Haemophilia B: database of point mutations and short additions and deletions—fourth edition, 1993

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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 Brownlee 1988, Giannelli 1989, Thompson 1990, Green *et al* 1991a) 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*, 1992) 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 It is not intended to replace primary publications although it does contain a significant amount of unpublished work.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 that were reported more than 5 times. 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 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. 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 an O-linked carbohydrate at least at serine 53 and 61 (Hase *et al*, 1988; Nishimura *et al*, 1992).

There are 806 patient entries in this fourth edition of the database compared with 574 patients last year (Giannelli *et al*, 1992). Besides point mutants, it includes 72 short (defined as less than 20 nucleotides) deletions or additions or both, made up from 54 deletions, 15 additions and 3 examples involving both additions and deletions. There are also 13 double mutations, 1 triple mutation, 12 inhibitor patients and 7 female haemophiliacs. The list excludes the 29 patients with partial or complete gene deletions or more complex rearrangements (Thompson, 1990)

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	6	6
Propeptide (-17 to -1)	b	6,326-6,375	54	6
Gla (1 to 46)	b c	6,376-6,489 6,678-6,701	66	43
EGF (1st) (47 to 84)	d	10,392-10,505	71	35
EGF (2nd) (85 to 127)	e	17,669-17,797	40	32
activation (128 to 195)	f	20,363-20,565	94	37
catalytic (196 to 415)	g h	30,039-30,153 30,822-31,372	45 354	24 146
Subtotal			730	329
Promoter			21	13
Donor splice sites			28	18
Acceptor splice sites			19	15
Cryptic splice ⁴			8	4
Poly(A) site			0	0
Totals			806	378

¹ Amino acid numbers used (Anson et al, 1984)² Excluding normal variants within double mutants³ For numbering, see Yoshitake et al (1985)⁴ These are possible new splice sites within exons

and others observed since. Of the 806 patients studied (see Summary Table), 378 are unique molecular events, the remainder being 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.* 41 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.* 30 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 (see Summary Table) shows that

mutations have been detected in all categories listed except the poly(A) site. Remarkably, there are now 13 molecularly unique mutants occurring within a short region of the promoter, and these are invaluable in studying gene regulation (Crossley et al, 1992). Missense mutations within exons give valuable information as to the importance of particular amino acid residues. The present list contains 234 different amino acid substitutions. Fifty three 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 7 of the 12 γ carboxyglutamyl 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 153 missense mutations were added, of which 58 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 reformatted and transferred to the EMBL file server during 1993.

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 as follows: Giannelli and Green representing the UK, Sweden and Iceland; High and Sommer representing USA; Poon representing Canada; Ludwig and Schwaab representing Germany; Reitsma representing The Netherlands; Goossens representing France; Yoshioka representing Japan; 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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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, LF-A1/HNF4- binding site, ARE	Ludwig et al	395
Leyden 1	<1–60 ⁵	<1–60	–20, T→A	None	Promoter	Crossley et al (1992)	2
Datteln	<1–36 ⁵	<1–36 ⁵	–20, T→A	None	Promoter, LF-A1/HNF4- binding site	Reitsma et al (1988)	3
Marseille	7–20 ⁵		–20, T→C	None	Promoter, de novo in MGF	Ludwig et al	
High Wycombe	13–70 ⁵		–6, G→A ⁴	None	Promoter	Ghanem et al (1993)	396
Leyden, USA1	10	13	–6, G→A ⁴	None	Promoter	Crossley et al (1990)	4
Calgary 18		–6, G→A ⁴	None	Promoter	Poon et al (1993)	Hirosawa et al (1990)	5
Rodez	1→norm ⁵		–6, G→A ⁴	None	Promoter	577	
Toulouse	1→30 ⁵	1–30 ⁵	–6, G→C	None	Promoter	Ghanem et al (1993)	578
Toronto 20	3		–5, A→T	None	Promoter	Gispert et al (1989)	6
UK 110	15		–5, A→G	None	Promoter	Picketts et al	7
UK 161	7		–5, A→G	None	Promoter	Saad, Rowley et al	579
Bangkok	5		6, 7 or 8, Δ1	None	Promoter	Saad, Rowley et al	580
Leyden, USA2	<2–37 ⁵		6, T→A	None	Promoter	Hall et al (1992)	581
Leyden, NZ	1–32 ⁵		8, T→C	None	Promoter	Freedenberg, Black (1991)	397
					Promoter, C/EBP binding site, de novo in mother	Royle et al (1990)	8
Leyden 2 <1–60 ⁵	<1–60 ⁵	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
Poitiers	12–norm ⁵		13, A→G	None	Promoter	Ghanem et al (1993)	398
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 et al (1993)	399
UK 22	2	<1	79, T→A	–30, I→N	Signal peptide	Green et al (1992b)	15
Toronto 23	<1		89, Δ1	–27	Frameshift	Lillicrap & Windsor	582
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)	Green, Montandon et al	16
Meaux	<1		112, Δ1	–19	Frameshift	Ghanem et al (1993)	401
Recklinghausen	<1	<1	114, Ins AT	–18	Frameshift	Ludwig et al	17
HB64	<1	2	117, G→A	–17, V→I	Donor splice (a)?	Bottema et al (1991a)	402
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, Rowley et al	404
Spain	<1		6,325, G→T		Acceptor splice (b)	Ghanem et al (1993)	405
(footnote 11)	1.8 ¹¹	34 ¹¹	6,364, C→T ⁴	–4, R→W	16 cases	Ref N ^{os} : (12,43,47,48,53, 65,77,84,108) PINs: (19–28, 406–8, 583–5)	
(footnote 11)	<1 ¹¹	43 ¹¹	6,365, G→T	–4, R→L	6 cases	Ref N ^{os} : (43,67,84) PINs: (30–32, 409, 410)	
(footnote 11)	<1 ¹¹	57 ¹¹	6,365, G→A ⁴	–4, R→Q	29 cases. Abnormal carboxylation, circulates with propeptide	Ref N ^{os} : (5,9,13,17,22,30, 43,47,57,67,70,74,75, 84,99,113,125, 136,140,146) PINs: (33–45, 411–8, 586–94)	
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 (1993)	595
NZ 14	23		6,385, G→A	4, G→S		Van de Water et al	596
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
Malmö 8	<1	<0.1	6,398-9, Δ2	8	Frameshift, de novo in MGF or MGM	Green et al (1991b)	50
Tours	<1	<0.1	6,398-9, Δ2	8	Frameshift	Ghanem et al (1993)	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, Rowley et al	597
UK 84	14	118	6,400, T→A	9, F→I		Green, Montandon et al	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
Los Angeles 4	<1	48	6,409, G→A	12, G→R		High et al (1993)	598
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, Rowley et al	599
HB299 (Kutahya)	0.4	<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
Le Mans	<1		6,424, G→A	17, E→K	Gla	Ghanem et al (1993)	424
Heessen	<1		6,427, T→C	18, C→R	de novo in mother(25)	Ludwig et al (1992a)	56
Zutphen	<1	100	6,427, T→C	18, C→R		Reitsma et al	57
HB116	<1		6,428, G→A	18, C→Y		Bottema et al (1991a)	425
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, Rowley et al	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		Green, Montandon, et al	58
Rheidt	2	32	6,449, T→C	25, F→S	de novo in MGF(27) or MGM(24)	Ludwig et al (1992a)	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, de novo in mother	Wang et al (1990b)	61
(footnote 11)	<1 ¹¹	<1 ¹¹	6,460, C→T ⁴	29, R→Stop	16 cases including 2 inhibitors	Ref N ^{os} : (27,48,49,52,67,70,76,86,91,116,139,153) PINs: (62-69, 428-31, 602-5)	
(footnote 11)	22 ¹¹	73 ¹¹	6,461, G→A ⁴	29, R→Q	7 cases including 4 with double mutation (see 30,134)	Ref N ^{os} : (20,43,54,68,69,137,143) PINs: (70-72, 432-4, 606)	
HB172	1		6,463, G→A	30, E→K	Gla de novo MGM (38)	Ketterling et al (1993)	607
Malmö 9	<1	<0.1	6,466, Δ1	31	Frameshift	Green et al (1991b)	73
UK 180			6,472, Ins GG	33	Frameshift	Saad, Rowley et al	435
UK 111	<1		6,472, G→T	33, E→Stop		Saad, Rowley et al	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, Rowley et al	436
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 et al (1991b)	78
UK 83	<1	1	6,491-4 or 6,492-5, Δ4		Donor splice (b)	Green, Montandon et al	79
Paris 1	<1		6,494, G→A		Donor splice (b)	Ghanem et al (1993)	437
NZ 13	1		6,494, G→A		Donor splice (b)	Van de Water et al	609
HB74/77	1	1	6,495, T→C		Donor splice (b)	Bottema et al (1990c)	80
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, Rowley et al	611
HB7, Japan	<1	<1	6,680-1, Δ2	39	Frameshift, Inhibitor	Matsushita et al (1990)	82
UK 156	2		6,688, G→A	42, W→Stop		Saad, Rowley et al	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, Rowley et al	614
UK 25	<1	<1	6,702, G→A	47, 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
Nantes	3,13		6,704, T→C	Donor splice (c), female to female transmission	Ghanem et al (1993)	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, Rowley et al	616
HB197	<1	27	10,389, A→G	Acceptor splice (d), de novo MGF (27)	Ketterling et al. (1993)	617
Toronto 16 (HB53)	3		10,391, G→A	Acceptor splice (d)	Koeberl et al (1990a)	87
Alabama	10	100	10,392, A→G		Davis et al (1987)	88
HB75	14	80	10,393, T→A		Bottema et al (1990c)	89
Oxford d3	1	90	10,393, T→A		Winship & Dragon (1991)	90
Tainan	28	101	10,394, G→A		Lin & Shen (1991)	441
Malmö 27	19	108	10,395, G→T	de novo in mother	Green et al (1991b)	91
UK 86			10,397-9,Δ3,Ins A	Frameshift	Green, Montandon et al	92
Clermont	<1		10,400, C→T		Costes et al	618
New London	<1	114	10,401, A→C	Decreased XIa activation	Lozier et al (1990)	93
UK 175	30		10,405, T→G	Female carrier	Saad, Rowley et al	619
Lhuis	<1	<1	10,405, T→G		Ghanem et al (1993)	620
HB97	<1	20	10,406, G→T		Bottema et al (1991a)	442
GER 5	<1		10,406, G→T	de novo in mother (23)	Knobloch & Zoll	621
Hollywood	11	58	10,415, C→G		Spitzer et al (1990b)	94
UK 7	10-12	49	10,415, C→G		Green et al (1989)	95
Unnamed	10	<30	10,415, C→G		Chen et al (1991a)	96
Malmö 21	12	52	10,415, C→T		Green et al (1991b)	97
Malmö 22		26	10,416, C→T		Green et al (1991b)	98
HB180	6	34	10,416, C→A	de novo MGF (38)	Ketterling et al. (1993)	622
Basel	<1		10,418, T→C		Alkan et al (1991)	99
Kleve	<1	<1	10,419, G→C		Ludwig et al (1991)	100
Toronto 2 (HB32)	1	2	10,419, G→A		Koeberl et al (1990a)	101
UK 160	18		10,427, G→A		Saad, Rowley et al	443
HB141	2		10,428, G→T	De novo in mother(40)	Bottema et al (1991b)	444
(footnote 11)	13 ¹¹	29 ¹¹	10,430, G→A ⁴	29 cases	Ketterling et al (1993)	
			60, G→S		Ref N ^{os} : (19-21,32,49,65, 68,69,102,104,106,136, 139,152)	
					PINs: (102-12, 390-1, 445-57, 624-6)	
HB154	<1	6	10,430, G→C		Bottema et al (1991b)	458
Toronto 6 (HB37)	1	2	10,431, G→A		Koeberl et al (1990a)	113
UK 176			10,437, G→A		Saad, Rowley et al	627
Oxford d1	3	117	10,442, G→A	β Hydroxyaspartate	Winship & Dragon (1991)	114
UK 6	8	87	10,443, A→G	β Hydroxyaspartate	Green et al (1989)	115
Madrid 4	5		10,449, T→C		Damas et al	628
Rouen	30		10,449, T→C		Ghanem et al (1993)	629
Trier	<1		10,458, A→G	Haplotype differs from GER 6	Ludwig et al	116
GER 6	<1		10,458, A→G	de novo in mother (33), Haplotype differs from 116	Knobloch & Zoll	630
Murten	<1		10,458, A→G		Ghanem et al (1993)	631
Almere			10,463, T→A		Deutz et al	632
UK 167			10,464, G→C		Saad, Rowley et al	633
UK 200	6		10,466, T→A		Saad, Rowley et al	634
UK 150			10,466, T→A		Saad, Rowley et al	635
Fort de France	<1		10,468, G→A		Ghanem et al (1993)	636
GER 7	<1		10,470, G→A		Knobloch & Zoll	637
Paris 3	<1		10,471, T→A		Ghanem et al (1993)	638
UK 67	6	12	10,479, G→T	Female carrier	Green, Montandon et al	117
UK 19			10,482, T→G		Green, Montandon et al	118
UK 132			10,507-10, Δ4		Green, Montandon et al	119
Toronto 8 (HB39)	2	3	10,512, A→G	Donor splice (d), normal carrier female	Koeberl et al (1990a)	120
Paris 5	<1		10,512, A→G	Double (see 30,864),N?	Ghanem et al (1993)	639
HB131	<1	<1	10,512, A→G	Double (see 17,799),N?	Bottema et al (1991b)	438
HB6	20		17,660-3, Δ 4	Triple (see 6575 & 30,897), N?		
Toronto 14 (HB48)	3	3	17,667, A→G	Acceptor splice (e)	Koeberl et al (1989)	121
Malmö 11	<1	<1	17,668, G→C	Acceptor splice (e)	Koeberl et al (1990a)	122
				Acceptor splice (e), de novo in MGF	Green et al (1991b)	123
Seattle 2	<1	<1	17,669, Δ1	Frameshift	Schach et al (1987)	124
HB147	2	2	17,669-75 Δ7	Frameshift de novo mother (33)	Ketterling et al. (1993)	640
UK 98	<2		17,677, T→C		Saad, Rowley et al	641
Königswinter	<1		17,678, G→C		Ludwig et al	125
UK 125	15		17,684, T→C		Saad, Rowley et al	642
Fukuoka	2	66	17,689, A→C ²		Nishimura et al (1991)	126
Chelles	<1		17,691, T→A		Ghanem et al (1993)	459

Amiens	<1		17,691, T→A	92, N→K		Ghanem et al (1993)	460
HB256	3	22	17,692, G→A	93, G→S	de novo mother (27)	Ketterling et al. (1993)	643
HB106	1	84	17,697, A→T	94, R→S		Bottema et al (1991a)	461
HB134	5		17,699, G→A	95, C→Y		Bottema et al (1991b)	462
HB157	<1	6	17,699, G→A	95, C→Y	Haplotype differs from 462	Bottema et al (1991b)	463
Edmonton 1	<1		17,700, C→A	95, C→Stop		Tam et al (1991)	127
Malmö 51	<1		17,700, C→G	95, C→W		Ljung et al	464
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
UK 243	<1		17,717, Ins A	101	Frameshift	Saad, Rowley et al	646
NZ 4	<1		17,718, Ins A	101	Frameshift	Van de Water et al	465
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 (1991b)	130
Malmö 42	20	24	17,736, G→A	107, None	cryptic splice?	Green et al (1991b)	131
Malmö 37	15	24	17,736, G→A	107, None	cryptic splice?	Green et al (1991b)	132
Malmö 55	18		17,736, G→A	107, None	cryptic splice?	Ljung et al	647
Malmö 56	17		17,736, G→A	107, None	cryptic splice?	Ljung et al	648
Unnamed	20	120	17,738, T→C	108, V→A		Chen et al (1991a)	133
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
Calgary 24	<1		17,754, 5 or 6 Δ1	114 or 115	Frameshift	Poon et al (1993)	651
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
UK 123	2	1	17,759, A→G	115, Y→C		Saad, Rowley et al	467
Malmö 7	<1	<0.1	17,761, C→T ⁴	116, R→Stop	Double (see 30,890), de novo in MGF	Montandon et al (1990a)	137
HB149	<1	3	17,761, C→T ⁴	116, R→Stop		Bottema et al (1991b)	468
Taipei 6	<1	<6	17,761, C→T ⁴	116, R→Stop		Lin et al (1993)	652
UK 112	<1		17,761, C→T ⁴	116, R→Stop		Saad, Rowley et al	653
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, 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
GER 2228A			17,778, G→T	121, Q→H		Wulff, Herrmann et al	654
NZ 9	18		17,778, G→T	121, Q→H		Van de Water et al	655
UK 246	<1		17,782, T→C	123, S→P		Saad, Rowley et al	656
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
Nörtingen	<1		17,798, G→T		Donor splice (e), de novo in MGF(27)	Ludwig et al (1992a)	141
Unnamed	<1	<1	17,798, G→T		Donor splice (e), de novo in mother	Thompson et al (1992b)	661
UK 102	<1		17,799, T→G	Donor splice (e)		Saad, Rowley et al	662
Paris 5	<1		17,799, T→C		Donor splice (e), double (see 10,512)	Ghanem et al (1993)	639
(footnote 11)	10 ¹¹	5 ¹¹	17,810, A→G		6 cases. New donor splice? Ref Nos: (53,69,102,116)		
GER 12			20,372, C→T	131, P→L		PINs: (142-4, 664-6)	
Dakar	<1	<1	20,374, T→C	132, C→R		Knobloch & Zoll	667
Taipei 7	<1	<6	20,374, T→C	132, C→R		Vidaud (1990)	145
JieLong 2	<1	<6	20,374, T→C	132, C→R		Lin et al (1993)	668
Malmö 12	<1	<0.1	20,375, G→T	132, C→F		Lin et al (1993)	669
GER 13	<1		20,375, G→T	132, C→F		Green et al (1991b)	146
HB115	<1		20,375, G→A	132, C→Y		Knobloch & Zoll	670
ChangHua 1	<1	<6	20,375, G→A	132, C→Y	Bottema et al (1991a)	471	
UK 78	<1		20,375, G→C	132, C→S		Lin et al (1993)	671
Chapel Hill 2	4	4	20,377, G→A	133, G→R		Saad, Rowley et al	672
UK 166	<1		20,380-1, Δ2	134		High et al (1993)	673
HB145	<1	<1	20387-8 Δ2	136	Frameshift	Saad, Rowley et al	674
HB179	2	<1	20387-8 Δ2	136	Frameshift, de novo in MGF (32)	Ketterling et al. (1993)	675
Malmö 44			20,398, Δ1	140	Frameshift, haplotype differs from HB145 de novo in mother (30)		
(footnote 11)	3 ¹¹	41 ¹¹	20,413, C→T ⁴	145, R→C	Frameshift, de novo in MGF or MGM	Green et al (1991b)	147
					16 cases. Decreased XIa activation	Ref Nos: (51,67,73,102, 116,135,137,141,143,152)	
						PINs: (148-52, 472-6, 677-82)	

(footnote 11)	6 ¹¹	113 ¹¹	20,414, G→A ⁴	145, R→H	17 cases. Decreased XIa activation	Ref N ^{os} : (11–13,28,35, 51,56,68,77,79,97,116, 126,143) PINs: (153–62, 477–9, 684–7)	
Toronto 21	7	60	20,414, G→T	145, R→L	Also 9,786, A→C in intron	Picketts et al (1990)	480
HB23	<1		20,466–78, Δ13	162	Frameshift, de novo in MGM (23)	Koerberl et al (1989) Ketterling et al (1993)	163
HB17	<1		20,497, C→T	173, Q→Stop		Koerberl et al (1989)	164
HB78	2	<1	20,501, Δ1	174	Frameshift, de novo in mother (26)	Bottema et al (1990c) Ketterling et al (1993)	165
Malmö 13	<1	0.5	20,510, Δ1	177	Frameshift	Green et al (1991b)	166
Brest	<1	85	20,512, T→C	178, F→L	Double (see 20,518), N?	Ghanem et al (1993)	167
(footnote 11)	<1 ¹¹	88 ¹¹	20,518, C→T ⁴	180, R→W	11 cases including 5 B _m	Ref N ^{os} : (6,31,37,43,56, 66,84,125,136) PINs: (168–73, 481–4, 690)	
Brest	<1	85	20,518, C→G	180, R→G	Double (see 20,512)	Ghanem et al (1993)	167
Madrid	<1	90	20,518, C→G	180, R→G	B _m	Solera et al (1991)	174
(footnote 11)	<1 ¹¹	112 ¹¹	20,519, G→A ⁴	180, R→Q	8 cases including 3 B _m , decreased XIa activation	Ref N ^{os} : (6,11,62,86,90, 102,139,145) PINs: (175–80, 485, 691)	
Taipei 8	<1	73	20,519, G→T	180, R→L		Lin et al (1993)	692
Creston 1	<2		20,519, G→C	180, R→P		Ritchie et al	486
Milano	<1	130	20,521, G→T	181, V→FB _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
UK 131	4,7		20,524, G→C	182, V→L		Saad, Rowley et al	693
Kashihara	<1	120	20,524, G→T	182, V→F	B _m ⁶	Sakai et al (1989)	183
Tokyo	23	100	20,525, T→C	182, V→A	B _m ⁶	Nishimura et al (1990)	694
UK 54	<1	97	20,527–9, Δ3	183, ΔG	In frame	Maekawa et al (1991)	487
Unnamed	<1	100	20,530, G→A	184, G→R		Green, Montandon et al	184
Bottrop 1	<1	92	20,531–3, Δ3	184, ΔG	In frame	Thompson et al (1992b)	695
UK 179	1		20,548, G→T	190, G→C		Ludwig et al	185
HB5 Japan	<1	<1	20,551, C→T	191, Q→Stop	Inhibitor, Double (see –793)	Saad, Rowley et al	696
Unnamed	<1	<1	20,551, C→A	191, Q→K		Matsushita et al (1990)	1
Seattle J	3	2	20,553, A→G	191, None	Cryptic splice	Chen et al (1991a)	186
NanTou 1	2	<6	20,554, T→G	192, F→V		Thompson et al (1992a)	488
Seattle K	4		20,560, T→C	194, W→R		Lin et al (1993)	697
Seattle L	<1	1	20,560, T→A	194, W→R		Thompson et al (1992a)	489
Malmö 5	<1	<0.1	20,561, G→A	194, W→Stop	Inhibitor	Thompson et al (1992a)	490
UK 114			20,561, G→A	194, W→Stop	Normal carrier female	Green et al (1989)	187
UK 44	<1	2	20,561, G→A	194, W→Stop		Green, Montandon et al	188
UK 233	<1		20,562, G→A	194, W→Stop		Saad, Rowley et al	491
Unnamed	<1	<1	20,563, C→T	195, Q→Stop		Saad, Rowley et al	698
Unnamed	<1	<1	20,564, A→G	195, Q→R		Thompson et al (1992b)	699
Oxford 1	<0.5	0.3	20,566, G→T		Donor splice (f)	Ludwig et al	189
Rotenburg	<1	<1	20,566, G→A		Donor splice (f)	Rees et al (1985)	190
UK 171	<1		30,038, G→A		Acceptor splice (g)	Ludwig et al	191
HB102	<1	<1	30,038, G→C		Acceptor splice (g)	Saad, Rowley et al	492
Calgary 22	21	19	30,038, G→C		Acceptor splice (g), female	Bottema et al (1991a)	493
UK 192	2		30,046, T→G	198, L→W		Poon et al (1993)	700
HB188	<1	<1	30,046, T→C	198, L→S	de novo in MGF (21)	Saad, Rowley et al	494
Paris 4			30,058, Δ4	202	Frameshift	Ketterling et al. (1993)	701
GER 16	<1		30,069, T→C	206, C→R	de novo in MGF	Ghanem et al (1993)	702
UK 169	<1		30,069, T→C	206, C→R		Knobloch & Zoll	703
Toronto 19	<1	<1	30,070, G→C	206, C→S		Saad, Rowley et al	704
UK 117			30,070, G→C	206, C→S		Taylor et al (1990)	192
HB142	<1		30,070, G→A	206, C→Y		Saad, Rowley et al	705
UK 43	<1		30,072, G→A	207, G→R		Bottema et al (1991b)	495
Luanda	1		30,072, G→A	207, G→R		Green, Montandon et al	193
Unnamed	<1	<1	30,072, G→T	207, G→Stop		David et al	706
Taipei 9	<1	56	30,073, G→A	207, G→E		Thompson et al (1992b)	707
UK 37		1	30,076, G→A	208, G→D		Lin et al (1993)	708
Wülschkau	7		30,084, G→T	211, V→F		Green, Montandon et al	194
Unnamed	4		30,084, G→T	211, V→F		Ludwig et al	195
Bottrop 2	<1	<1	30,090, G→T	213, E→Stop		Chen et al (1991a)	196
HB72	4	<1	30,096, T→C	215, W→R		Ludwig et al	197
Newcastle 1	4		30,096, T→C	215, W→R	Lillicrap et al	Bottema et al (1990c)	198
Unnamed	<1	0.1	30,097, G→A	215, W→Stop		496	
TaiDung	<1	<6	30,098, G→T	215, W→C		Chen et al (1991a)	199
Unnamed	4		30,100, T→C	216, I→T		Lin et al (1993)	709
HB41	7		30,100, T→C	216, I→T		Chen et al (1991a)	200
Malmö 39	4	4	30,100, T→C	216, I→T		Koerberl et al (1990a)	201
GER 17			30,100, T→C	216, I→T		Green et al (1991b)	202
						Knobloch & Zoll	710

HB65	15	4	30,101, T→G	216, I→M		Bottema et al (1991a)	497
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	Same haplotype as 203	Koeberl et al (1990a)	204
Calgary 8	11	15	30,112, C→T	220, A→V		Poon et al (1993)	711
UK 93	2		30,117, T→A	222, C→S		Saad, Rowley et al	498
HB24	1		30,119, T→G	222, C→W		Koeberl et al (1989)	205
Toronto 17 (HB58)	37		30,134, T→C	None	Double, (see 6,461), N	Koeberl et al (1990a)	70
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 (1991a)	72
(footnote 11)	14 ¹¹	13 ¹¹	30,150, G→A ⁴	233, A→T	12 cases including 1 female carrier	Ref N ^{os} : (20,51,68,79,86,116,129) PINs: (206-14, 499, 712-3)	
Caen 3	<1	<1	30,152, Ins A	233	Frameshift	Ghanem et al (1993)	714
Iceland 1	3	119	30,800, Ins A	None	Double (see 31,119), N	Green et al (1992a)	215
Beauvais 1			30,800, Ins A	None	Ghanem et al (1993)	715	
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 (1991b)	217
HB114	<1		30,821, G→A		Acceptor splice (h)	Bottema et al (1991a)	500
UK 95	6,10		30,821, G→A	Female carrier	Acceptor splice (h)	Saad, Rowley et al	716
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 (1992b)	219
UK 140	<1		30,857, Δ1	246	Frameshift	Saad, Rowley et al	501
(footnote 11)	<1 ¹¹	<1 ¹¹	30,863, C→T ⁴	248, R→Stop	15 cases including 1 inhibitor	Ref N ^{os} : (13,15,48,51,52,69,86,102,130,146) PINs: (220-9, 502-5, 717)	
(footnote 11)	5 ¹¹	5 ¹¹	30,864, G→A ⁴	248, R→Q	20 cases including 1 double (see 10,512)	Ref N ^{os} : (12,15,19,20,28,43,69,85,102,116,139) PINs:(120, 230-3, 392, 506-12, 718-24)	
UK 92	<1		30,873, T→A	251, I→N		Saad, Rowley et al	725
(footnote 11)	<1 ¹¹	<1 ¹¹	30,875, C→T ⁴	252, R→Stop	12 cases	Ref N ^{os} : (12,16,18,38,43,51,52,66,101,116,119,131) PINs: (234-40, 513-4, 726-8)	
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
HB131	<1	<1	30,897, A→G	259, Y→C	Triple (see 6575 & 10,512), de novo in MGF (29)	Bottema et al (1991b)	438
HB8	24		30,900, A→G	260, N→S		Ketterling et al (1993)	242
NZ 12	9		30,900, A→G	260, N→S		Van de Water et al	623
UK 88	7		30,924, A→G	268, H→R		Green, Montandon et al	243
GER 18	1.5		30,926, G→A	269, D→N	de novo in mother (38)	Knobloch & Zoll	688
Malmö 50	<1		30,927, A→T	269, D→V	Proposed active site Asp	Ljung et al	515
UK 152			30,927, A→G	269, D→G	Proposed active site Asp	Saad, Rowley et al	689
UK 138	<1		30,927, A→G	269, D→G	Proposed active site Asp	Saad, Rowley et al	729
Besançon 2	<1		30,927, A→G	269, D→G	Proposed active site Asp	Ghanem et al (1993)	730
HB208	<1	5	30,928, C→A	269, D→E	de novo mother (34)	Ketterling et al. (1993)	731
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
HB96	<1	<1	30,930, T→C	270, I→T		Bottema et al (1991a)	516
Toronto 1 (HB31)	1	4	30,933, C→T	271, A→V		Koeberl et al (1990a)	246
UK 75	16		30,933, C→T	271, A→V		Saad, Rowley et al	732
UK 237	20		30,933, C→T	271, A→V		Saad, Rowley et al	733
HB143	<1	2	30,936, T→G	272, L→R	De novo in MGF (23)	Bottema et al (1991b)	517
UK 48			30,942, Δ1	274	Frameshift, normal carrier female	Ketterling et al (1993)	
San Antonio	<1	14	30,945, T→C	275, L→P		Green, Montandon et al	247
HB101	<1	<1	30,945, T→C	275, L→P		Jagadeeswaran	248
Malmö 1	<1	<0.1	30,950-7, Δ 8	277	Frameshift, Inhibitor	Bottema et al (1991a)	518
Zoeterwoude	13	13	30,956,	T→A279, L→I		Green et al (1989)	249
Mantes-la-Jolie	<1		30,957, T→C	279, L→S		Reitsma et al	250
Unnamed	<1	<1	30,981, C→T	287, P→L		Ghanem et al (1993)	734
GER 2234A			30,981, C→A	287, P→H		Chen et al (1991a)	251
HB109	<1	<1	30,985, T→G	288, I→M		Wulff, Herrmann et al	735
UK 58	2		30,987, G→T	289, C→F		Bottema et al (1991a)	519
Oxford h2	2	3	30,992, G→C	291, A→P		Saad, Rowley et al	736
UK 13	10		30,992, G→A	291, A→T		Winship & Dragon (1991)	252
UK 33	7	19	30,992, G→A	291, A→T		Montandon et al (1989)	253
UK 41	9	11	30,992, G→A	291, A→T		Green et al (1992a)	254
UK 71	7	10	30,992, G→A	291, A→T		Green et al (1992a)	255
UK 239	10		30,992, G→A	291, A→T		Saad, Rowley et al	520
HB100	<1	<1	31,001, G→T	294, E→Stop	De novo in MGM (24)	Saad, Rowley et al	737
						Bottema et al (1991a)	521

UK 72	<1		31,004, Ins CA	295	Frameshift	Ketterling et al (1993)	738
Fumel	<1		31,005, A→G	295, Y→C		Saad, Rowley et al	739
GER 2121C			31,007, Δ1	296	Frameshift	Ghanem et al (1993)	740
(footnote 11)	5 ¹¹	8 ¹¹	31,008, C→T ⁴	296, T→M	41 cases	Wulff, Herrmann et al	741
						Ref N ^{os} : (20,49,51,52,59, 64-5,67-9,79,86,102, 114,116,130,136,139, 143,152)	
						PINs: (256-74, 393-4, 522-31, 742-52)	
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 (1992a)	533
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 (1991a)	277
Seattle P	14	50	31,041, T→C	307, V→A	Same haplotype as 277	Thompson et al (1992a)	534
Malmö 26	3	4	31,041, T→G	307, V→G		Green et al (1991b)	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
Cenon	<1		31,047, G→A	309, G→D		Ghanem et al (1993)	753
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
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 (1991)	285
NZ 6	<1		31,051, G→A	310, W→Stop		Van de Water et al	535
GER 21	3		31,051, G→C	310, W→C	de novo in mother (28)	Knobloch & Zoll	755
HB250	<1	5	31,051, G→C	310, W→C	de novo MGF (22)	Ketterling et al (1993)	756
HB26	3		31,052, G→A	311, G→R		Koeberl et al (1989)	286
HB139	2	100	31,052, G→A	311, G→R	Same haplotype as 286	Bottema et al (1991b)	536
Amagasaki	<1	100	31,053, G→A	311, G→E	B _m ⁶	Miyata et al (1991)	287
UK 137	<1	100	31,059, T→G	313, V→G	Green, Montandon et al	288	
Kiryu	2.5	100	31,059, T→A	313, V→D	B _m	Kuze et al (1992)	757
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
UK 143			31,071, G→A	317, G→E	Female carrier	Saad, Rowley et al	758
Toronto 7 (HB38)	<1	90	31,080, C→A	320, A→D		Koeberl et al (1990a)	291
UK 147	4		31,080, C→A	320, A→D		Saad, Rowley et al	537
NZ 7	3		31,080, C→A	320, A→D		Van de Water et al	538
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
Oxford h5	4	4	31,103, G→T	328, V→F		Winship (1990)	292
GER 22			31,103, G→T	328, V→F	de novo in MGF	Knobloch & Zoll	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		Green, Montandon et al	293
Ratingen 2	<1	<1	31,110-12, Δ3 ⁹	331, ΔV	In frame	Ludwig et al	294
GER 23	<1		31,110-12, Δ3 ⁹	331, ΔV	In frame, de novo in mother (19)	Knobloch & Zoll	761
Oxford h1	7	96	31,113, T→C	331, V→A		Winship & Dragon (1991)	295
Brünov	4		31,115, G→T	332, D→Y	Same haplotype as GER 24	Ludwig et al	296
GER 24			31,115, G→T	332, D→Y	Same haplotype as 296	Knobloch & Zoll	762
NZ 10	3		31,115, G→T	332, D→Y		Van de Water et al	763
(footnote 11)	<1 ¹¹	<1 ¹¹	31,118, C→T ⁴	333, R→Stop	16 cases including 1 female carrier	Ref N ^{os} : (12,20,28,43,66, 70,77,79,86,93,106,116)	
						PINs: (297-303, 541-3, 764-9)	
HB83	13	70	31,118, C→G	333, R→G		Bottema et al (1990c)	304
HB153	<1	63	31,118, C→G	333, R→G	Haplotype differs from 304	Bottema et al (1991b)	544
HB110	2	150	31,119, G→T	333, R→L		Bottema et al (1991a)	545
(footnote 11)	2 ¹¹	88 ¹¹	31,119, G→A ⁴	333, R→Q	19 cases including 1 double (see 30,800)	Ref N ^{os} : (12,20,28,43,48, female carrier, and 102,103,116,136,142,146)	49,52,84,86,99,
						PINs: (215, 305-15, 546-8, 770-3)	
Hong Kong 6	9	100	31,122, C→A	334, A→D		Chan et al (1991)	316
Malmö 57	27		31,122, C→A	334, A→D		Ljung et al	774
UK 8	2	2	31,127, T→C	336, C→R		Green et al (1989)	317
UK 139	<1		31,127, T→C	336, C→R		Saad, Rowley et al	549
Unnamed	<1	5	31,127, T→C	336, C→R		Chen et al (1991a)	318
UK 94	1		31,127, T→C	336, C→R		Saad, Rowley et al	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 (footnote 11)	4 <1 ¹¹	120 <1 ¹¹	31,130, C→A 31,133, C→T ⁴	337, L→I 338, R→Stop	10 cases including 1 double (see 48)	Fraser et al (1992) Ref N ^{os} : (36,41,49,78,82, 101,129) PINs: (320–6, 399, 777–8)	550
GER 26 HB241 UK 170	10 <1		31,134, G→C 31,140, C→G 31,141, 2 or 3 Ins AA	338, R→P 340, T→R 340 or 341	de novo in MGF (27) Frameshift, normal carrier female Frameshift	Knobloch & Zoll Ketterling et al. (1993) Saad, Rowley et al	779 780 551
Samli	<1	<1	31,149–51, Δ3 31,158–62, Δ5 31,158, Ins G	343		Ludwig et al	327
Gladbeck Unnamed	4 <1	87 <1	31,151, A→T 31,157, 8 or 9 Ins AA	344, I→F 346	Frameshift	Ludwig et al Chen et al (1991b)	328 329
Seattle R	<1	<1	31,157, 8 or 9 Ins AA	346	Frameshift	Thompson et al (1992a)	552
UK 135			31,157–9 or 31,160–2 Δ3	346 or 347 ΔN	In frame	Saad, Rowley et al	553
HB108 Unnamed HB124	<1 3 <1	2 103 40	31,161, A→T 31,163, A→G 31,165, G→A	347, N→I 348, M→V 348, M→I	De novo in MGF (28)	Bottema et al (1991a) Chen et al (1991a) Bottema et al (1991a) Ketterling et al (1993)	554 330 555
Offenbach	<1		31,166 or 7, Δ1	349	Frameshift, de novo in MGM(29)	Ludwig et al (1992a)	331
Kingston 4 UK 17 Malmö 47 GER 27	35 <1 <1 <1	45 <1	31,170, G→C 31,170, G→A 31,194–5, 2	350, C→S 31,170, G→A 350, C→Y 358	Somatic mosaic 350, C→Y Frameshift, de novo in mother (18)	Taylor et al (1991) Green, Montandon et al Ljung et al Knobloch & Zoll	332 333 556 781
GER 28 Unnamed UK 164 Bordeaux 2 Poissy Modane Madrid 5 UK 144 Los Angeles 2 Eagle Rock Seattle S UK 35 NZ 8 Mechtal HB80 UK 30 Unnamed Varel	1.5 2 1 <1 1.5 <1 <1 <1 1–5 3 2 <1 <1 2 2 <1 <1	130 100 53 100 130 89	31,197, A→G 31,200, C→T 31,200, C→T 31,200, C→T 31,200, C→G 31,200, C→G 31,202, T→C 31,208, G→T 31,208, G→A 31,209, G→T 31,209, G→C 31,209, G→A 31,209, G→A 31,211, G→C 31,211, G→C 31,211, G→A 31,212, A→T 31,213–14, TA→CG	359, D→G 360, S→L 360, S→L 360, S→L 360, S→Stop 360, S→Stop 361, C→R 363, G→Stop 363, G→R 363, G→V 363, G→A 363, G→E 363, G→E 364, D→H 364, D→H 364, D→N 364, D→V 365, S→G	De novo in MGF	Knobloch & Zoll Chen et al (1991a) Saad, Rowley et al Ghanem et al (1993) Ghanem et al (1993) Damas et al Saad, Rowley et al High et al (1993) Bajaj et al (1990) Thompson et al (1992a) Green, Montandon et al Van de Water et al Ludwig et al (1992b) Bottema et al (1990c) Green, Montandon et al Chen et al (1991a) Ludwig et al (1988,1992b)	782 334 783 784 785 786 787 557 558 335 559 336 788 337 338 339 340 341
GER 29 Schmallenberg UK 162 Toronto 4 (HB35) KaoHsiung 2 HB87 Limoges Unnamed HB300 Chambéry Bergamo Calgary 20 UK 190 HB132 HB73 Malmö 16 Unnamed GER 30 Brantford Barcelos Hong Kong 5 UK 76 Hong Kong 4 GER 31 GER 32 Malmö 49 Takatsuki	<1 1.8 1 <1 <1 6 <1 3 <1 <1 7 3 <1 15 <1 <1 5 <1 7 <1 <1 <1 2	90 100 32 14 156 >100 13 <1 1 <10 1 <10	31,214, A→G 31,215, G→T 31,215, G→T 31,216, T→A 31,216, T→G 31,218, G→A 31,218, G→A 31,220, G→A 31,220, G→A 31,220, G→A 31,223, C→A 31,223, C→A 31,224, C→T 31,224, C→T 31,227, A→G 31,248, C→A 31,253, T→C 31,257, T→G 31,258, A→C 31,259, A→C 31,260, C→G 31,260, C→T 31,261, Δ1 31,270, Ins T 31,274, T→C 31,276, G→A 31,278, G→A	365, S→G 365, S→I 365, S→I 365, S→R 365, S→R 366, G→E 366, G→E 367, G→R 367, G→R 367, G→R 368, P→T 368, P→T 368, P→L 368, P→L 369, H→R 376, T→N 378, F→L 379, L→Stop 379, L→F 380, T→P 380, T→S 380, T→I 380 383 385, W→R 385, W→Stop 386, G→D	B _m De novo in MGF Active site, Inhibitor, silent mutation at aa364 Active site Active site Active site Active site Active site B _m Double (see 31,012) de novo in mother Frameshift Frameshift B _m ⁶	Knobloch & Zoll Ludwig et al (1992b) Saad, Rowley et al Koeberl et al (1990a) Lin et al Bottema et al (1991a) Ghanem et al (1993) Chen et al (1991a) Caglayan et al Ghanem et al (1993) Bertina et al (1990) Poon et al (1993) Saad, Rowley et al Bottema et al (1991b) Bottema et al (1990c) Green et al (1991b) Chen et al (1991a) Knobloch & Zoll Tam et al (1991) David et al Chan et al (1991) Green, Montandon et al Chan et al (1991) Knobloch & Zoll Knobloch & Zoll Ljung et al Kuze et al (1992)	789 342 790 343 791 560 792 344 793 794 345 795 561 532 346 347 348 796 349 562 350 351 352 797 798 563 799

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 & Zoll	801
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
						Nishimura et al (1990)	
Albuquerque 3	2	48	31,290, C→T	390, A→V		Tarnower & Smith (1991)	357
UK 193	<1	71	31,290, C→T	390, A→V		Saad, Rowley et al	802
Unnamed	2	30	31,290, C→A	390, A→E		Wang et al (1990a)	358
						Chen et al (1991a)	
UK 151			31,290, C→A	390, A→E		Saad, Rowley et al	565
Paris 6	<1	90	31,307, G→A	396, G→R	B _m ⁶	Ghanem et al (1993)	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
Los Angeles 5	1	112	31,308, G→C	396, G→A		High et al (1993)	803
UK 172			31,308, G→T	396, G→V		Saad, Rowley et al	804
(footnote 11)	3.5 ¹¹	72 ¹¹	31,311, T→C	397, I→T	30 cases including 3 B _m ⁶ . At least 24 have the same rare haplotype	Ref N ^{os} : (3,10,20,42,65, 68,102,123,136,138,148) PINs: (362-80, 566-73, 805-7)	
UK 163			31,314, A→C	398, Y→S		Saad, Rowley et al	808
Lousada	2		31,318, Ins ATATATACC	399	In frame	David et al	809
HB43	8		31,326, C→T	402, S→F		Koeberl 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 & Zoll	810
Calgary 12	30	60	31,329, G→A ⁴	403, R→Q		Poon et al (1993)	811
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
HB20	1		31,340, T→C	407, W→R		Koeberl et al (1989)	384
HB92	<1	2	31,340, T→C	407, W→R	Haplotype differs from 384, de novo in mother (31)	Bottema et al (1991a)	575
						Ketterling et al (1993)	
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, 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
HB66	3	1	31,356, C→A	412, T→K	De novo in mother (30)	Bottema et al (1991a)	576
						Ketterling et al (1993)	

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).

(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.

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 = 17, 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, 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.

¹¹ Mutations which have occurred more than five times 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.