G→A ⁴	-4, R→Q		37 cases: Refs(7,11,15-17,21,26,35,48, 53,74,76,79,83-4,113,129,144,148,160,165,171) PINs(33-45,411-8,586-94,834-41)	
HB608, Fr	<1		6,370, Ins T	-2	Frameshift	Tartary et al (1993)	842
Seattle E	<1	37	6,372, G→T	-2, K→N		Thompson et al (1992a)	419
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
Autun	<1	<1	6,379, Δ1	2	Frameshift	Ghanem et al (1993)	420
Calgary 16	1	60	6,380, A→T	2, N→I		Poon et al (1992)	595
(footnote 11)	21		6,385, G→A	4, G→S		2 cases: Refs(165,129) PINs(596,843)	
HB47	7		6,390, A→G		New donor splice in exon(b)	Koeberl et al (1990a)	389
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
(footnote 11)	<1	<0.1	6,398-9, Δ2	8	Frameshift	2 cases: Refs(48,55) PINs(50,421)	
HB151	2	45	6,398, A→G	8, E→G	Gla	Bottema et al (1991b)	422
UK 244	4		6,398, A→C	8, E→A	Gla	Saad et al (1994)	597
UK 84	14	118	6,400, T→A	9, F→I		Saad et al (1994)	51
Madrid 3	<1	<1	6,401-10, Δ10	9	Frameshift, Inhibitor	Solera et al	423
Bonn 2	<1	<1	6,402-6, Δ5	9	Frameshift, Inhibitor de novo in mother(22)	Ludwig et al (1992a)	52
Oxford b3	<1	0.2	6,406, C→T	11, Q→Stop		Winship & Dragon (1991)	53
(footnote 11)	<1,13	46	6,409, G→A	12, G→R		2 cases: Refs(52,63) PINs(598,844)	
Hong Kong 1	3	97	6,410, G→C	12, G→A		Chan et al (1991)	54
UK 182	<1		6,410, G→A	12, G→E		Saad et al (1994)	599
HB299 (Kutahya)	<1	<1	6,411, Δ1	12	Frameshift	Caglayan et al	600
Mühlheim/Ruhr	4	4	6,416-17, Δ2	14	Frameshift, somatic mosaic?	Ludwig et al	55
GER 2705	<1		6,420-5, Δ6	15, ΔR,E	In Frame	Wulff, Herrmann et al	845
(footnote 11)	<1	58	6,424, G→A	17, E→K	Gla	2 cases: Refs(48,148) PINs(424,846)	
(footnote 11)	<1	100	6,427, T→C	18, C→R		2 cases: Refs(91,123) PINs(56-7)	
(footnote 11)	1.5	27	6,428, G→A	18, C→Y		2 cases: Refs(14,148) PINs(425,847)	
GER 2232A			6,434, A→T	20, E→V	Gla	Wulff, Herrmann et al	848
Nagoya 4	<1	52	6,436, G→A	21, E→K	Gla	Hamaguchi et al (1991)	426
UK 197	1		6,441, Δ1	22	Frameshift	Saad et al (1994)	601
Jie Long	<1	35	6,442, T→C	23, C→R		Lin & Shen (1991)	427
UK 115	<1	19	6,443, G→A	23, C→Y		Saad et al (1994)	58
(footnote 11)	2	32	6,449, T→C	25, F→S		2 cases: Refs(91,176) PINs(59,849)	
HB840, Fr	<1	42	6,451, G→C	26, E→Q	Gla	Tartary et al (1993)	850
Seattle 3	<1	30	6,454, G→A	27, E→K	Gla	Chen et al (1989b)	60
(footnote 11)	<1	3	6,455, A→T	27, E→V	Gla	2 cases: Refs(73,169) PINs(61,851)	
DK 3	<1	90	6,456, A→C	27, E→D	Gla	Nielsen et al	852
(footnote 11)	<1	<1	6,460, C→T ⁴	29, R→Stop		28 cases: Refs(16,31,52-4,56,74,77, 83,98,129,148-9,160,176) PINs(62-69,428-31,602-5,853-64)	

Table 1. (cont.)

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
(footnote 11)	22	66	6,461, G→A ⁺	29, R→Q	5 double (see 30,134)	9 cases: Refs(16,24,48,75-6,129-30,	
155,165) PINs (70-2,432-4,606,865-6)							
HB172	1		6,463, G→A	30, E→K	Gla de novo MGM (38)	Ketterling et al (1993)	607
GER 2254	<1		6,463, G→T	30, E→Stop		Wulff, Herrmann et al	867
Malmö 9	<1	<0.1	6,466, ΔI	31	Frameshift	Green et al (1991b)	73
UK 180			6,472, Ins GG	33	Frameshift	Saad et al (1994)	435
UK 111	<1		6,472, G→T	33, E→Stop		Haris et al (1994)	608
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
UK 89	7		6,488, C→T	38, T→I		Saad et al (1994)	436
(footnote 11)	<1	<1	6,491-4 or 6,492-5, Δ4		1 Double (see 31,103), Donor splice (b)	3 cases: Refs(25,116,129) PINs(77-9)	
(footnote 11)	2		6,492, G→C		Donor splice (b)	2 cases: Ref(102) PINs(868-9)	
(footnote 11)	<1		6,494, G→A		Donor splice (b)	2 cases: Refs(48,165) PINs(437,609)	
(footnote 11)	1	1	6,495, T→C		Donor splice (b)	2 cases: Refs(13,129) PINs(80,870)	
HB131	<1	<1	6,575, C→G		Triple (see 10,512 and 30,897), N	Bottema et al (1991b)	438
Malmö 10	<1	0.2	6,666-75, Δ10		Acceptor splice (c), de novo in MGF or MGM	Green et al (1991b)	81
HB216	5		6,677, G→C		Acceptor splice (c), de novo mother (34)	Ketterling et al. (1993)	610
UK 242	<1		6,677, G→A		Acceptor splice (c)	Saad et al (1994)	611
HB7, Japan	<1	<1	6,680-1, Δ2	39	Frameshift, Inhibitor	Matsushita et al (1990)	82
HB1060, Fr	<1		6,684, ΔI	41	Frameshift	Tartary et al	871
UK 156	2		6,688, G→A	42, W→Stop		Saad et al (1994)	613
Hoogeveen	14	96	6,690, A→G	43, K→E		Reitsma et al	83
Malmö 52	<1		6,693, C→T	44, Q→Stop		Ljung et al	439
UK 87	9		6,696, T→A	45, Y→N		Saad et al (1994)	614
HB170	9	59	6,696, T→G	45, Y→I		Gostout et al (1993)	872
GER 2249			6,697, A→G	45, Y→C		Wulff, Herrmann et al	873
UK 25	<1	<1	6,702, G→A	47, I→N	Donor splice (c)?	Saad et al (1994)	84
Oxford 2	0.5	0.4	6,704, T→G		Donor splice (c)	Winship (1986)	85
(footnote 11)	1	<1	6,704, T→C		Donor splice (c)	2 cases: Refs(48,93) PINs(86,440)	
HB20 (Bogazici)	5		6,707, G→C		Donor splice (c)	Caglayan et al	615
UK 128	1.3		6,707, G→A		Donor splice (c)	Saad et al (1994)	616
HB197	<1	27	10,389, A→G		Acceptor splice (d), de novo MGF (27)	Ketterling et al. (1993)	617
UK 289	<1		10,390, A→T		Acceptor splice (d)	Saad, Rowley et al	874
Toronto 16 (HB53)	3		10,391, G→A		Acceptor splice (d)	Koeberl et al (1990a)	87
Alabama	10	100	10,392, A→G	47, I→G		Davis et al (1987)	88
(footnote 11)	7	85	10,393, T→A	47, I→E		2 cases: Refs(13,175) PINs(89,90)	
Tainan	28	101	10,394, G→A	48, G→R		Lin & Shen (1991)	441
Malmö 27	19	108	10,395, G→T	48, G→V	de novo in mother	Green et al (1991b)	91
UK 86	1		10,397-9, Δ3, Ins A	49	Frameshift	Saad et al (1994)	92
Clermont	<1		10,400, C→T	50, Q→Stop		Ghanem et al (1993)	618
New London	<1	114	10,401, A→C	50, Q→P	Decreased Xla activation	Lozier et al (1990)	93
UK 145	24		10,402, G→C	50, Q→H		Saad et al (1994)	875
(footnote 11)	<1	<1	10,405, T→G	51, C→W		2 cases: Refs(48,129) PINs(619-20)	
(footnote 11)	<1	20	10,406, G→T	52, E→Stop		2 cases: Refs(14,74) PINs(442,621)	
(footnote 11)	10	46	10,415, C→G	55, P→A		3 cases: Refs(24,53,139) PINs(94-6)	
Malmö 21	12	52	10,415, C→T	55, P→S		Green et al (1991b)	97
Malmö 22	26		10,416, C→T	55, P→L		Green et al (1991b)	98
HB180	6	34	10,416, C→A	55, P→Q	de novo MGF (38)	Ketterling et al. (1993)	622
(footnote 11)	<1		10,418, T→C	56, C→R		2 cases: Refs(3,172) PINs(99,876)	
HB130, Fr	1	2	10,418, T→A	56, C→S		Tartary et al (1993)	877
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
UK 160	18		10,427, G→A	59, G→S		Saad et al (1994)	443
HB141	2		10,428, G→T	59, G→V	De novo in mother(40)	Bottema et al (1991b)	444
(footnote 11)	13	28	10,430, G→A ⁺	60, G→S		41 cases: Refs(16,23-5,37,54,69,75-6,	
113,115,117,129-30,148,155,160,175) PINs(102-12,390-1,445-57,624-6,878-9)							
HB154	<1	6	10,430, G→C	60, G→R		Bottema et al (1991b)	458
Toronto 6 (HB37)	1	2	10,431, G→A	60, G→D		Koeberl et al (1990a)	113
GER 39			10,434-5, Δ2	61	Frameshift, female carrier	Knobloch & Zoll	890
UK 176			10,437, G→A	62, C→Y		Haris et al (1994)	627
Oxford d1	3	117	10,442, G→A	64, D→N	β Hydroxyaspartate	Winship & Dragon (1991)	114
UK 6	8	87	10,443, A→G	64, D→G	β Hydroxyaspartate	Green et al (1989)	115
HB630, Fr	12	46	10,444, T→G	64, D→E	β Hydroxyaspartate	Tartary et al (1993)	891
(footnote 11)	18	91	10,449, T→C	66, I→T		3 cases: Refs(31,48,148) PINs(628-9,892)	
(footnote 11)	<1		10,458, A→G	69, Y→C		5 cases: Refs(48,74,129,176)	
(footnote 11)						PINs(116,630-1,893-4)	
UK 167			10,463, T→A	71, C→S		2 cases: Refs(38,102) PINs(632,895)	
UK 200	6		10,464, G→C	71, C→S		Saad et al (1994)	633
(footnote 11)			10,465, T→A	71, C→Stop		Saad et al (1994)	634
Fort de France	<1		10,466, T→A	72, W→R		2 cases: Refs(129-30) PINs(635,896)	
Iran 1	1	1	10,468, G→A	72, W→Stop		Ghanem et al (1993)	636
GER 7	<1		10,469, T→C	73, C→R		David et al	897
GER 2332S	<1		10,470, G→A	73, C→Y		Knobloch & Zoll	637
Paris 3	<1		10,470, G→T	73, C→F		Wulff, Herrmann et al	898
UK 67	6	12	10,471, T→A	73, C→Stop		Ghanem et al (1993)	638
UK 19			10,479, G→T	76, G→V	Female carrier	Saad et al (1994)	117
Unnamed	12	66	10,482, T→G	77, F→C		Saad et al (1994)	118
Unnamed	5	15	10,482, T→C	77, F→S		Thompson & Chen	899
			10,506-9 or 10-13, Δ4		Donor splice (d)	Thompson & Chen	900
UK 229			10,507, T→A		Donor splice (d)	Saad et al (1994)	901
UK 132			10,507-10, Δ4		Donor splice (d), normal carrier female	Saad et al (1994)	119

Table 1. (cont.)

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
(footnote 11)	1	1	10,512, A→G		2 Double (see 17,799 & 30,864).1 Triple (see 6,575 & 30,897) N?	3cases:Ref(15,48,76)PINs(120,438,639)	
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
Cardiff 4/UK 329	3	4	17,667, A→C		Acceptor splice (e)	Bowen & Bloom (1993)	902
Malmö 11	<1	<1	17,668, G→C		Acceptor splice (e), de novo in MGF	Green et al (1991b)	123
Seattle 2	<1	<1	17,669, Δ1	85	Frameshift	Schach et al (1987)	124
HB147	2	2	17,669-75 Δ7	85	Frameshift de novo	Ketterling et al. (1993)	640
UK 98	<2		17,677, T→C	88, C→R		Saad et al (1994)	641
Königswinter	<1		17,678, G→C	88, C→S		Ludwig et al	125
(footnote 11)	<1	9	17,678, G→A	88, C→Y		2 cases:Refs(148,165) PINs(903-4)	
(footnote 11)	15		17,684, T→C	90, I→T		2 cases:Refs(129,176) PINs(642,905)	
(footnote 11)	2	66	17,689, A→C ²	92, N→H		2 cases:Refs(26,105) PINs(126,906)	
(footnote 11)	<1	86	17,691, T→A	92, N→K		3 cases:Refs(48,148) PINs(459-60,907)	
HB256	3	22	17,692, G→A	93, G→S	de novo mother (27)	Ketterling et al. (1993)	643
(footnote 11)	2	30	17,693, G→A	93, G→D		2 cases:Refs(103,176) PINs(908-9)	
NZ 27	1		17,696, Ins A	94	Frameshift	Van de Water et al	910
HB106	1	84	17,697, A→T	94, R→S		Bottema et al (1991a)	461
(footnote 11)	2	6	17,699, G→A	95, C→Y		2 cases:Ref(15) PINs(462-3)	
(footnote 11)	<1		17,700, C→A	95, C→Stop		3 cases:Refs(70,129,146) PINs (127,911-2)	
(footnote 11)	<1	2	17,700, C→G	95, C→W		2 cases:Refs(86,103) PINs(464,913)	
HB267, Fr	<1	<1	17,704, C→G	97, Q→E		Tartary et al (1993)	914
GER 8			17,705, A→C	97, Q→P		Knobloch & Zoll	644
Taichung	<1	<13	17,706, Δ1	97	Frameshift	Lin et al (1993)	645
Hamilton 1 (HB45)	<1		17,710, T→C	99, C→R		Koeberl et al (1990a)	128
Unnamed	<1		17,711, G→A	99, C→Y		Tagliavacca et al	915
(footnote 11)	<1		17,713-8, Ins A	101	Frameshift	2 cases:Refs(129,165) PINs(465,646)	
UK 50	<1	<1	17,727, Ins TT	105	Frameshift	Saad et al (1994)	129
(footnote 11)	18	21	17,736, G→A	107, None	cryptic splice?	5 cases:Refs(55,86) PINs(130-2,647-8)	
Unnamed	20	120	17,738, T→C	108, V→A		Chen et al (1991a)	133
Unnamed	<1		17,740, G→C	109, C→S		Tagliavacca et al	916
GER 9	<1		17,741, G→T	109, C→F		Knobloch & Zoll	649
HB111	7	<1	17,743, T→C	110, S→P		Bottema et al (1991a)	466
Taipei 5	<1	<6	17,746, T→C	111, C→R		Lin et al (1993)	650
HB310, Fr	<1	<1	17,746, Ins 26	111	Frameshift	Tartary et al (1993)	917
Cardiff 3/UK 327	<1		17,747, G→C	111, C→S		Bowen & Bloom (1993)	918
Calgary 24	<1		17,754, 5 or 6 Δ1	114 or 115	Frameshift	Poon et al (1992)	651
(footnote 11)			17,756, G→A	114, G→E		2 cases:Ref(176) PINs(919-20)	
(footnote 11)	9	4	17,756, G→C	114, G→A		2 cases:Refs(124,175) PINs(134-5)	
(footnote 11)	1	1	17,759, A→G	115, Y→C		2 cases:Refs(93,129) PINs(136,467)	
(footnote 11)	<1	<1	17,761, C→T ⁴	116, R→Stop	1 Double (see 30,890)	7 cases:Refs(15,84,99,103,129,165) PINs(137,468,652-3,921-3)	
UK 28	5	5	17,761, C→A	116, None	cryptic splice?	Saad et al (1994)	138
Würzburg	<1		17,764, Ins C	117	Frameshift, de novo in MGF(27) or MGM(21)	Ludwig et al (1992a)	139
UK 9	<1	0.4	17,773, A→T	120, N→Y		Green et al (1989)	140
(footnote 11)			17,778, G→T	121, Q→H		4 cases:Ref(165,176)PINs(654-5,924-5)	
(footnote 11)	<1		17,782, T→C	123, S→P		2 cases:Refs(129,145) PINs(656,924)	
HB88	2		17,786, G→A	124, C→Y		Bottema et al (1991a)	469
Taiwan	<1	<6	17,795, C→T	127, A→V		Lin et al (1993)	657
GER 10			17,796, A→T	127, None	Donor splice (e)	Knobloch & Zoll	658
GER 11			17,796, A→C	127, None	Donor splice (e)	Knobloch & Zoll	659
GER 37			17,796, A→G	127, None	Donor splice (e)	Knobloch & Zoll	660
HB68	1		17,797, G→A	128, V→M	Donor splice (e)	Bottema et al (1991a)	470
(footnote 11)	<1	<1	17,798, G→T		Donor splice (e) in mother	2 cases:Refs(91,161) PINs(141,661)	
UK 102	<1		17,799, T→G		Donor splice (e)	Saad et al (1994)	662
Paris 5	<1		17,799, T→C		Donor splice (e), double (see 10,512)	Ghanem et al (1993)	639
HB214			17,799, T→A		Donor splice (e)	Gostout et al (1993)	927
(footnote 11)	7	6	17,810, A→G		New donor splice ?	14 cases:Refs(61,76,113,129-30,165) PINs(142-4,664-6,928-35)	
GER 12			20,372, C→T	131, P→L		Knobloch & Zoll	667
(footnote 11)	<1	<1	20,374, T→C	132, C→R		4 cases:Refs(84,102,167) PINs(145,668-9,936)	
UK 227			20,374, T→G	132, C→G		Saad et al (1994)	937
(footnote 11)	<1	<0.1	20,375, G→T	132, C→F		3 cases:Refs(55,73,172) PINs(146,670,938)	
(footnote 11)	<1	<6	20,375, G→A	132, C→Y		3 cases:Refs(14,84,148) PINs(471,671,939)	
UK 78	<1		20,375, G→C	132, C→S		Saad et al (1994)	672
GER 2276	<1		20,376, T→G	132, C→W		Wulff, Herrmann et al	940
Chapel Hill 2	4	4	20,377, G→A	133, G→R		High et al (1993)	673
HB246, Fr	<1	<1	20,378, G→A	133, G→E		Tartary et al (1993)	941
UK 166	<1		20,380-1, Δ2	134	Frameshift	Saad et al (1994)	674
(footnote 11)	<1	<1	20,387-8 Δ2,	136	Frameshift	3 cases:Ref(72) PINs(675-6,942)	
Malmö 44			20,398, Δ1	140	Frameshift, de novo in MGF or MGM	Green et al (1991b)	147
Unnamed	2	40	20,413, C→G	145, R→L		Thompson & Chen	943
S 17			20,413, C→A	145, R→S		Nielsen et al	944
(footnote 11)	3	43	20,413, C→T ⁴	145, R→C	Decreased XIa activation	23 cases:Refs(54,73-4,80,113,129-30,	
155-6,158,162,165,175-6) PINs(148-52,472-6,677-82,945-52)							
(footnote 11)	7	106	20,414, G→A ⁴	145, R→H	Decreased XIa activation	25 cases:Refs(1,13-16,26,33,38,40,55,	
59,75,84,86,107,129,142,158,165,176) PINs(153-62,477-9,684-7,953-60)							
Toronto 21	7	60	20,414, G→T	145, R→L	Also 9,786, A→C in intron	Picketts et al (1990)	480
Unnamed	<1		20,464, G→T	162, E→Stop		Tagliavacca et al	961
HB23	<1		20,466-78, Δ13	162	Frameshift, de novo in MGM (23)	Koeberl et al (1989)	163
						Ketterling et al (1993)	

Table 1. (cont.)

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
HB17	<1		20,497, C→T	173, Q→Stop		Koeberl et al (1989)	164
HB78	2	<1	20,501, Δ1	174	Frameshift, de novo in mother (26)	Bottema et al (1990c)	165
Malmö 13	<1	0.5	20,510, Δ1	177	Frameshift	Ketterling et al (1993)	
Brest	<1	85	20,512, T→C	178, F→L	Double (see 20,518), N?	Green et al (1991b)	166
(footnote 11)	<1	88	20,518, C→T ⁺	180, R→W	B _m	Ghanem et al (1993)	167
73,91,102,129,141,148,155)	<1	80	20,518, C→G	180, R→G	1 Double (see 20,512), B _m	17 cases: Refs(8,16,36,42,48,59,70, PINs(167,174,968)	
(footnote 11)	<1	112	20,519, G→A ⁺	180, R→Q	B _m , decreased XIa activation	3 cases: Refs(1,48,134)	
148,160,167,176) PINs(175-80,485,691,969-74)	<1	73	20,519, G→T	180, R→L		14 cases: Refs(8,13,66,74,97,102,113, 2 cases: Refs(84,165) PINs(692,975)	
(footnote 11)	<2		20,519, G→C	180, R→P		Ritchie et al	486
Creston 1	<1	130	20,521, G→T	181, V→F	B _m	Bertina et al (1990)	181
Milano	<1		20,522, T→A	181, V→D		Wulff, Herrmann et al	976
GER 2280S	10	132	20,524, G→C	182, V→L	B _m ⁶	2 cases: Refs(61,151) PINs(182,693)	
(footnote 11)	<1	120	20,524, G→T	182, V→F	B _m ⁶	Sakai et al (1989)	183
Kashihara	23	100	20,525, T→C	182, V→A	B _m ⁶	Nishimura et al (1990)	694
Tokyo	2	72	20,525, T→G	182, V→G		Maekawa et al (1991)	487
Unnamed	13		20,527, G→A	183, G→S		Thompson & Chen	977
DK 11	<1	97	20,527-9, Δ3	183, ΔG	In frame	Nielsen et al	978
UK 54	<1	100	20,530, G→A	184, G→R		Saad et al (1994)	184
Unnamed	1		20,530-2	184, ΔG	In frame	Thompson et al (1992b)	695
UK 261	<1	92	20,531-3, Δ3	184, ΔG	In frame	Saad et al (1994)	979
Bottrop 1	<1		20,540, C→A	187, A→D		Ludwig et al	185
(footnote 11)	1		20,548, G→T	190, G→C		2 cases: Refs(26,165) PINs(980-1)	
UK 179	<1	36	20,549, G→T	190, G→V		Saad et al (1994)	696
FuChou	<1		20,551, C→T	191, Q→Stop	Inhibitor, Double (see -793)	Lin et al	982
(footnote 11)	<1	<1	20,551, C→A	191, Q→K	Inhibitor	2 cases: Refs(1,95) PINs(1,983)	
Unnamed	3	2	20,553, A→G	191, None	Cryptic splice	Chen et al (1991a)	186
Seattle J	2	<6	20,554, T→G	192, F→V		Thompson et al (1992a)	488
NanTou 1	4	4	20,560, T→C	194, W→R		Lin et al (1993)	697
Seattle K	<1	1	20,560, T→A	194, W→R		Thompson et al (1992a)	489
Seattle L	<1	<1	20,561, G→A	194, W→Stop	1 Inhibitor	Thompson et al (1992a)	490
(footnote 11)	<1		20,562, G→A	194, W→Stop		6 cases: Refs(52-3,86,102,129) PINs(187-8,491,984-6)	
UK 233	<1	<1	20,563, C→T	195, Q→Stop		Saad et al (1994)	698
Unnamed	<1	<1	20,564, A→G	195, Q→R		Thompson et al (1992b)	699
(footnote 11)	<1	<1	20,565, G→A	195, None	Donor splice (f)	2 cases: Refs(73,93) PINs(189,987)	
(footnote 11)	<0.5	0.3	20,566, G→T		Donor splice (f)	2 cases: Refs(158,176) PINs(988-9)	
Oxford 1	<1	<1	20,566, G→A		Donor splice (f)	Rees et al (1985)	190
(footnote 11)	<1		20,567, T→C		Donor splice (f)	2 cases: Refs(93,102) PINs(191,990)	
UK 272	<1		30,038, G→A		Donor splice (f)	Saad, Rowley et al	991
UK 171	<1	<1	30,038, G→C		Acceptor splice (g)	Saad et al (1994)	492
(footnote 11)	2		30,046, T→G	198, L→W	Acceptor splice (g)	2 cases: Refs(14,113) PINs(493,700)	
UK 192	<1	<1	30,046, T→C	198, L→S		Saad et al (1994)	494
HB188	<1		30,050, Δ1	199	de novo in MGF (21)	Ketterling et al. (1993)	701
GER 43	<1		30,058, Δ4	202	Frameshift	Knobloch & Zoll	992
Paris 4	<1		30,069, T→C	206, C→R	Frameshift	Ghanem et al (1993)	702
(footnote 11)	<1	<1	30,070, G→C	206, C→S		2 cases: Refs(74,129) PINs(703-4)	
(footnote 11)	<1		30,070, G→A	206, C→Y		2 cases: Refs(129,151) PINs(192,705)	
(footnote 11)	<1		30,072, G→A	207, G→R		2 cases: Refs(15,52) PINs(495,993)	
Unnamed	<1	<1	30,072, G→T	207, G→Stop		2 cases: Refs(33,129) PINs(193,706)	
(footnote 11)	<1	56	30,073, G→A	207, G→E		Thompson et al (1992b)	707
UK 37	6	1	30,076, G→A	208, G→D		2 cases: Refs(84,176) PINs(708,994)	
(footnote 11)	16		30,084, G→T	211, V→F		Saad et al (1994)	194
(footnote 11)	<1	<1	30,089, T→G	212, N→K	All same haplotype	2 cases: Refs(24,93) PINs(195-6)	
Bottrop 2	1	<1	30,090, G→T	213, E→Stop		5 cases: Ref(102) PINs(995-9)	
(footnote 11)	<1		30,096, T→C	215, W→R		Ludwig et al	197
Unnamed	<1	0.1	30,097, G→A	215, W→Stop		3 cases: Refs(13,82,158) PINs(198,496,1000)	
TaiDung	<1	<6	30,098, G→T	215, W→C		Chen et al (1991a)	199
(footnote 11)	5	4	30,100, T→C	216, I→T		Lin et al (1993)	709
HB65	15	4	30,101, T→G	216, I→M		4 cases: Refs(24,55,73,76) PINs(200-2,710)	
GER 2274	5	9	30,107, G→A	219, A→T		Bottema et al (1991a)	497
(footnote 11)	2		30,112, C→T	220, A→V		Wulff, Herrmann et al	1001
UK 93	1		30,117, T→A	222, C→S		3 cases: Refs(76,113) PINs(203-4,711)	
HB24	<1		30,119, T→G	222, C→W		Saad et al (1994)	498
(footnote 11)	13	12	30,150, G→A ⁺	233, A→T	4 Double (see 6,461), N 1 Double (see 31,221), N	Koeberl et al (1989)	205
(footnote 11)	<1	<1	30,152, Ins A	233		5 cases: Refs(16,26,75-6) PINs(70-2,865,1002)	
Caen 3	1	1	30,154, G→A			18 cases: Refs(1,24,55,75,86,93, PINs(206-14,499,712-3,1003-8)	
HB626, Fr	<1		30,821, G→A		Frameshift	Ghanem et al (1993)	714
(footnote 11)	<1		30,834, T→A	238, I→N	Donor splice (g)	Tartary et al (1993)	1009
(footnote 11)	<1		30,839-41, Δ3	240, ΔE	2 Double(see 13 & 31,119), N	3 cases: Refs(26,48,56) PINs(215,715,820)	
UK 276	20		30,845, Δ1	242	1 Inhibitor, Acceptor splice (h)	4 cases: Refs(14,25,95,130) PINs(216-7,500,716)	
(footnote 11)	<1	22	30,854, G→A	245, E→K		Saad, Rowley et al	1010
HB660, Fr	2	74	30,855, A→T	245, E→V	In frame, same haplotype	4 cases: Ref(176) PINs(1011-4)	
Spijkenisse	3	39	30,863, C→G	248, R→G	Frameshift	Tartary et al (1993)	1015
Monschau	<1	3	30,863, C→T ⁺	248, R→Stop		Reitsma et al	218
UK 140	<1		30,864, G→A ⁺	248, R→Q		Ludwig et al (1992b)	219
GER 952	<1				Frameshift	Saad et al (1994)	501
(footnote 11)	<1	<1				Wulff, Herrmann et al	1016
113,129,145,147-8,168) PINs(220-9,502-5,717,1017-28)	4	4			2 inhibitors	27 cases: Refs(15-7,19,52-6,76,93, 28 cases: Refs(14,16,19,23-4,33,48,	

Table 1. (cont.)

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
76,91,102,113,129-30,155,176) PINs(120,230-3,392,506-12,718-24,1030-7)							
UK 92	<1		30,873, T→A	251, I→N		Saad et al (1994)	725
(footnote 11)	<1	<1	30,875, C→T ^d	252, R→Stop		15 cases:Refs(1,14,20,22,43,48,55-6,	
70,73,112,129,133,150,176) PINs(234-40,513-4,726-8,1038-40)							
UK 16	13		30,876, G→T	252, R→L		Saad et al (1994)	241
Malmö 7	<1	<0.1	30,890, C→T	257, H→Y	Double (see 17,761), N	Montandon et al (1990a)	137
DK 10	<1	<8	30,890, Δ1	257	Frameshift	Nielsen et al (1992)	1041
(footnote 11)	<1	<1	30,897, A→G	259, Y→C	1 Triple(see 6575 & 10,512)	2 cases:Refs(15,70,165) PINs(438,1042)	
(footnote 11)	16		30,900, A→G	260, N→S		2 cases:Refs(75,165) PINs(242,623)	
UK 88	7		30,924, A→G	268, H→R		Saad et al (1994)	243
HB786, Fr	8	2	30,925, T→G	268, H→Q		Tartary et al (1993)	1043
GER 18	1.5		30,926, G→A	269, D→N	de novo in mother (38)	Knobloch et al (1993)	688
Malmö 50	<1		30,927, A→T	269, D→V	Proposed active site Asp	Ljung et al	515
(footnote 11)	<1		30,927, A→G	269, D→G	Proposed active site Asp	3 cases:Refs(48,129) PINs(689,729-30)	
HB208	<1	5	30,928, C→A	269, D→E	de novo mother (34)	Ketterling et al. (1993)	731
(footnote 11)	1	1	30,929, A→T	270, I→F		2 cases:Refs(52,129) PINs(244,1044)	
(footnote 11)	<1	<1	30,930, T→C	270, I→T		2 cases:Refs(14,93) PINs(245,516)	
(footnote 11)	12	4	30,933, C→T	271, A→V		4 cases:Refs(76,129)	
HB143	<1	2	30,936, T→G	272, L→R	De novo in MGF (23)	Bottema et al (1991b)	517
						Ketterling et al (1993)	
UK 48			30,942, Δ1	274	Frameshift, normal carrier female	Saad et al (1994)	247
GER 3147	<1		30,945, T→A	275, L→Q		Wulff, Herrmann et al	1046
(footnote 11)	<1	7	30,945, T→C	275, L→P		3 cases:Refs(14,67,129)	
						PINs(248,518,1047)	
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
Mantes-la-Jolie	<1		30,957, T→C	279, L→S		Ghanem et al (1993)	734
HB270			30,972, A→G	284, Y→C	Double (see 31,328)	Sommer et al	1048
(footnote 11)	<1	1	30,973, C→A	284, Y→Stop		2cases:Refs(70,148) PINs(1049-50)	
Unnamed	<1	<1	30,981, C→T	287, P→L		Chen et al (1991a)	251
GER 2234A			30,981, C→A	287, P→H		Wulff, Herrmann et al	735
HB109	<1	<1	30,985, T→G	288, I→M		Bottema et al (1991a)	519
(footnote 11)	2		30,987, G→T	289, C→F		2 cases:Refs(52,129) PINs(736,1051)	
Oxford h2	2	3	30,992, G→C	291, A→P		Winship & Dragon (1991)	252
(footnote 11)	8	13	30,992, G→A	291, A→T		6 cases:Refs(56,98,129)	
						PINs(253-5,520,737,1052)	
HB100	<1	<1	31,001, G→T	294, E→Stop	De novo in MGM (24)	Bottema et al (1991a)	521
						Ketterling et al (1993)	738
UK 72	<1		31,004, Ins CA	295	Frameshift	Saad et al (1994)	739
Fumel	<1		31,005, A→G	295, Y→C		Ghanem et al (1993)	740
GER 2121C			31,007, Δ1	296	Frameshift	Wulff, Herrmann et al	741
(footnote 11)	5	8	31,008, C→T ^d	296, T→M		63 cases:Refs(16,24,54-5,63,68,	
74-6,86,103,113,127,129-30,145,147-9,155,158,160,165,175-6)PINs(256-74,393-4,522-31,742-52,1053-75)							
GER 2722			31,008, C→A	296, T→K		Wulff, Herrmann et al	1076
HB132			31,012, C→T	None	Double (see 31,224) N	Bottema et al (1991b)	532
Malmö 18	<1	0.3	31,035, G→A	305, G→D	de novo in MGF	Green et al (1991b)	275
Seattle O	<1	<1	31,039, T→A	306, Y→Stop		Thompson et al (1991)	533
(footnote 11)	16	45	31,041, T→C	307, V→A		3 cases:Refs(9,24,160)PINs(276-7,534)	
Malmö 26	3	4	31,041, T→G	307, V→G		Green et al (1991b)	278
GER 45	2		31,043, A→C	308, S→R		Knobloch & Zoll	1077
(footnote 11)	5	26	31,044, G→A	308, S→N		2 cases:Refs(129,148) PINs(279,1078)	
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
(footnote 11)	<1		31,047, G→A	309, G→D		2 cases:Refs(48,52) PINs(753,1079)	
Toronto 21	<1	86	31,049, T→C	310, W→R		Picketts et al	283
GER 20	4		31,050, G→T	310, W→L		Knobloch & Zoll	754
(footnote 11)	<1	<1	31,051, G→A	310, W→Stop		3 cases:Refs(147,165,168)	
						PINs(284-5,535)	
(footnote 11)	1	5	31,051, G→C	310, W→C		2 cases:Refs(70,74) PINs(755-6)	
GER 2223A	<1		31,051, G→T	310, W→C		Wulff, Herrmann et al	1080
(footnote 11)	3	100	31,052, G→A	311, G→R		2 cases:Refs(15,75) PINs(286,536)	
Amagasaki	<1	100	31,053, G→A	311, G→E	B _m ⁶	Miyata et al (1991)	287
UK 219	<1		31,053, G→T	311, G→V		Saad et al (1994)	1081
UK 137	<1	100	31,059, T→G	313, V→G		Saad et al (1994)	288
Kiryu	2.5	100	31,059, T→G	313, V→D	B _m	Kuze (1992)	757
UK 11	<1	<2	31,059-60, Δ2	313	Frameshift	Green et al (1989)	289
GER 830			31,067, A→G	316, K→E		Wulff, Herrmann et al	1082
Goldbach	<1		31,070, G→C	317, G→R		Ludwig et al	290
UK 143			31,071, G→A	317, G→E	Female carrier	Saad et al (1994)	758
(footnote 11)	2	90	31,080, C→A	320, A→D		4 cases:Refs(76,129,165)	
						PINs(291,537-8,1083)	
Bruxelles			31,080, C→T	320, A→V		Ghanem et al (1993)	758
Riegelsberg	<1	<1	31,084-90, Δ7	321	Frameshift, double (see 37), de novo in mother(30)	Ludwig et al (1992a)	14
HB82	4	4	31,091, C→T	324, Q→Stop		Bottema et al (1991a)	539
ChangHua 2	<1	<6	31,092, A→C	324, Q→P		Lin et al (1993)	759
HB122	4		31,096, C→G	325, Y→Stop	de novo in mother (26)	Bottema et al (1991a)	540
HB273	<1	<1	31,096, C→A	325, Y→Stop		Gostout et al (1993)	1084
(footnote 11)	4	4	31,103, G→T	328, V→F		2 cases:Refs(74,174) PINs(292,760)	
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		Saad et al (1994)	293
(footnote 11)	<1	<1	31,110-12, Δ3 ⁹	331, ΔV	In frame	2 cases:Refs(74,93) PINs(294,761)	
Oxford h1	7	96	31,113, T→C	331, V→A		Winship & Dragon (1991)	295
(footnote 11)	4		31,115, G→T	332, D→Y		3 cases:Refs(74,165) PINs (296,762-3)	
(footnote 11)	<1	<1	31,118, C→T ^d	333, R→Stop		18 cases:Refs(14,24,33,48,52,70,74,	
77,84,86,100,117,129,160) PINs(297-303,541-3,764-9,1079-80)							
(footnote 11)	6	66	31,118, C→G	333, R→G		3 cases:Refs(13,15,176)	
						PINs(304,544,1087)	

Table 1. (cont.)

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
HB110 (footnote 11)	2	150	31,119, G→T	333, R→L	1 double (see 30,800)	Bottema et al (1991a)	545
(footnote 11)	2	93	31,119, G→A ⁴	333, R→Q		25 cases:Refs(1,14,16,24,26,32,48,	
53-4,56,74,91,109,113-4,129-30,148,155,163,168)	18	100	PINs(215,305-15,546-8,770-3,1088-93)	334, A→D		2 cases:Refs(21,86) PINs(316,774)	
(footnote 11)	1	3	31,122, C→A	336, C→R		4 cases:Refs(24,53,129)	
(footnote 11)			31,127, T→C			PINs(317-8,549,775)	
Malmö 24	<1	<1	31,128, G→A	336, C→Y		Green et al (1991b)	319
GER 25	<1		31,129, T→A	336, C→Stop		Knobloch & Zoll	776
Calgary 3	4	120	31,130, C→A	337, L→I		Fraser et al (1992)	550
HB281		72	31,130, C→T	337, L→F		Gostout et al (1993)	1094
(footnote 11)	<1	<1	31,133, C→T ⁴	338, R→Stop	1 double(see 48)	13 cases:Refs(1,41,46,52,54,85,89,	
112-3,146,148) PINs(320-6,399,777-8,1095-7)	13	27	31,134, G→C	338, R→P		2 cases:Refs(70,73) PINs(779,1092)	
(footnote 11)	<1		31,140, C→G	340, T→R	de novo in MGF (27)	Ketterling et al. (1993)	780
HB241			31,141, 2 or 3	340 or 341	Frameshift, normal	Saad et al (1994)	551
UK 170			Ins AA		carrier female		
Samli	<1	<1	31,149-51, Δ3	343	Frameshift	Ludwig et al	327
			31,158-62, Δ5				
(footnote 11)	1	87	31,158, Ins G				
			31,151, A→T	344, I→F		3 cases:Refs(93,176)	
GER 2120C			31,156, T→A	345, Y→Stop		PINs(328,1099,1100)	
Unnamed	<1	<1	31,157, 8 or 9	346	Frameshift	Wulff, Herrmann et al	1101
			Ins AA			Chen et al (1991b)	329/552
UK 135			31,157-9 or	346 or 347	In frame	Saad et al (1994)	553
			31,160-2 Δ3	ΔN			
HB108	<1	2	31,161, A→T	347, N→I		Bottema et al (1991a)	554
Unnamed	3	103	31,163, A→G	348, M→V		Chen et al (1991a)	330
DK 9	<1	12	31,164, T→A	348, M→K		Nielsen et al	1102
(footnote 11)	<1	71	31,165, G→A	348, M→I		2 cases:Refs(14,70,148)PINs(555,1103)	
Offenbach	<1		31,166 or 7, Δ1	349	Frameshift, de novo in	Ludwig et al (1992a)	331
					MGM(29)		
(footnote 11)	<1	45	31,170, G→C	350, C→S	1 Somatic mosaic	2 cases:Refs(152,176) PINs(332,1104)	
(footnote 11)	<1	<1	31,170, G→A	350, C→Y		3 cases:Refs(73,86,129)	
						PINs(333,556,1105)	
HB244, Fr	1	5	31,170, G→T	350, C→F		Tartary et al (1993)	1106
GER 47			31,176, G→A	352, G→D		Knobloch & Zoll	1107
UK 234	4		31,187, G→A	356, G→R		Saad et al (1994)	1108
GER 27	<1		31,194-5, Δ2	358	Frameshift, de novo	Knobloch et al (1993)	781
					in mother (18)		
GER 28	1.5		31,197, A→G	359, D→G		Knobloch & Zoll	782
(footnote 11)	1	130	31,200, C→T	360, S→L		3 cases:Refs(24,48,129)PINs(334,783-4)	
(footnote 11)	<1		31,200, C→G	360, S→Stop		3 cases:Refs(48,148) PINs(785-6,1109)	
Madrid 5	<1	<1	31,202, T→C	361, C→R		Damas et al	787
GER 2248	<1		31,202, T→A	361, C→S		Wulff, Herrmann et al	1110
UK 144	<1		31,208, G→T	363, G→Stop		Saad et al (1994)	557
Los Angeles 2	<1	110	31,208, G→A	363, G→R		High et al (1993)	558
Eagle Rock	1-5	100	31,209, G→T	363, G→V		Bajaj et al (1990)	335
Seattle S	3	100	31,209, G→C	363, G→A	De novo in MGF	Thompson et al (1992a)	559
(footnote 11)	1	53	31,209, G→A	363, G→E		2 cases:Refs(129,165) PINs(336,788)	
Unnamed	<1	<1	31,210-13,	364	Frameshift, de novo	Thompson & Chen (1994)	1111
			Ins AGAT		in MGF		
(footnote 11)	1	97	31,211, G→C	364, D→H		2 cases:Refs(13,92) PINs(337-8)	
(footnote 11)	1		31,211, G→A	364, D→N	B _m	2 cases:Refs(129,172) PINs(339,1112)	
Unnamed	<1	130	31,212, A→T	364, D→V	De novo in MGF	Chen et al (1991a)	340
Varel	<1	89	31,213-14,	365, S→G	Active site,	Ludwig et al (1988,1992b)	341
			TA→CG		Inhibitor, silent		
					mutation at aa364		
GER 29			31,214, A→G	365, S→G	Active site	Knobloch & Zoll	789
DK 29	2		31,215, G→A	365, S→N	Active site	Nielsen et al	1113
Schmallenberg	<1		31,215, G→T	365, S→I	de novo in MGF	Ludwig et al (1992b)	342
Toronto 4 (HB35)	1	90	31,216, T→A	365, S→R	Active site	Koerberl et al (1990a)	343
KaoHsiung 2	<1	100	31,216, T→G	365, S→R	Active site	Lin et al	791
(footnote 11)	3	32	31,218, G→A	366, G→E		2 cases:Refs(14,48) PINs(560,792)	
(footnote 11)	<1	14	31,220, G→A	367, G→R		3 cases:Refs(19,24,48) PINs(344,793-4)	
Hartfleu	<1		31,221, G→A	367, G→E	Double (see 30,134)	Costes et al	1002
(footnote 11)	2	156	31,223, C→A	368, P→T	B _m	3 cases:Refs(8,113,145)	
						PINs(345,795,1114)	
(footnote 11)	2	62	31,224, C→T	368, P→L	1 double (see 31,012)	4 cases:Refs(15,103,129)	
						PINs(561,532,1115-6)	
HB73	<1	<1	31,227, A→G	369, H→R		Bottema et al (1990c)	346
Nimes 2	1	1	31,239, T→A	373, V→E		Aguilar-Martinez et al(1994)1117	
(footnote 11)	1	1	31,241, G→T	374, E→Stop		2 cases:Refs(32,129) PINs(1118-9)	
Malmö 16	15	13	31,248, C→A	376, T→N		Green et al (1991b)	347
Unnamed	<1	<1	31,253, T→C	378, F→L		Chen et al (1991a)	348
GER 30	<1		31,257, T→G	379, L→Stop	de novo in mother	Knobloch et al (1993)	796
(footnote 11)	8		31,258, A→C	379, L→F		2 cases:Refs(146,172) PINs(349,1120)	
Barcelos	<1		31,259, A→C	380, T→P		David et al (1993)	562
Hong Kong 5	7	<10	31,260, C→G	380, T→S		Chan et al (1991)	350
UK 76	<1	1	31,260, C→T	380, T→I		Green, Montandon et al	351
UK 259	1.4		31,260, C→A	380, T→N		Saad, Rowley et al	1121
Hong Kong 4	<1	<10	31,261, Δ1	380	Frameshift	Chan et al (1990)	352
GER 31	<1		31,270, Ins T	383	Frameshift	Knobloch & Zoll	797
UK 162	1.8		31,272, G→T	384, S→I		Saad, Rowley et al	790
GER 32	<1		31,274, T→C	385, W→R		Knobloch & Zoll	798
GER 2227A			31,274, T→A	385, W→R		Wulff, Herrmann et al	1122
Malmö 49	<1		31,276, G→A	385, W→Stop		Ljung et al	563
UK 278	1		31,276, G→T	385, W→C		Saad et al (1994)	1123
GER 2251			31,277, G→A	386, G→S		Wulff, Herrmann et al	1124

Table 1. (cont.)

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
Takatsuki	2	120	31,278, G→A	386, G→D	B _m ⁶	Kuze (1992)	799
UK 293	<1		31,278, G→C	386, G→A		Saad et al (1994)	1125
HB86	2	95	31,281, A→G	387, E→G		Bottema et al (1991a)	564
GER 33			31,283, G→T	388, E→Stop		Knobloch & Zoll	800
GER 34	<1		31,286-7, Δ2	389	Frameshift, de novo in mother	Knobloch et al (1993)	801
(footnote 11)	3	2	31,287, G→A	389, C→Y		6 cases: Refs(93,102,129-30,148)	
(footnote 11)	3	40	31,289, G→A	390, A→T		PINs(353-4,1126-9)	
(footnote 11)	1	90	31,290, C→T	390, A→V	B _m	3 cases: Refs(52,148,165) PINs(1130-2)	
(footnote 11)	2	30	31,290, C→A	390, A→E		4 cases: Refs(104,129,137,143,147)	
UK 262			31,303, A→C	394, K→N		PINs(355-7,802)	
UK 119	<1		31,305, A→G	395, Y→C		2 cases: Refs(24,129,168) PINs(358,565)	
(footnote 11)	<1	100	31,307, G→A	396, G→R	B _m ⁶	Saad, Rowley et al	1133
UK 29	<1		31,307-20, Δ14	396	Frameshift	Saad et al (1994)	1134
Los Angeles 5	1	112	31,308, G→C	396, G→A		2 cases: Refs(48,166) PINs(359-60)	
						Saad et al (1994)	361
						High et al (1993)	803
UK 172			31,308, G→T	396, G→V		Saad et al (1994)	804
(footnote 11)	3	73	31,311, T→C	397, I→T	B _m ⁶ At least 25 have same Haplotype	31 cases: Refs(5,12,24,47,69,75,113,	
138,155,158-9,170) PINs(363-80,566-73,805-7,1135)							
(footnote 11)			31,314, A→C	398, Y→S		2 cases: Ref(129) PINs(808,1136)	
Lousada	2		31,318, Ins	399	In frame	David et al (1993)	809
			ATATATACC				
HB43	8		31,326, C→T	402, S→F		Koerberl et al (1990a)	381
Lincoln Park	3	9	31,327-8, Δ2	402	Frameshift	Rao et al (1990)	382
			Ins AAGGTACCAA				
GER 35	<1		31,321-8, Δ8	400	Frameshift, de novo in mother (29)	Knobloch et al (1993)	810
GER 2229A			31,328, C→T ⁴	403, R→W		Wulff, Herrmann et al	1137
HB270			31,328, C→T ⁴	403, R→W	Double (see 30,972)	Sommer et al	1042
(footnote 11)	24	60	31,329, G→A ⁴	403, R→Q		3 cases: Refs(1,113,129)	
						PINs(811,1138-9)	
Chatenay-Malabry	<1		31,329, Δ1	403	Frameshift	Ghanem et al (1993)	683
Unnamed	4		31,331, T→C	404, Y→H		Ludwig et al	383
GER 36			31,332, A→G	404, Y→C		Knobloch & Zoll	663
Seattle T	23	26	31,334, G→T	405, V→F		Thompson et al (1992a)	574
(footnote 11)	<1	2	31,340, T→C	407, W→R		2 cases: Refs(14,70,75) PINs(384,575)	
UK 53	<1	<1	31,342, G→A	407, W→Stop		Saad et al (1994)	385
Italy 1	1	1	31,344, T→C	408, I→T		David et al	1140
Oxford h4	<1	0.2	31,344 or 5, Δ1	408	Frameshift	Winship & Dragon (1991)	386
HB62	<1		31,346, Ins GATT	408	Frameshift, de novo in mother	Bottema et al (1989b)	387
						Ketterling et al (1993)	
Bordeaux	<1	<1	31,352, A→T	411, K→Stop		Attree et al (1989)	388
Unnamed	<1	<1	31,350-5, Δ1	410-412	Frameshift, de novo in mother	Thompson & Chen (1994)	1141
HB66	3	1	31,356, C→A	412, T→K	De novo in mother (30)	Bottema et al (1991a)	576
(footnote 11)	1.5	<1	32,528, A→G	3' UTR	New donor splice?	Ketterling et al (1993)	
						5 cases: Refs(158,178) PINs(1142-6)	

¹For nucleotide numbering see Yoshitake *et al* (1985); for amino acid numbering Anson *et al* (1984).

²Nucleotide change predicted from amino acid sequence.

³The 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).
- (viii) *de novo*: refers to a new mutation originating in mother, or maternal grandmother (MGM) - mother, but not grandmother carrying the mutation, and RFLP analysis indicating the mutant gene is inherited from the grandmother, or maternal grandfather (MGF) - mother but not grandparents carrying the mutation and RFLP analysis indicating the mutant gene is inherited from the grandfather. Parental age at conception of child carrying, or affected by, the mutant gene is given in brackets, if known.

⁴Indicates mutation of a CG to either TG or CA.

⁵% varies with age, rising after puberty.

⁶Bovine prothrombin time is moderately prolonged.

⁷Patients are uniquely named, except for 'Vancouver, Fr' and 'Angers', where the authors have not distinguished different patients with the same mutation.

⁸The position of insertions (*Ins*) corresponds to the first nucleotide of the inserted base. E.g. In Recklinghausen, 114, *Ins* AT, patient identity number = 17, the inserted dinucleotide AT occupies nucleotides 114 and 115 and displaces the residues normally found there, which now become residues 116 and 117.

⁹Or, 31,111-3, or 31,112-4, or 31,113-5.

¹⁰The PIN number is a patient identification number, used as an aid to patient identification now and in the future. It is not the intention that the PIN number should 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. The reason for the slightly higher number of PINS (576) than patient entries (574) is because of amalgamation

of separate entries. This arose as originally separate studies are now known to refer to one and the same patient, or to patients related by pedigree.

¹¹Mutations which have occurred more than once have been summarized. Factor IX clotting and antigen levels have been entered as an average of the available figures. The comments column gives the number of repeats reported plus any further comments that may relate to individual patients.