Haemophilia B (sixth edition): a database of point mutations and short additions and deletions

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ABSTRACT

The sixth 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 <30 bp) identified in haemophilia B patients. The 1380 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 database 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 *et al.*, 1993 (139) and Tuddenham & Giannelli, 1994 (180)] 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 one in ~30 000 males and only very rarely females.

The purpose of this database is to update that of last year [Giannelli *et al.*, 1994 (59)] 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 It is not intended to replace primary publications, although it does contain a significant amount of unpublished work.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 (58)] 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 summarized and a full list of references 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 Xq27.1 and its entire sequence of 33 kb is known [Yoshitake *et al.*, 1985 (195)]. It contains eight exons (a–h) encoding six major domains of factor IX. (i) Exon a, encoding a hydrophobic signal peptide which targets the protein for secretion from the hepatocyte into the blood stream. (ii) Exons b and c, encoding a propeptide and a *gla* domain, the latter containing 12 γ -carboxyglutamyl residues. This post-translational modification is required for correct folding of and calcium binding by factor IX. (iii) Exon d, encoding 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 (69)]. (iv) Exon e, encoding a type A or second epidermal growth factor-like (EGF) domain, which lacks the conserved carboxylate residues of the EGF type B domain. (v) Exon f, encoding an activation domain, within which factor XIa and VIIa plus tissue factor cleave twice, converting factor IX to IXa. (vi) Exons g and h, encoding 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 His221, Asp269 and Ser365 all participate in the classical catalytic mechanism.

Factor IX is initially synthesized in the liver as a precursor molecule, either 46, 41 or 39 amino acids [it is not known which,

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although 39 is probable; Pang *et al.*, 1994 (120)] longer at its N-terminus than the 415 amino acid 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 γ -carboxylation of the 12 N-terminal glutamyl residues carried out by a vitamin K-dependent carboxylase and the partial β -hydroxylation of Asp64, N-linked carbohydrate side chains are added at residues 157 and 167 and O-linked carbohydrates at Ser53, Ser61, Thr159 and Thr169 [Hase *et al.*, 1994 (71); Nishimura *et al.*, 1992 (118); Agarwala *et al.* 1994 (196)]

There are 1380 patient entries in this sixth edition of the database, compared with 1142 patients last year [Giannelli *et al.*, 1994 (59)]. Besides point mutants, it includes 113 short (defined as <30 nt) deletions or additions or both, made up of 86 deletions, 21 additions and six examples involving both additions and deletions. There are also 18 double mutations, one triple mutation, 14 inhibitor patients, two somatic mosaics and 21 females (either affected or non-symptomatic carriers). The list excludes 29 patients with partial or complete gene deletions or more complex rearrangements [Thompson, 1990 (168)] and others observed since [Ketterling *et al.*, 1994 (80,81); Saad *et al.*, 1994 (142)]. Of the 1380 patients studied, 552 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.*, 1994 (59)], such mutants are believed to be genuine 'hot spots' for mutation. However, it is now becoming clear that the high number of repeat observations at some CG doublets (e.g. 71 examples at nt 31 008) are caused, at least in part, by a founder effect. A founder effect is now well established [Thompson *et al.*, 1994 (174); Bottema *et al.*, 1990b (16)] for a mutation at a residue other than CGs (e.g. 31 examples at nt 31 311) and there are many examples in the database of repeating mutations. 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 17 molecularly unique mutants occurring within a short region of the promoter and these are invaluable in studying gene regulation [Crossley *et al.*, 1992 (35); Picketts *et al.*, 1993 (122); Reijnen *et al.*, 1993 (132)]. Missense mutations within exons give valuable information as to the importance of particular amino acid residues. The present list contains 333 different amino acid substitutions (probably detrimental). Ninety five residues of factor IX show two or more amino acid substitutions. These include the active site Ser365 and the proposed active site Asp269, but none is yet known for the proposed active site His221. Mutations at nine 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 all 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 224 missense mutations were added, of which 43 are new.

The fourth (1993) edition of this database is now available on the Internet. It can be reached on

<ftp://ftp.ebi.ac.uk/pub/databases/haemb/>.

The format used in the 1993 file server version of the database is somewhat related to that used for the familiar EMBL nucleic acid sequence database and should allow easy computer searching for particular features. The new entries in the sixth edition of the database will be available by the end of 1995.

The database 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 the USA; Poon representing Canada; Ludwig and Schwaab representing Germany; Reitsma representing The Netherlands; Goossens representing France; Yoshioka representing Japan; 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 in WordPerfect 5.1 and dBase formats.

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Table 1.

Patient	Clotting/Antigen (Normal = 100%)	Nucleotide (Normal & mutation ^{1,2})	Position ³ Amino Acid Change ⁴	Comments	Reference	Patient Identity Number
HB5, Japan	<1	-793	G-A	Double (see 20,551), N?	Matsushita et al (1990)	1
UK 232	3	-26	G-A	Promoter	Rowley et al	1147
Brandenburg	<1	-26	G-A	Promoter, LF-A1/HNF4- binding site, ARE	Ludwig et al; Crossley et al (1992)	395
HB388	2	-23	G-C	Promoter, LF-A1/HNF4- binding site, ARE	Ketterling et al (1995)	1148
Unnamed	<1	-21	T-G	Promoter, LF-A1/HNF4- binding site	Reijnen et al (1993)	812
(footnote 11)	<1	-10	T-G	Promoter, LF-A1/HNF4- binding site	2 cases: refs (104, 133)	396
Marseille	<1	-36	T-A	Promoter, LF-A1/HNF4- binding site, de novo in MGF	Ghanem et al (1993)	1149
HB396	7	-20	T-C	Promoter, LF-A1/HNF4- binding site	Ketterling et al (1995)	
(footnote 11)	3	-19	G-C	Promoter, LF-A1/HNF4- binding site	13 cases: refs (8, 20, 33, 34, 56, 73, 113, 125, 140, 142, 154, 163)	
	2.5-76	-6	G-A	Promoter, 4 with same haplotype	125, 140, 142, 154, 163	
Toulouse	1	-30	G-C	Promoter	Gispert et al (1989)	6
(footnote 11)	7	-5	A-G	Promoter	2 cases: refs (142)	7
Toronto 20	3	-5	A-T	Promoter	Picketts et al (1993)	581
(footnote 11)	<1	6	T-A	Promoter, C/EBP-binding site	2 cases: refs (54, 115)	8
Bangkok	5	8	-T	Promoter, C/EBP-binding site, de novo in mother	Heil et al (1992)	12
Leyden, NZ	1	8	T-C	Promoter, C/EBP-binding site	Royce et al (1990)	13
Leyden 3	1	8	T-C	Promoter, C/EBP-binding site	Reitsma et al (1989)	
Aachen	<1	13	-A	Promoter, C/EBP-binding site	Ludwig et al	14
(footnote 11)	1.5-54	13	A-C	Promoter, C/EBP-binding site	7 cases: refs (32, 33, 36, 56, 86, 134, 143)	399
Riegelsberg	<1	13	A-G	Promoter, C/EBP-binding site	Ludwig et al (1992a)	822
Calgary 4	<1	37	G-A	Double (see 31,084), N	Poon et al (1993)	823
B61	<1	48	A-T	Double (see 31,133), N	Deutz-Terlouw et al	
Yungling	<1	48	A-T	N? only change found	Lin et al	
(footnote 11)	<1	59	-A	Frameshift	3 cases: refs (31, 66, 177)	1157
(footnote 11)	1	79	T-A	Signal peptide	2 cases: refs (92, 189)	1158
(footnote 11)	<1	89	-A	Frameshift	Rowley et al	400
UK 302	40	91	G-T	New donor splice?	Rowley et al	401
UK 343	2	92	-AT	Frameshift	Bottassa et al (1991b)	17
HB130	20	111	T-C	Signal peptide	Ludwig et al (1994)	825
Meaux	<1	112	-G	Frameshift	Ghanem et al (1993)	16
Recklinghausen	<1	113	+AT	Frameshift	Nielsen et al (1994)	402
DK 27	<5	113	T-G	Signal peptide	2 cases: refs (140, 142)	827
UK 36	1	114	-ACAGGTT	Frameshift, Donor splice (a)	Sead et al (1994)	18
(footnote 11)	<1	116	A-G	Donor splice (a)	Bottassa et al (1991a)	1160
HB64	<1	117	G-A	Donor splice (a)?	2 cases: refs (140, 142)	1161
UK 245	<1	117	G-C	Donor splice (a)?	Sead, Rowley et al	403
(footnote 11)	2	118	G-T	Donor splice (a)	Bottassa et al (1991b)	404
Malmo 33	3	122	G-A	Donor splice (a), de novo in MGF	Sead, Rowley et al	1162
UK 206	11	122	G-C	Donor splice (a)	2 cases: refs (142, 143)	405
Lisboa 1	1	122	G-T	Donor splice (a)	Green et al (1991b)	830
HB135	1	122	G-T	Donor splice (a)	Rowley et al	1163
UK 70	<1	6320	T-G	Donor splice (a)	David et al	
Porto Alegre 7	<1	6325	G-A	Donor splice (a)	Bottassa et al (1991b)	
Spain	<1	6325	G-C	Acceptor splice (b)	Sead et al (1994)	
Nice	<1	6325	G-T	Acceptor splice (b)	Bandinelli et al	
Hong Kong 9	<1	6325	G-T	Acceptor splice (b)	Ghanem et al (1993)	
(footnote 11)	2	6332	-T	Acceptor splice (b)	Costes et al	
	<1	6364	C-T	Frameshift	Chan et al (1995)	
	<1	6365	G-A	Circulates with propeptide	19 cases: refs (9, 18, 56, 61-3, 83, 97, 135, 140, 142)	
	<1	6365	G-A	Circulates with propeptide	43 cases: refs (9, 10, 15, 19, 20, 22, 25, 32, 42, 56, 61, 62, 72, 83, 87, 90, 95, 125, 140, 163, 175, 177, 181, 188)	
	<1	6365	G-T	Frameshift	9 cases: refs (9, 56, 83, 87, 194)	
HB608, Fr	<1	6369	+T	Frameshift	Tartary et al (1993)	842
GER 2269P	<1	6370	-TT	Frameshift	Wulff, Hermann et al	1365
Seattle E	<1	6372	G-T	Abnormal carboxylation, circulates with propeptide	Thompson et al (1992a)	419
Cambridge	<1	6375	G-Y	Abnormal carboxylation, circulates with propeptide	Diuguid et al (1986)	46
London, Ont 1(HB54)	6	6379	A-G	Abnormal carboxylation, circulates with propeptide	Koeberl et al (1990a)	47

Autun	<1	6380	-A	2	Frameshift	Ghanem et al (1993)	420
Calgary 16	1	6380	A-T	2, H-I		Poon et al (1993)	595
GER 101	18	6385	G-A	4, G-S		5 cases: refs (140, 142, 181)	1366
UK 381	4	6386	G-A	4, G-D		Kochhan & Olek	1176
HB47	7	6388	A-G	5, K-E		Rowley et al	389
UK 12	<1	6390	-T	6	New donor splice in exon(b)	Koerberl et al (1990a)	48
Oxford b2	5	6395	A-C	7, E-A	Frameshift, Inhibitor	Green et al (1989)	49
(footnote 11)	<1	6395	A-T	7, E-V	Gla	Winship & Dragon (1991)	597
(footnote 11)	<1	6398	-AG	8	Frameshift,	2 cases: refs (140, 181)	422
UK 244	4	6398	A-C	8, E-A	Gla	2 cases: refs (56, 64)	51
HB151	2	6398	A-G	8, E-G	Gla	Sead et al (1994)	423
UK 84	14	6400	T-A	9, F-I	Gla	Bottoma et al (1991b)	51
Medrid 3	<1	6401	-TTGTTCA	9, F-C	Frameshift, Inhibitor	Sead et al (1994)	423
Porto Alegre 3	10	6401	T-G	9, F-C		Solera et al	1179
Bonn 2	<1	6402	-TGTTT	9, Q-Stop	Frameshift, Inhibitor de novo in mother(22)	Bandinelli et al	52
Oxford b3	<1	6406	C-T	11, G-R		Ludwig et al (1992a)	53
(footnote 11)	6	6409	G-A	12, G-R		Winship & Dragon (1991)	599
UK 182	46	6410	G-A	12, G-E		2 cases: refs (61, 72)	54
Hong Kong 1	97	6410	G-C	12, G-A		Sead et al (1994)	600
HB299 (Kutahya)	<1	6411	-G	12	Frameshift	Chan et al (1991)	55
Muhlheim/Ruhr	4	6416	-TT	14	Frameshift, somatic mosaic?	Coglayan et al	1181
HB379	1	6418	-GAG	15	Frameshift	Ludwig et al	848
GER 2705	<1	6420	-GAGAGA	15, Del R,	In frame	Thorland et al (1995)	426
(footnote 11)	1	6424	G-A	17, E-K	Gla	Mulff, Herrmann et al	601
GER 102	<1	6424	G-C	17, E-Q		2 cases: refs (56, 163)	427
(footnote 11)	2	6427	T-C	18, C-R		Kochhan & Olek	58
(footnote 11)	<1	6428	G-A	18, C-Y		2 cases: refs (102, 135)	850
GER 2232A	<1	6434	A-T	20, E-V	Gla	2 cases: refs (18, 163)	1182
Nagoya 4	52	6436	G-A	21, E-K	Gla	Mulff, Herrmann et al	60
UK 197	1	6441	-G	22	Frameshift	Hamaguchi et al (1991)	848
Jie Long	<1	6442	T-C	23, C-R		Sead et al (1994)	426
UK 115	<1	6443	G-A	23, C-Y		Lin & Shen (1991)	427
(footnote 11)	2	6449	T-C	25, F-S		Sead et al (1994)	58
HB840, Fr	<1	6451	G-C	26, E-Q	Gla	2 cases: refs (102, 194)	850
Ribeirao Preto 12	<1	6451	G-T	26, E-Stop		Tartary et al (1993)	1182
Seattle 3	<1	6454	G-A	27, E-K	Gla	Figueiredo et al	60
(footnote 11)	<1	6455	A-T	27, E-V	Gla	Chen et al (1989b)	850
(footnote 11)	<1	6456	A-C	27, E-D	Gla	2 cases: refs (84, 186)	1182
(footnote 11)	<1	6460	C-T	29, R-Stop		2 cases: refs (115, 140)	60
(footnote 11)	<1	6461	G-A	29, R-Q	5 double (see 30134)	34 cases: refs (9, 20, 38, 51, 57, 61-3, 65, 83, 88, 94, 110, 140, 142, 163, 164, 175, 194)	607
HB172	1	6463	G-A	30, E-K	Gla de novo MGM (38)	13 cases: refs (20, 29, 51, 56, 86, 87, 140, 142, 143, 169, 181)	867
GER 2254	<1	6463	G-T	30, E-Stop		Ketterling et al (1993)	73
Malmo 9	<1	6466	-G	31	Frameshift	Mulff, Herrmann et al	1194
HB580	<1	6467	-TT	30	Frameshift	Green et al (1991b)	435
UK 180	<1	6472	+GG	33	Frameshift	Thorland et al (1995)	608
UK 111	<1	6472	G-T	33, E-Stop		Sead et al (1994)	74
HB9	4	6474	A-C	33, E-D	Gla	Haris et al (1994)	75
UK 10	<1	6485	-GAA	37, Del R	In frame	Koerberl et al (1989)	76
Unnamed	<1	6488	C-G	38, T-R		Green et al (1989)	1196
(footnote 11)	8	6490	C-T	38, T-I		Ludwig et al	1196
Ribeirao Preto 6	<1	6492	G-A		Donor splice (b)	2 cases: refs (140, 142)	1196
(footnote 11)	<1	6492	-GAGT		Donor splice (b), 1 double (see 31103)	Figueiredo et al	438
(footnote 11)	2	6494	G-A		Donor splice (b)	3 cases: refs (30, 128, 142)	1197
(footnote 11)	<1	6495	T-C		Donor splice (b)	2 cases: ref (115)	1197
(footnote 11)	1	6575	C-G		Donor splice (b)	2 cases: refs (56, 181)	438
HB131	<1	6575	A-G		Triple (see 10, 512 and 30, 897), N	2 cases: refs (17, 142)	1197
Lubeck	1	6653	-4		New acceptor splice?	Bottoma et al (1991b)	1198
NZ29	2	6659			Acceptor splice (c)?	David et al	1198

Malmo 10 (footnote 11)	<1	0.2	6666 6677	-TATTCCTT G-A	Acceptor splice (c), de novo in MGF or MGF Acceptor splice (c)	Green et al (1991b) 2 cases: refs (140, 142)	81
(footnote 11)	5		6677	G-C	Acceptor splice (c)	2 cases: refs (79, 194)	82
HB7, Japan	<1	<1	6680	-Tg	Frameshift, Inhibitor	Natsushita et al (1990)	871
HB1060, Fr	<1		6687	-T	Frameshift	Tartary et al	613
UK 156	2		6688	G-A		Saad et al (1994)	83
Hoogeveen	14	96	6690	A-G		Reitsma et al	439
Malmo 52	<1		6693	C-T		Ljung et al	614
UK 87	9		6696	T-A		Saad et al (1994)	872
HB170	9	59	6696	T-G		Gostout et al (1993)	875
GER 2249			6697	A-G		Kulff, Herrmann et al	
(footnote 11)	<1	<1	6702	G-A	Donor splice (c)?	2 cases: refs (142, 194)	85
(footnote 11)	<1	<1	6704	T-C	Donor splice (c)	2 cases: refs (56, 104)	616
Oxford 2	0.5	0.4	6704	T-G	Donor splice (c)	Winship (1986)	615
UK 128	1,3		6707	G-A	Donor splice (c)	Saad et al (1994)	617
HB20 (Bogazici)	5		6707	G-C	Donor splice (c)	Winship (1986)	874
HB197	<1	27	10389	A-G	Acceptor splice (c)	Caglayan et al	87
UK 289	<1		10390	A-T	Acceptor splice (d), de novo MGF (27)	Ketterling et al. (1993)	90
Toronto 16 (HB53)	3		10391	G-A	Acceptor splice (d)	Saad, Rowley et al	441
(footnote 11)	17	100	10392	A-G		Koerberl et al (1990a)	91
Oxford d3	1	90	10393	T-A		2 cases: refs (41, 159)	92
Tainan	28	101	10394	G-A		Winship & Dragon (1991)	1202
Malmo 27	19	108	10395	G-T		Lin & Shen (1991)	618
UK 86	1		10397	GAT-A	de novo in mother	Green et al (1991b)	875
HB389	4		10398	A-G	Frameshift	Saad et al (1994)	1203
Clermont	<1		10400	C-T		Rowley et al	
New London	<1	114	10401	A-C	Decreased Xla activation	2 cases: refs (56, 142)	97
UK 145	24		10402	G-C		2 cases: refs (18, 83)	622
UK 398	42		10403	T-C	Carrier female	3 cases: refs (29, 62, 152)	98
(footnote 11)	<1	<1	10405	T-G		Green et al (1991b)	877
(footnote 11)	<1	<1	10406	G-T		Ketterling et al. (1993)	101
(footnote 11)	10	46	10415	C-G	de novo MGF (38)	Green et al (1991b)	100
Malmo 21	12	52	10415	C-T		Ketterling et al. (1993)	1204
HB180	6	34	10416	C-A		Green et al (1991b)	443
Malmo 22	26		10416	C-T		Saad et al (1994)	444
HB130, Fr	1	2	10418	T-A		50 cases: refs (20, 28-30, 44, 63, 78, 86, 87, 125, 129, 140, 142, 143, 163, 169, 175, 177, 192)	
(footnote 11)	<1		10418	T-C		Bottema et al (1991b)	458
Toronto 2 (HB32)	1	2	10419	G-A		Rowley et al	1208
KLeve	<1	<1	10419	G-C	normal carrier female	Rowley et al	113
UK 373	10		10426	T-G	Frameshift, female carrier	Koerberl et al (1990a)	890
UK 160	18		10427	G-A		Knobloch & Zoll	627
HB141	2		10428	G-T	B Hydroxyaspartate	Harris et al (1994)	114
(footnote 11)	13	28	10430	G-A	Hydroxyaspartate	Winship & Dragon (1991)	115
						Green et al (1989)	891
						Tartary et al (1993)	
						5 cases: refs (38, 56, 163)	
						5 cases: refs (56, 83, 142, 194)	
						2 cases: refs (45, 115)	
						2 cases: refs (56, 104)	
						Saad et al (1994)	633
						Saad et al (1994)	634
						Saad et al (1994)	635
						Thorland et al (1995)	1215
HB154	<1	6	10430	G-C		Bottema et al (1991b)	458
UK 375	<1		10430	G-T		Rowley et al	1208
Toronto 6 (HB37)	1	2	10431	G-A		Koerberl et al (1990a)	113
GER 39			10434	-GT		Knobloch & Zoll	890
UK 176	3	117	10437	G-A		Harris et al (1994)	627
Oxford d1	8	87	10442	G-A		Winship & Dragon (1991)	114
UK 6	12	46	10443	A-G		Green et al (1989)	115
HB630, Fr	17	91	10449	T-G		Tartary et al (1993)	891
(footnote 11)	<1		10458	T-C		5 cases: refs (38, 56, 163)	
(footnote 11)	<1		10463	A-G		5 cases: refs (56, 83, 142, 194)	
UK 167	6		10464	T-A		2 cases: refs (45, 115)	
UK 200			10465	G-C		Saad et al (1994)	633
UK 150			10466	T-A		Saad et al (1994)	634
HB404	1		10467	G-A		Saad et al (1994)	635

(footnote 11)	1	10468	G-A	72, C-R	2 cases: refs (56, 177)	897
Iran 1	1	10469	T-C	73, C-R	David et al.	637
GER 7	<1	10470	G-A	73, C-Y	Knobloch & Zoll	898
GER 2332S	<1	10471	G-T	73, C-F	Wulff, Herrmann et al.	638
Paris 3	<1	10472	T-A	73, C-Stop	Ghanem et al. (1993)	1217
UK 288	14	10473	G-A	76, G-R	Rowley et al.	117
UK 67	6	10474	G-T	76, G-V	Saad et al. (1994)	899
Unlabeled	12	10482	T-C	77, F-S	Chen et al. (1995)	118
UK 19	<1	10483	T-G	77, F-C	Saad et al. (1994)	1218
Eindhoven	<1	10484	G-A	78, E-K	Bertina & Veltkamp (1978)	1219
UK 356	<1	10487	G-A	79, G-R	Rowley et al.	901
UK 229	<1	10507	T-A		Saad et al. (1994)	
(footnote 11)	8	10510	T-C		2 cases: ref (142)	
(footnote 11)	5	10510	-GTAA		2 cases: refs (140, 171)	1222
UK 218	5	10510	G-A		Rowley et al.	120
Toronto 8 (HB39)	2	10512	A-G		Koerberl et al. (1990a)	639
Paris 5	<1	10512	A-G		Ghanem et al. (1993)	1170
UK 38	4	10512	A-G		Rowley et al.	438
HB131	<1	10512	A-G		Bottama et al. (1991b)	1223
UK 220	9	17647	C-G		Rowley et al.	121
HB6	20	17662	-CTTT		Koerberl et al. (1989)	1372
GER 2489G	<1	17665	T-C		Wulff, Herrmann et al.	902
Cardiff 4/UK 329	4	17667	A-C		Bowen & Bloom (1993)	122
Toronto 14 (HB48)	3	17667	A-G		Koerberl et al. (1990a)	123
Malmo 11	<1	17668	G-C		Green et al. (1991b)	124
Seattle 2	<1	17669	-A		Schach et al. (1987)	640
(footnote 11)	<1	17677	T-C		2 cases: refs (140, 194)	
HB147	2	17678	-GTAACT		Ketterling et al. (1993)	
(footnote 11)	<1	17678	G-A	88, C-R	2 cases: refs (163, 181)	
(footnote 11)	<1	17678	G-C	88, C-Y	2 cases: refs (104, 194)	
(footnote 11)	15	17684	T-C	90, I-T	3 cases: refs (140, 142, 194)	
(footnote 11)	2	17689	A-C	92, N-H	2 cases: refs (32, 116)	643
(footnote 11)	<1	17691	T-A	92, N-K	3 cases: refs (56, 163)	
HB256	3	17692	G-A	93, G-S	Ketterling et al. (1993)	910
(footnote 11)	2	17693	B-A	93, G-B	2 cases: refs (114, 194)	461
NZ 27	1	17695	+A	94	Van de Water et al. (1991a)	
HB106	<1	17697	A-T	94, R-S	2 cases: ref (19)	
(footnote 11)	<1	17699	G-A	95, C-Y	4 cases: refs (79, 140, 142, 161)	
(footnote 11)	2	17700	C-A	95, C-Stop	2 cases: refs (97, 114)	
(footnote 11)	<1	17700	C-G	95, C-W	Tartary et al. (1993)	914
HB267, Fr	<1	17704	C-G	97, Q-E	Knobloch & Zoll	644
GER 8	<1	17705	A-C	97, Q-P	Tartary et al. (1993)	645
Taichung	<1	17706	-G	97	Knobloch & Zoll	128
Hamilton 1 (HB45)	<1	17710	T-C	99, C-R	Lin et al. (1993)	915
Unlabeled	<1	17711	G-A	99, C-Y	Koerberl et al. (1990a)	
(footnote 11)	<1	17717	+A	101	Tagliavacca et al.	129
UK 50	<1	17727	+TT	105	2 cases: refs (140, 181)	133
(footnote 11)	18	17736	G-A	107, None	Saad et al. (1994)	916
Unlabeled	20	17738	T-C	108, V-A	5 cases: refs (64, 97)	649
Unlabeled	<1	17741	G-C	109, C-S	Chen et al. (1991a)	466
GER 9	<1	17741	G-T	109, C-F	Tagliavacca et al.	917
HB111	7	17743	T-C	110, S-P	Knobloch & Zoll	650
HB310, Fr	<1	17745	+26	111	Lin et al. (1993)	651
Taipei 5	<1	17746	T-C	111, C-R	Bowen & Bloom (1993)	
Cardiff 3/UK 327	<1	17747	G-C	111, C-S	Poon et al. (1993)	
Calgary 24	<1	17756	-G	114, or 115	2 cases: ref (194)	
(footnote 11)	9	17756	G-A	114, G-E	2 cases: refs (136, 192)	
(footnote 11)	1	17756	G-C	114, G-A	2 cases: refs (104, 142)	
(footnote 11)	5	17759	A-G	115, Y-C	Saad et al. (1994)	
UK 28	<1	17761	C-A	116, None	10 cases: refs (19, 85, 95, 112, 114, 142,	138
(footnote 11)	<1	17761	C-T	116, R-Stop	1 double (see 30890)	

UK 11	13	97	20527	G-A	183, G-S	183, Del G, In frame	Nielsen et al (1994)	1978
UK 54	<1		20529	-156			Saad et al (1994)	184
(footnote 11)	1	100	20530	-GGA	184, G-R	-G	3 cases: refs (142, 170, 177)	
Unnamed	<1	100	20531	G-A	184, Del G	In frame	Thompson et al (1992b)	695
Botrop 1	<1	92	20540	-GAG	187, A-D		Ludwig et al	185
(footnote 11)	<1		20548	G-T	190, G-C		2 cases: refs (32, 181)	
UK 179	1	36	20549	G-T	190, G-V		Saad et al (1994)	696
(footnote 11)	<1		20551	C-A	191, G-K	Inhibitor	2 cases: refs (57, 96)	
Unnamed	<1	<1	20551	C-T	191, Q-Stop	1 inhibitor & double (see -793)	Chen et al (1991a)	186
(footnote 11)	<1	<1	20553	A-G	191, None	Cryptic splice	2 cases: refs (1, 106)	
Seattle J	3	2	20553	T-G	192, F-V		Thompson et al (1992a)	488
Nantou 1	2	<6	20554	G-T	194, W-L		Lin et al (1993)	697
Rennes	<1		20560	G-T	194, W-R		Ghanem et al	1257
(footnote 11)	2	2	20560	G-A	194, W-Stop	1 Inhibitor	2 cases: refs (175)	
(footnote 11)	<1	<0.1	20561	G-A	194, W-Stop		8 cases: refs (36, 62, 97, 115, 140, 142)	
(footnote 11)	<1	2	20562	G-T	194, W-Stop		3 cases: refs (140, 142)	
Unnamed	<1	<1	20563	C-T	195, Q-Stop		Thompson et al (1992b)	699
(footnote 11)	<1	<1	20564	A-G	195, Q-R	Donor splice (f)	2 cases: refs (84, 104)	
(footnote 11)	<1	<1	20565	G-A	195, None	Donor splice (f)	2 cases: refs (31, 194)	
(footnote 11)	<1	<1	20566	G-A		Donor splice (f)	2 cases: refs (84, 115)	
Oxford 1	<0.5	<1	20566	G-T		Donor splice (f)	Rees et al (1985)	190
UK 272	<1	0.3	20567	T-C		Donor splice (f)	Saad, Rowley et al	991
UK 171	<1	<1	30038	G-A		Acceptor splice (g)	Saad et al (1994)	492
(footnote 11)	<1	<1	30038	G-C		Acceptor splice (g)	2 cases: refs (18, 125)	
H8188	<1	<1	30046	T-C	198, L-S	de novo in MCF (21)	Ketterling et al. (1993)	701
UK 192	2	<1	30046	T-G	198, L-W		Saad et al (1994)	494
GER 43	<1	<1	30050	-T	199	Frameshift	Saad et al (1994)	992
UK 394	<1	<1	30058	-TTG	202, -Y	Frameshift	Knobloch & Zoll	1259
Paris 4	<1		30059	-TGAT	202	Frameshift	Rowley et al	702
(footnote 11)	<1	<1	30069	T-C	206, C-R		Ghanem et al (1993)	
(footnote 11)	<1	<1	30070	G-A	206, C-Y		2 cases: refs (83, 142)	
(footnote 11)	<1	<1	30070	G-C	206, C-S		4 cases: refs (19, 61, 140)	
(footnote 11)	<1	<1	30072	G-A	207, G-R		2 cases: refs (142, 166)	
Unnamed	<1	<1	30072	G-T	207, G-Stop		2 cases: refs (39, 142)	
(footnote 11)	<1	56	30073	G-A	207, G-E		Thompson et al (1992b)	707
UK 37	5	1	30076	G-A	208, G-D		2 cases: refs (95, 194)	
(footnote 11)	5		30084	G-T	211, V-F		Saad et al (1994)	194
(footnote 11)	16	<1	30089	T-G	212, N-K	All the same haplotype	2 cases: refs (29, 104)	
Botrop 2	<1	<1	30090	G-T	213, E-Stop		5 cases: ref (115)	
(footnote 11)	2	<1	30096	T-G	215, W-R		Ludwig et al	197
Unnamed	<1	0.1	30097	G-A	215, W-G		3 cases: refs (20, 31, 93)	
Ribeirao Preto 11	<1	<1	30098	G-T	215, W-C		Figueiredo et al	1262
Taidung	5	4	30100	T-C	216, I-T		Chen et al (1991a)	199
HB65	15	4	30101	T-G	216, I-H		Lin et al (1993)	709
UK 342	3		30106	C-T	218, T-I		4 cases: refs (29, 64, 84, 87)	
GER 2274	5		30108	G-A	219, A-T		Bottema et al (1991a)	497
(footnote 11)	5	9	30112	C-T	220, A-V		Rowley et al	1263
UK 93	2		30117	T-A	222, C-S		Huliff, Herrmann et al	1001
(footnote 11)	1		30119	T-G	222, C-W		3 cases: refs (87, 125)	
UK 334	<1		30123	G-T	224, E-Stop		Saad et al (1994)	498
(footnote 11)	13	12	30134	T-C	None	5 double (see 6461; 1 double (see 31221)	2 cases: refs (86, 140)	
(footnote 11)	<1		30150	G-A	233, A-T		Rowley et al	1265
							7 cases: refs (20, 29, 32, 86, 87, 169, 181)	
							24 cases: refs (1, 29, 31, 64, 86, 97, 104, 140, 142, 143, 159, 161, 163, 181)	
							Ghanem et al (1993)	1268
Caen 3	<1	<1	30152	A-A	233	Frameshift	Tantary et al (1993)	714
HB626, Fr	1	1	30154	G-A	None	Donor splice (g)	3 cases: refs (32, 56, 65)	1009
(footnote 11)	10		30802	-TTTATT		2 double (see 31, 119 and +13), N	Rowley et al	1273
UK 207	<1	<1	30808-13	G-A	234, G-A	Acceptor splice (h)	4 cases: refs (18, 30, 106, 142)	
(footnote 11)	17		30821	G-C		Acceptor splice (h)	Rowley et al	1274
UK 316			30822					

GER 2128C	20	A-G	237, N=0	In frame. ALL same haplotype	Wulff, Herrmann et al	1379
UK 276	<1	T-A	238, I+N	Frameshift	Saad, Rowley et al	1010
(footnote 11)	<1	-GAG	240, -E		4 cases: ref (194)	
HB660, Fr	22	-G	242		Tartary et al (1993)	1015
Spijkenisse	2	G-A	245, E-K		Reitsma et al	218
Monschau	39	A-T	245, E-V		Ludwig et al (1992b)	201
UK 140	<1	-C	246	Frameshift	Saad et al (1994)	501
GER 952	<1	C-G	248, R-G		Wulff, Herrmann et al	1016
(footnote 11)	<1	C-T	248, R-Stop		31 cases: refs (19, 20, 22, 57, 61-65, 87, 104, 125, 140, 142, 160, 162, 163, 177, 185)	
(footnote 11)	4	G-A	248, R-Q		37 cases: refs (18, 20, 23, 28, 29, 39, 56, 57, 87, 103, 115, 125, 140, 142, 143, 159, 169, 177, 194)	
UK 92	<1	T-A	251, I+N		Saad et al (1994)	725
(footnote 11)	<1	C-T	252, R-Stop		18 cases: refs (1, 9, 18, 26, 27, 40, 50, 56, 64, 65, 79, 84, 124, 140, 142, 147, 165, 194)	
UK 16	13	G-T	252, R-L		Saad et al (1994)	241
Porto Alegre 2	9	A-G	256, H+R		Bandinelli et al	1290
DK 10	<1	-C	257	Frameshift	Nielsen et al (1992)	1041
Malmo 7	<1	C-T	257, H+Y	Double (see 17,761), N	Montandon et al (1990a)	137
GER 2131H	<1	-C	257	Frameshift	Wulff, Herrmann et al	1381
(footnote 11)	1	A-G	259, Y-C	1 triple (see 6575 and 10512)	3 cases: refs (19, 79, 140, 181)	
(footnote 11)	16	A-G	260, N-S		2 cases: refs (86, 181)	
Le Francois	<1	C-G	266, Y-Stop		Ghanem et al	1292
HB786, Fr	6	A-G	268, H+Q		2 cases: refs (140, 142)	
(footnote 11)	8	T-G	268, H+Q		Tartary et al (1993)	1043
GER 18	1.5	G-A	269, D-N	de novo in mother (38)	Knobloch et al (1993)	688
(footnote 11)	<1	A-G	269, D-G	Proposed active site Asp	3 cases: refs (56, 142)	
(footnote 11)	<1	A-T	269, D-V	Proposed active site Asp	2 cases: refs (97, 194)	
HB208	<1	C-A	269, D-E	de novo mother (34)	Ketterling et al (1993)	731
(footnote 11)	<1	A-T	270, I-F		3 cases: refs (61, 142, 177)	
Confolens	<1	+T	290	Frameshift	Ghanem et al	1295
(footnote 11)	<1	T-C	270, I-T		2 cases: refs (18, 104)	
(footnote 11)	<1	C-T	271, A-V		5 cases: refs (87, 140, 142)	
(footnote 11)	16	T-A	272, L-H		Rowley et al	1297
UK 286	<1	T-G	272, L-R	De novo in MGF (23)	Bottema et al (1991b); Ketterling et al (1993)	517
HB143	2	T-C	273, L-P		Odom et al (1994)	1298
San Antonio I	<1	GG-C	274	Frameshift	Rowley et al	1299
UK 391	<1	-A	274	Frameshift, normal carrier female	Saad et al (1994)	247
UK 48	<1	T-A	274		Wulff, Herrmann et al	1046
GER 3147	<1	T-C	275, L-Q		3 cases: refs (18, 76, 142)	
(footnote 11)	<1	-GACCCCT	277, L-P		Green et al (1989)	249
Malmo 1	<1	T-A	277, L-I	Frameshift, Inhibitor	Reitsma et al	250
Zoeterwoude	13	T-C	279, L-S		Ghanem et al (1993)	734
Mantes-la-Jolie	<1	A-G	284, Y-C	Double (see 31,328)	Soaner et al	1048
HB270	<1	C-A	284, Y-Stop		2 cases: refs (79, 163)	
GER 2234A	<1	C-A	287, P-H		Wulff, Herrmann et al	735
Unnamed	<1	C-T	287, P-L		Chen et al (1991a)	251
HB109	<1	T-G	288, I-H		Bottema et al (1991a)	519
(footnote 11)	2	G-T	289, C-F		2 cases: refs (61, 142)	
(footnote 11)	8	G-A	291, A-P		6 cases: refs (65, 110, 142)	
Oxford h2	2	G-C	291, A-P		Yinship & Oregon (1991)	252
HB100	3	G-T	294, E-Stop	De novo in MGM (24)	Bottema et al (1991a); Ketterling et al (1993)	521
UK 72	<1	+CA	295	Frameshift	Saad et al (1994)	739
Fuesel	<1	A-G	295, Y-C		Ghanem et al (1993)	740
UK 196	<1	C-A	295, Y-Stop		Rowley et al	1301
GER 2121C	<1	-A	296	Frameshift	Wulff, Herrmann et al	741
Salon	18	A-G	296, T-A		Ghanem et al	1302
GER 2722	<1	C-A	296, T-K		Wulff, Herrmann et al	1076
(footnote 11)	4	C-T	296, T-M		78, 83, 86, 87, 97, 114, 125, 139, 140, 142,	

HB132 (footnote 11)	3	31012	C-T	None	Double (see 31, 224) N	143, 160, 162-164, 169, 171, 175, 177, 181, 192, 194)	532
Malmo 18	<1	31029	G-T	303, G-V	de novo in MGF	2 cases: refs (140, 171)	275
Seattle 0	<1	31035	G-A	305, G-D		Green et al (1991b)	533
UK 382	<1	31039	T-A	306, Y-Stop		Rowley et al (1991)	1312
(footnote 11)	16	31041	T-G	307, V-A		3 cases: refs (13, 29, 175)	278
Malmo 26	3	31043	T-C	307, V-G		Green et al (1991b)	1077
GER 45	2	31044	A-C	308, S-R		Knobloch & Zoll	280
(footnote 11)	5	31045	G-A	308, S-W		2 cases: refs (142, 163)	281
Essexden	<1	31046	T-G	308, S-R		Ludwig et al	282
Oxford h3	<1	31047	G-A	309, G-S		Winship & Dragon (1991)	283
(footnote 11)	<1	31047	G-T	309, G-D		(2 cases: refs (56, 61))	754
Unamed	<1	31047	G-T	309, G-V		Thompson et al (1989)	1080
Toronto 21	<1	31049	T-C	310, W-R		Picketts et al	1081
GER 20	4	31050	G-T	310, W-L		Knobloch & Zoll	289
(footnote 11)	<1	31051	G-A	310, W-Stop		3 cases: refs (162, 181, 185)	1082
(footnote 11)	2	31051	G-C	310, W-C		2 cases: refs (79, 83)	758
GER 2223A	<1	31051	G-T	310, W-C		Muliff, Herrmann et al	1316
(footnote 11)	2	31052	G-A	311, G-R		3 cases: refs (107, 177)	539
(footnote 11)	1	31053	G-A	311, G-E		2 cases: refs (107, 177)	1084
UK 219	<1	31053	G-T	311, G-V		Sead et al (1994)	77
(footnote 11)	1	31059	T-G	313, V-G	Bu	2 cases: refs (89, 108, 142)	293
UK 11	<1	31060	-CT	313	Frameshift	Green et al (1989)	1318
GER 830	<1	31067	A-G	316, K-E		Muliff, Herrmann et al	295
Goldbach	<1	31070	G-C	317, G-R	Female carrier	Ludwig et al	1319
UK 143	2	31071	G-A	317, G-E		4 cases: refs (87, 142, 181)	545
(footnote 11)	<1	31080	C-A	320, A-W		Ghanea et al (1993)	319
Bruxelles	<1	31084	C-T	320, A-W	Frameshift, double (see 37), de novo in mother (30)	Ludwig et al (1992a)	776
Riegelsberg	1	31091	-AGTTCTT	321		Ghanea et al	550
Tours 3	4	31091	C-G	324, Q-E		Bottema et al (1991a)	1334
HB82	<1	31091	C-T	324, Q-Stop		2 cases: refs (95, 144)	
(footnote 11)	<1	31092	A-C	324, Q-P		Gostout et al (1993)	
HB273	<1	31096	C-G	325, Y-Stop	de novo in mother (26)	Bottema et al (1991a)	
HB122	4	31096	C-G	325, Y-Stop	Double (see 6, 491-4), N	Poort et al (1990)	
Ursem	1	31103	G-A	328, V-I		2 cases: refs (83, 191)	
(footnote 11)	7	31110	G-T	328, V-F	In frame	Sead et al (1994)	
UK 90	<1	31113	T-C	330, L-P		2 cases: refs (83, 104)	
(footnote 11)	<1	31113	-TTG	331, -V		Figueiredo et al	
Ribeirao Preto 4	<1	31113	T-A	331, V-D		Winship & Dragon (1991)	
Oxford h1	7	31113	T-C	331, V-A		3 cases: refs (83, 181)	
(footnote 11)	3	31115	G-T	332, D-Y		23 cases: refs (17, 19, 194)	
(footnote 11)	6	31118	C-G	333, R-G		79, 83, 88, 95, 97, 112, 129, 140, 142, 175)	
(footnote 11)	<1	31118	C-T	333, R-Stop		32 cases: refs (1, 18, 20, 29, 32, 39, 51, 56, 62, 63, 65, 83, 102, 123, 125, 126, 140, 142, 143, 163, 169, 179, 185, 194)	
(footnote 11)	2	31119	G-A	333, R-Q	1 double (see 30800)	Bottema et al (1991a)	
HB110	2	31119	G-T	333, R-L		2 cases: refs (140)	
(footnote 11)	10	31121	G-A	334, A-T		2 cases: refs (25, 97)	
(footnote 11)	18	31122	C-A	334, A-D		5 cases: refs (29, 62, 140, 142)	
(footnote 11)	<1	31127	T-C	336, C-R		Green et al (1991b)	
Malmo 24	<1	31128	G-A	336, C-Y		Knobloch & Zoll	
GER 25	<1	31129	T-A	336, C-Stop		Fraser et al (1992)	
Calgary 3	4	31130	C-A	337, L-1		2 cases: refs (61, 140)	
(footnote 11)	72	31130	C-T	337, L-F		Rowley et al	
UK 347	2	31131	T-C	337, L-P		(15 cases: refs (1, 48, 53, 61, 63, 96, 100, 124, 125, 161, 163, 177))	
(footnote 11)	<1	31133	C-T	338, R-Stop		12 cases: refs (81, 84)	
(footnote 11)	13	31134	G-C	338, R-P			

HB241	<1	31140	C-G	340, T-R	de novo in MGF (27)	Ketterling et al. (1993)	780
UK 170	<1	31143	+AA	340 or 341	Frameshift, normal carrier female	Seed et al. (1994)	551
SamLi	<1	31149	-CCA	343	Frameshift	Ludwig et al.	327
		31158	-ACAAC				
		31158	+G				
(footnote 11)	<1	31151	A-T	344, I-F		3 cases: refs (104, 194)	1101
GER 2120C	<1	31156	T-A	345, Y-Stop		Mulff, Hermann et al.	1386
GER 2266G	<1	31157	-A	346	Frameshift	Mulff, Hermann et al.	329
Unamed	<1	31158	+AA	346	Frameshift	Chen et al. (1991b)	327
SamLi	<1	31158	ACAAC-G	343	Frameshift	Ludwig et al.	553
UK 135	<1	31161	-ACA	346 or 347	In frame	Seed et al. (1994)	554
HB108	2	31163	A-T	347, N-I		Bottoma et al. (1991a)	530
Unamed	3	31163	A-G	348, N-V		Chen et al. (1991a)	1102
DK 9	<1	31164	T-A	348, H-K		Nielsen et al. (1994)	1337
(footnote 11)	<1	31165	G-A	348, H-I		2 cases: refs (18, 79, 163)	
UK 251	<1	31166	T-C	349, F-L		Roxley et al.	
(footnote 11)	<1	31170	G-A	350, C-Y		3 cases: refs (84, 97, 142)	
(footnote 11)	<1	31170	G-C	350, C-S		3 cases: refs (85, 167, 194)	
HB244, Fr	45	31176	G-T	350, C-F		Tertiary et al. (1993)	1106
(footnote 11)	<1	31176	G-A	352, G-D		2 cases: refs (84, 140)	
(footnote 11)	3	31176	G-C	352, G-A		2 cases: refs (51, 146)	
UK 234	4	31187	G-A	356, G-R		Seed et al. (1994)	1108
GER 27	<1	31196	-GA	358	Frameshift, de novo in mother (18)	Knobloch et al. (1993)	781
GER 28	1.5	31197	A-G	359, D-G		Knobloch & Zoll	782
(footnote 11)	<1	31200	C-G	360, S-Stop		3 cases: refs (56, 163)	
(footnote 11)	1	31200	C-T	360, S-L		4 cases: refs (29, 56, 142, 146)	
(footnote 11)	<1	31202	T-A	361, C-S		2 cases: refs (140, 194)	
Madrid 5	<1	31202	T-C	361, C-R		Damas et al.	787
GER 9P	<1	31202	T-G	361, C-G		Mulff, Hermann et al.	1388
UK 275	<1	31203	G-A	361, C-Y		Rowley et al.	1343
Los Angeles 2	<1	31208	G-A	363, G-R		High et al. (1993)	558
UK 144	<1	31208	G-T	363, G-E		Seed et al. (1994)	557
(footnote 11)	<1	31209	G-A	363, G-E		2 cases: refs (142, 181)	
Seattle S	3	31209	G-C	363, G-A		Thompson et al. (1992a)	559
Eagle Rock	1-5	31209	G-T	363, G-W		Bajaj et al. (1990)	335
(footnote 11)	<1	31211	G-A	364, D-N		2 cases (refs (142, 189)	
(footnote 11)	<1	31211	G-C	364, D-H		2 cases: refs (17, 103)	
Unamed	<1	31212	+ATAG	364	Frameshift, de novo in MGF	Thompson & Chen (1994)	1111
Unamed	<1	31212	A-T	364, D-W	De novo in MGF	Chen et al. (1991a)	340
VarL	<1	31213	TA+CG	365, S-G	Active site	Ludwig et al. (1992b)	341
GER 29	<1	31214	A-G	365, S-G	Active site	Knobloch & Zoll	789
DK 29	<1	31215	G-A	365, S-N	Active site de novo in MGF	Nielsen et al. (1994)	1113
Schwallenberg	2	31216	T-A	365, S-I	Active site	Ludwig et al. (1992b)	342
Toronto 4 (HB35)	<1	31216	T-G	365, S-R	Active site	Koerberl et al. (1990a)	343
Kaohsiung 2	90	31218	G-A	366, G-E		Lin et al.	791
(footnote 11)	<1	31220	G-A	367, G-E		2 cases: refs (18, 56)	
(footnote 11)	<1	31221	G-A	367, G-E		4 cases: refs (23, 29, 56, 177)	
(footnote 11)	1	31223	C-A	368, P-T	One double (see 30, 134)	2 cases: refs (32, 140)	
(footnote 11)	2	31224	C-T	368, P-L	One double (see 31012)	3 cases: refs (12, 125, 160)	
(footnote 11)	2	31226	C-A	369, H-N		4 cases: refs (19, 114, 142)	
San Antonio 11	<1	31227	A-G	369, H-R		Odow et al. (1994)	
HB73	<1	31227	A-G	369, H-R		Bottoma et al. (1990c)	1346
Unamed	5	31228	T-A	373, H-Q		Thompson & Chen	346
(footnote 11)	1	31239	T-A	373, V-E		2 cases: refs (2, 140)	1347
(footnote 11)	<1	31241	G-T	374, E-Stop		3 cases: refs (40, 142, 194)	
Nalad 16	15	31248	C-A	376, T-N		Green et al. (1991b)	347
Unamed	<1	31253	T-C	378, F-L		Chen et al. (1991a)	348
GER 30	<1	31257	T-G	379, L-Stop	de novo in mother	Knobloch et al. (1993)	796
(footnote 11)	8	31258	A-C	379, L-F		2 cases: refs (161, 189)	562
Barcelos	<1	31259	A-C	380, T-P		David et al. (1993)	1121
UK 259	1.4	31260	C-A	380, T-N		Saad, Rowley et al.	

Hong Kong 5	7	<10	31260	C-G	380, T-S	Frameshift	Chan et al (1991)	350
UK 76	<1	1	31260	C-T	380, T-I	Frameshift	Green, Montandon et al	351
Hong Kong 4	<1	<10	31261	-T	380		Chan et al (1990)	352
GER 31	<1	<1	31270	+T	383		Knobloch & Zoll	797
UK 162	1-8		31272	G-T	384, S-I		Saad, Rowley et al	790
GER 2227A	<1		31274	T-A	385, W-R		Muliff, Herrmann et al	1122
GER 32	<1		31274	T-C	385, W-R		Knobloch & Zoll	798
Malmo 49	<1		31276	G-A	385, W-Stop		Ljung et al	563
UK 278	1		31276	G-T	385, W-C		Saad et al (1994)	1123
GER 2251	2	120	31277	G-A	386, G-S	Bul	Muliff, Herrmann et al	1124
Takatsuki	<1		31278	G-A	386, G-D		Kuze (1992)	799
(footnote 11)	2		31281	G-C	387, E-G		2 cases: refs (84, 142)	564
HB86	2	95	31283	G-T	388, E-Stop		Bottema et al (1991a)	800
GER 33	24		31286	T-G	389, C-G		Knobloch & Zoll	1349
UK 388	<1		31287	G-A	389, C-Y		Rowley et al	1350
UK 401	1	2	31288	-TG	389	Frameshift, de novo in mother	6 cases: refs (104, 115, 142, 143, 163)	801
HB1000, Fr	<1	45	31289	G-A	390, A-T		Knobloch et al (1993)	1351
(footnote 11)	2		31290	G-T	390, A-S		Rowley et al	358
UK 151	2	30	31290	C-A	390, A-E		Heng et al (1990a); Chen et al (1991a)	1133
Unnamed	1	90	31303	C-T	390, A-V		5 cases: refs (116, 142, 153, 157, 162, 177)	1353
(footnote 11)	4		31304	T-C	394, K-H		Saad, Rowley et al	1134
UK 262	<1		31305	A-G	395, Y-H		Thorland et al (1995)	803
HB411	<1	100	31307	G-A	395, Y-C		Saad et al (1994)	804
UK 119	<1	112	31308	G-C	396, G-R		High et al (1993)	361
(footnote 11)	1		31309	G-T	396, G-V		Saad et al (1994)	
Los Angeles 5	<1	73	31311	-AATAT	396	Frameshift	31 cases: refs (6, 16, 29, 31, 55, 78, 86, 125, 151, 169, 174, 187)	
UK 172	3			T-C	397, I-T	At least 25 have same haplotype	2 cases: ref (142)	809
UK 29				A-C	398, Y-S	In frame	David et al (1993)	
(footnote 11)	2		31314	+ATATATA	399		Rowley et al	1354
Lousada	14		31317	CC	399, T-I	Frameshift, de novo in mother (29)	Knobloch et al (1993)	810
UK 370	<1		31326	-CCGGTA	400		Koeberl et al (1990a)	381
GER 35	8		31326	T	402, S-F	Frameshift	Rao et al (1990)	382
HB43	3	9	31327	CC-AAGGT	402		4 cases: refs (140, 150, 194)	
Lincoln Park	33	126	31328	ACGAA	403, R-W	1 double (30972)	5 cases: refs (1, 11, 125, 142, 193)	683
(footnote 11)	29		31329	G-A	403, R-Q	Frameshift	Ghanem et al (1993)	383
(footnote 11)	<1		31330	-G	403		Ludvig et al	663
Chatenay-Malabry	4		31331	T-C	404, Y-H		Knobloch & Zoll	574
Unnamed	23	26	31332	A-G	404, Y-C		Thompson et al (1992a)	385
GER 36	1	2	31334	G-T	405, V-F		2 cases: refs (18, 79, 86)	1140
Seattle T	<1	<1	31340	T-C	407, W-R		Saad et al (1994)	387
(footnote 11)	1	1	31342	G-A	407, W-Stop	Frameshift, de novo in mother	David et al	388
UK 53	<1	0.2	31344	T-C	408, I-T	Frameshift	Bottema et al (1989b); Ketterling et al (1993)	1141
Italy 1	<1	<1	31345	+GATT	408		Winship & Dragon (1991)	576
HB62	<1	<1	31345	-T	408		Attree et al (1989)	331
Oxford h4	<1	<1	31352	A-T	411, K-Stop		Thompson & Chen (1994)	
Bordeaux	<1	<1	31355	-A	410-412	Frameshift, de novo in mother	Bottema et al (1991a); Ketterling et al (1993)	
Unnamed	3	1	31356	C-A	412, T-K	De novo in mother (30)	Ludvig et al (1992a)	
HB66	<1	<1	31667	-G	349	Frameshift, de novo in MGN(29)	11 cases: refs (31, 140, 184)	
Offenbach	1	<1	32528	A-G	3' UTR	New donor splice?		

Footnotes:

- 1 For nucleotide numbering see Yoshitake et al (1985); for amino acid numbering Anson et al (1984).
- 2 Nucleotide change predicted from amino acid sequence.
- 3 The following comments or abbreviations are used:
 - (i) Inhibitor - patients developing anti-factor IX antibodies in response to therapeutic factor IX.
 - (ii) Frameshift - caused by the addition (symbol ins) or deletion (symbol Δ) affecting nucleotides corresponding to the stated amino acid number and terminating at a new stop codon shortly after.
 - (iii) Double - a double mutant, entered twice in the data base and cross-referenced.
 - (iv) N - indicates the mutation, usually a double mutant, is probably a normal variant - not causing the disease.
 - (v) The exon (a-h) immediately adjacent to donor or acceptor splice sites is noted.
 - (vi) Glu 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 (Hough & Honey, 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 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.