Haemophilia B: database of point mutations and short additions and deletions

F.Giannelli, P.M.Green, K.A.High[1], J.N.Lozier[1], D.P.Lillicrap[2], M.Ludwig[3], K.Olek[3], P.H.Reitsma[4], M.Goossens[5], A.Yoshioka[6], S.Sommer[7] and G.G.Brownlee[8]*

Paediatric Research Unit, Guy's Tower, London Bridge, London SE1 9RT, UK, [1]School of Medicine, Division of Hematology, University of North Carolina, Chapel Hill, NC 27599, USA, [2]Department of Pathology, Richardson Laboratory, Queen's University, Kingston K7L 3N6, Canada, [3]Institute of Experimental Haematology and Blood Transfusion, Sigmund-Freud-Strasse 25, 5300 Bonn 1 and Institute of Clinical Biochemistry, University of Bonn, FRG, [4]Hemostasis and Thrombosis Research Unit, University Hospital, PO Box 9600, 2300 RC Leiden, The Netherlands, [5]National Institute of Health and Medical Research, 51 Av.du Maréchal de Lattre de Tassigny, 94010 Creteil, France, [6]Department of Pediatrics, Nara Medical College, Kashihara City, Nara, Japan, [7]Mayo Clinic, 200 Southwest First Street, Rochester, MN 55905, USA and [8]Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford OX1 3RE, UK

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INTRODUCTION

The data base below lists known point mutations and short deletions and additions in the factor IX gene, which cause the bleeding disorder haemophilia B or Christmas disease (for reviews, see Brownlee 1988, Giannelli 1989, Thompson 1990). Mutations result in defective clotting factor IX – a 415 amino-acid-long glycoprotein synthesised in the liver and an essential component of the middle phase of the intrinsic clotting cascade. The disease is a rare inherited and X-linked recessive disorder affecting 1 in 30,000 males. Heterozygote female 'carriers' of the disease are unaffected, except in very rare circumstances.

The factor IX gene lies on the long arm of the X chromosome at Xq2.7 and its entire sequence of 33 kbases 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, needed for the vitamin K-dependent carboxylase modification of 12 N-terminal glutamyl residues to γ-carboxyglutamyl residues. This modification occurs during biosynthesis in the endoplasmic reticulum of the hepatocyte and is required for calcium binding. (3) exon d – a *type B, or first epidermal growth factor-like domain*, which shows homology to epidermal growth factor (EGF) and, in addition, contains conserved carboxylate residues including a β-hydroxyaspartate at amino acid 64. This domain binds an additional Ca^{2+} with high affinity (Handford et al, 1990) and may also bind to factor VIII. (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. Its function is unknown. (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 as a precursor molecule, some 40 amino acids longer at its N-terminus than the 415-long mature factor IX, which is found in plasma. The processing steps, which sequentially remove the hydrophobic signal peptide and the propeptide, occur in the hepatocyte prior to secretion. In addition to the γ-carboxylation of the N-terminal glutamyl residues, 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 serine 53.

There are 221 entries in the database including 14 short (defined as less than 20 nucleotides) deletions (11 cases) or short additions (3 cases), 6 double mutations and 1 female patient. The list excludes 29 patients with partial or complete gene deletions or more complex rearrangements (Thompson, 1990). Of the 216 known mutations within the gene (see Summary Table), 115 are unique molecular events, the remainder being repeats. As is well known, most, but not all (see below), of these repeats occur at CG dinucleotides and involve a CG→TG or CA change. Such mutants are believed to be genuine 'hotspots' for mutation (although the independent origin of identical mutations has not been demonstrated in every case), because of methylation of cytosine to 5′ methylcytosine. This modified cytosine is susceptible to deamination giving rise to thymine, in either the coding or non-coding strand of the gene. We calculate from the

* To whom correspondence should be addressed

Summary Table derived from main database

Location[1]	Exon	Nucleotide number[3]	Number of mutants[2]	Number of unique cases
Signal peptide (−46 to −19)	a	30−117	0	0
Propeptide (−18 to −1)	b	6,326−6,372	25	4
Gla (1 to 46)	b c	6,373−6,489 6,678−6,702	22	16
EGF (1st) (47 to 84)	d	10,392−10,505	15	9
EGF (2nd) (85 to 127)	e	17,669−17,797	10	9
activation (128 to 195)	f	20,363−20,565	31	14
catalytic (196 to 415)	g h	30,039−30,153 30,822−31,366	91	46
Subtotal			194	98
Promoter			9	5
Donor splice sites			9	8
Acceptor splice sites			4	4
Poly(A) site			0	0
Totals			**216**	**115**

[1] Amino acid numbers used (Anson et al, 1984)
[2] Excluding normal variants within double mutants
[3] For numbering, see Yoshitake et al (1985)

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

Patient[7]	Clotting (normal =100%)	Antigen (normal =100%)	Nucleotide[1] position & mutation	Amino acid[1] change	Comments[3]	Reference
HB5, Japan	<1	<1	−793, G → A	None	Double (see 20,551), N	Matsushita et al (1990)
Leyden 1	<1 → 60	<1 → 60	−20, T → A	None	Promoter	Reitsma et al (1988)
Datteln	<1 → 36[5]	<1 → 36[5]	−20, T → A	None	Promoter	Ludwig et al
High Wycombe	13−70[5]		−6, G → A[4]	None	Promoter	Crossley et al
Leyden, USA	Variable	Variable	−6, G → A[4]	None	Promoter	Fahner et al (1988)
Toulouse	1 → 30[5]	1 → 30[5]	−6, G → C	None	Promoter	Gispert et al (1989)
Leyden 2	<1 → 60	<1 → 60	13, A → G	None	Promoter	Reitsma et al (1989)
HB13	32		13, A → G	None	Promoter	Koeberl et al (1989)
Norwich	3−35[5]		13, A → G	None	Promoter	Crossley et al (1989)
Leyden 3	<1 → 60	<1 → 60	13, Δ 1	None	Promoter	Reitsma et al (1989)
Boxtel	4	36	6,364, C → T[4]	−4, R → W		Reitsma et al
Heiden	<1		6,364, C → T[4]	−4, R → W		Ludwig et al
Lienen	<1	40	6,364, C → T[4]	−4, R → W		Ludwig et al
Malmö 6	<1	26−34	6,364, C → T[4]	−4, R → W		Green et al (1989)
Malmö 19	2−3	36	6,364, C → T[4]	−4, R → W		Green et al (1990)
Malmö 20	2	27	6,364, C → T[4]	−4, R → W		Green et al (1990)
Malmö 40			6,364, C → T[4]	−4, R → W		Green et al (1990)
Bendorf	<1		6,365, G → T	−4, R → L		Ludwig et al
Beuten	<1	45	6,365, G → T	−4, R → L		Ludwig et al
Gleiwitz	<1	49	6,365, G → T	−4, R → L		Ludwig et al
Kingston 1	<1	27	6,365, G → T	−4, R → L		Koeberl et al (1990a)
Oxford 3	<1	89	6,365, G → A[4]	−4, R → Q		Bentley et al (1986)
San Dimas	<1	98	6,365, G → A[4]	−4, R → Q	Abnormal carboxylation; circulates with propeptide	Ware et al (1989)
HB56	<1		6,365, G → A[4]	−4, R → Q		Bottema et al (1990a)
Dortmund	<1		6,365, G → A[4]	−4, R → Q		Ludwig et al
Hong Kong 2	4		6,365, G → A[4]	−4, R → Q		Chan et al
Hong Kong 3	1		6,365, G → A[4]	−4, R → Q		Chan et al

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Kawachi-nagano	<1	46	6,365 G → A[2,4]	−4, R → Q	Sugimoto et al (1989)
Kingston 2	<1		6,365, G → A[4]	−4, R → Q	Koeberl et al (1990a)
Münster	<1		6,365, G → A[4]	−4, R → Q	Ludwig et al
Strasbourg II	<1	40	6,365, G → A[4]	−4, R → Q	de la Salle
Troed-y-Rhiw	4	75	6,365, G → A[4]	−4, R → Q	Liddell et al (1989a)
UK 3	1	48	6,365, G → A[4]	−4, R → Q	Green et al (1989)
UK 4	1	45	6,365, G → A[4]	−4, R → Q	Green et al (1989)
Cambridge	<1	80	6,375, G → C/T[2]	−1, R → S	Abnormal carboxylation; circulates with propeptide — Diuguid et al (1986)
London, Ont 1	6		6,379, A → G	2, N → D	Koeberl et al (1990a)
UK 12	<1		6,392, Δ 1	6	Frameshift, Inhibitor — Green et al (1989)
Oxford b2	6	5	6,395, A → C	7, E → A	Gla — Winship (1989)
Bonn 2	<1	<1	6,402−6, Δ 5	9	Frameshift, Inhibitor — Ludwig et al
Oxford b3	<0.5	0.2	6,406, C → T	11, Q → Stop	Winship (1989)
Hong Kong 1	3		6,410, G → C	12, G → A	Chan et al
Heessen	<1		6,427, T → C	18, C → R	Ludwig et al
Zutphen	<1	100	6,427, T → C	18, C → R	Reitsma et al
Rheidt	2	32	6,449, T → C	25, F → S	Ludwig et al
Seattle 3	<1	30	6,454, G → A	27, E → K	Gla — Chen et al (1989b)
Chongqing	<1	3	6,455, A → T	27, E → V	Gla — Wang et al (1990b)
HB28	<1	<1	6,460, C → T[4]	29, R → Stop	Koeberl et al (1990b)
HB61	<1	7	6,460, C → T[4]	29, R → Stop	Koeberl et al (1990b)
Malmö 4	<1	<0.1	6,460, C → T[4]	29, R → Stop	Inhibitor — Green et al (1989)
UK 14	<1	2	6,460, C → T[4]	29, R → Stop	Montandon et al (1989)
UK 24	1		6,460, C → T[4]	29, R → Stop	Green et al (1990)
HB2	30		6,461, G → A[4]	29, R → Q	Double (see 30,134) — Koeberl et al (1989)
Toronto 17	37		6,461, G → A[4]	29, R → Q	Koeberl et al (1990a)
HB9	4		6,474, A → C	33, E → D	Gla — Koeberl et al (1989)
UK 10	<1	12	6,484−6, Δ 3	37, Δ R	In frame — Green et al (1989)
Ursem	1	<1	6,492−5, Δ 4		Double (see 31,103), donor splice (b) probably causes disease — Poort et al
HB7, Japan	<1	<1	6,680−1, Δ 2	39	Frameshift, Inhibitor — Matsushita et al (1990)
Hoogeveen	14	96	6,690, A → G	43, K → E	Reitsma et al
Oxford 2	0.5	0.4	6,704, T → G		Donor splice (c) — Winship (1986)
Pirmasens	<1	<1	6,704, T → C		Donor splice (c) — Ludwig et al
Toronto 16	3		10,391, G → A		Acceptor splice (d) — Koeberl et al (1990a)
Alabama	10	100	10,392, A → G	47, D → G	Davis et al (1987)
New London	<1	114	10,401, A → C	50, Q → P	Decreased XIa activation — Lozier et al (1990)
Hollywood	11	58	10,415, C → G	55, P → A	Spitzer et al (1989)
UK 7	10−12	49	10,415, C → G	55, P → A	Green et al (1989)
Kleve	<1	<1	10,419, G → C	56, C → S	Ludwig et al
Toronto 2	1	2	10,419, G → A	56, C → Y	Koeberl et al (1990a)
Durham	14		10,430, G → A[4]	60, G → S	Denton et al (1988)
Kingston 3	10	11	10,430, G → A[4]	60, G → S	Koeberl et al (1990a)
Lelystad	13	34	10,430, G → A[4]	60, G → S	Poort et al
Oud en Nieuw Gastel	12	31	10,430, G → A[4]	60, G → S	Poort et al (1989b)
Purmerend	17	22	10,430, G → A[4]	60, G → S	Poort et al
UK 27	10		10,430, G → A[4]	60, G → S	Green et al (1990)
Toronto 6	1	2	10,431, G → A	60, G → D	Koeberl et al (1990a)
UK 6	8	87	10,443, A → G	64, D → G	β Hydroxyaspartate — Green et al (1989)
Trier	<1		10,458, A → G	69, Y → C	Ludwig et al
Toronto 8	2	3	10,512, A → G		Double (see 30,864), donor splice (d) — Koeberl et al (1990a)
HB6	20		17,660−3, Δ 4		Acceptor splice (e) — Koeberl et al (1989)
Toronto 14	3	3	17,667, A → G		Acceptor splice (e) — Koeberl et al (1990a)
Seattle 2	<1	<1	17,669, Δ 1	85	Frameshift — Schach et al (1987)
Königswinter	<1		17,678, G → C	88, C → S	Ludwig et al
Fukuoka	2	66	17,689, A → C[2]	92, N → H	Suehiro et al (1989a)
Hamilton 1	<1		17,710, T → C	99, C → R	Koeberl et al (1990a)
Leamington	13		17,756, G → C	114, G → A	Ritchie et al (1989)
Oxford e1	5	4	17,756, G → C	114, G → A	Winship (1989)
Nastetten	<1		17,759, A → G	115, Y → C	Ludwig et al
Malmö 7	<1	<0.1	17,761, C → T[4]	116, R → Stop	Double (see 30,890) — Montandon et al (1990)
Würzburg	<1		17,763−4, Ins C	117	Frameshift — Ludwig et al
UK 9	<1	0.4	17,773, A → T	120, N → Y	Green et al (1989)
Nörtingen	<1		17,798, G → T		Donor splice (e) — Ludwig et al
Toronto 13	10		17,810, A → G		Donor splice (e) — Koeberl et al (1990a)
Toronto 15	10		17,810, A → G		Donor splice (e) — Koeberl et al (1990a)
Dakar	<1	<1	20,374, T → C	132, C → R	Vidaud (1990)
Albuquerque	1	30	20,413, C → T[4]	145, R → C	Decreased XIa activation — Toomey et al (1988)
Cardiff 1	<1	66	20,413, C → T[4]	145, R → C	Liddell et al (1989b)
UK 21	1		20,413, C → T[4]	145, R → C	Green et al (1990)

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UK 23	2	43	20,413, C → T^4	145, R → C		Green et al (1990)
Chapel Hill	8	100	20,414, G → A^4	145, R → H	Decreased XIa activation	Noyes et al (1983)
Chicago 2	7	160	20,414, G → A^4	145, R → H	Decreased XIa activation	Diuguid et al (1989)
HB25	4		20,414, G → A^4	145, R → H	Decreased XIa activation	Koeberl et al (1989)
Malmö 17	4–11	91	20,414, G → A^4	145, R → H		Green et al (1990)
Malmö 23	7	148	20,414, G → A^4	145, R → H		Green et al (1990)
Malmö 32	5–8	115	20,414, G → A^4	145, R → H		Green et al (1990)
Malmö 36		110	20,414, G → A^4	145, R → H		Green et al (1990)
Malmö 38			20,414, G → A^4	145, R → H		Green et al (1990)
Nagoya-3	<1	60	20,414, G → A^4	145, R → H		Hamaguchi et al (1990)
						Suehiro et al (1990)
HB23	<1		20,466–78, Δ 13	162	Frameshift	Koeberl et al (1989)
HB17	<1		20,497, C → T	173, Q → Stop		Koeberl et al (1989)
BM Nagoya	<1	100	20,518, C → $T^{2,4}$	180, R → W	B_m	Suehiro et al (1989b)
Deventer	<1	130	20,518, C → T^4	180, R → W	B_m	Bertina et al (1989)
Dernbach	<1	69	20,518, C → T^4	180, R → W		Ludwig et al
Hilo	<1	120	20,519, G → A^4	180, R → Q	B_m, decreased XIa activation	Huang et al (1989)
						Monroe et al (1989)
Hilo, Fr	<1	120	20,519, G → A^4	180, R → Q	B_m^6	Vidaud (1990)
Novara	<1	112	20,519, G → A^4	180, R → Q	B_m	Bertina et al (1989)
Rheine 2	<1		20,519, G → A^4	180, R → Q		Ludwig et al
Altenhunden	<1		20,519, G → A^4	180, R → Q		Ludwig et al
Milano	<1	130	20,521, G → T	181, V → F	B_m	Bertina et al (1989)
Cardiff 2	15	132	20,524, G → C	182, V → L	B_m^6	Taylor et al (1990)
Kashihara	<1	120	20,524, G → T	182, V → F	B_m^6	Sakai et al (1989)
Bottrop	<1	92	20,531–3, Δ 3	184, Δ G	In frame	Ludwig et al
HB5 Japan	<1	<1	20,551, C → T	191, Q → Stop	Inhibitor, Double (see −793)	Matsushita et al (1990)
Unnamed	<1	<1	20,552, A → T	191, Q → L		Chen et al (1990)
Malmö 5	<1	<0.1	20,561, G → A	194, W → Stop	Inhibitor	Green et al (1989)
Oxford 1	<0.5	0.3	20,566, G → T		Donor splice (f)	Rees et al (1985)
Rotenburg	<1	<1	20,566, G → A		Donor splice (f)	Ludwig et al
Wültschkau	7		30,084, G → T	211, V → F		Ludwig et al
Unnamed	<1	<1	30,097, G → A	215, W → Stop		Chen et al (1990)
Toronto 5	<1	3	30,112, C → T	220, A → V		Koeberl et al (1990a)
Toronto 11	4		30,112, C → T	220, A → V		Koeberl et al (1990a)
HB24	1		30,119, T → G	222, C → W		Koeberl et al (1989)
HB2	30		30,134, T → C	None	Double (see 6,461), N	Koeberl et al (1989)
HB1	12		30,150, G → A^4	233, A → T		Koeberl et al (1989)
Malmö 28	22		30,150, G → A^4	233, A → T		Green et al (1990)
Malmö 29	5–22	12	30,150, G → A^4	233, A → T		Green et al (1990)
Malmö 30	8–15		30,150, G → A^4	233, A → T		Green et al (1990)
Malmö 31	11	15	30,150, G → A^4	233, A → T		Green et al (1990)
Opladen	10	13	30,150, G → A^4	233, A → T		Ludwig et al
Iceland 1	3	119	30,800, Ins A	None	Double (see 31,119), N	Green
HB6, Japan	<1	<1	30,821, G → A		Inhibitor, Acceptor splice (h)	Matsushita et al (1990)
Spijkenisse	2	74	30,854, G → A	245, E → K		Reitsma et al
Monschau	3	39	30,855, A → T	245, E → V		Ludwig et al
HB60	<1	<1	30,863, C → T^4	248, R → Stop		Koeberl et al (1990b)
Malmö 3	<1	<0.1	30,863, C → T^4	248, R → Stop	Inhibitor	Green et al (1989)
Malmö 14	<1	<0.1	30,863, C → T^4	248, R → Stop		Green et al (1990)
Malmö 15	<1	<0.1	30,863, C → T^4	248, R → Stop		Green et al (1990)
UK 26	<1	4	30,863, C → T^4	248, R → Stop		Green et al (1990)
UK 47	<1		30,863, C → T^4	248, R → Stop		Green et al (1990)
Unnamed	<1	<1	30,863, C → T^4	248, R → Stop		Wang et al (1990a)
Seattle 4	3–4	3–4	30,864, G → A^4	248, R → Q		Chen et al (1989b)
						Zhang et al (1989b)
Toronto 8	2	3	30,864, G → A^4	248, R → Q	Double (see 10,512)	Koeberl et al (1990a)
Leiria	<1	<1	30,875, C → T^4	252, R → Stop		Siguret et al (1988)
Malmö 41	<1	6	30,875, C → T^4	252, R → Stop		Green et al (1990)
Portland	<1	<1	30,875, C → T^4	252, R → Stop		Chen et al (1989a)
Toronto 18	3		30,875, C → T^4	252, R → Stop		Taylor (1990)
Malmö 7	<1	<0.1	30,890, C → T	257, H → Y	Double (see 17,761), N	Montandon et al (1990)
HB8	24		30,900, A → G	260, N → S		Koeberl et al (1989)
Toronto 1	1	4	30,933, C → T	271, A → V		Koeberl et al (1990a)
San Antonio	<1	14	30,945, T → C	275, L → P		Jagadeeswaran
Malmö 1	<1	<0.1	30,950–7, Δ 8	277	Frameshift, Inhibitor	Green et al (1989)
Zoeterwoude	13	13	30,956, T → A	279, L → I		Reitsma et al
Unnamed	<1	<1	30,981, C → T	287, P → L		Chen et al (1990)
Oxford h2	2	3	30,992, G → C	291, A → P		Winship (1989)
UK 13	4–16		30,992, G → A	291, A → T		Montandon et al (1989)
Beberbeck	4	7	31,008, C → T^4	296, T → M		Ludwig et al
B.Liebenzell	6	7	31,008, C → T^4	296, T → M		Ludwig et al
HB19	<1		31,008, C → T^4	296, T → M		Koeberl et al (1989)
Malmö 25	4	15	31,008, C → T^4	296, T → M		Green et al (1990)

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Neuhausen	4	9	31,008, C → T[4]	296, T → M		Ludwig et al
UK 32	6	5	31,008, C → T[4]	296, T → M		Green et al (1990)
Unnamed	5	18	31,041, T → C	307, V → A		Bottema et al (1989)
Unnamed	<1	58	31,047, G → T	309, G → V		Thompson et al (1989)
Unnamed	<1	<1	31,051, G → A	310, W → Stop		Wang et al (1990a)
HB26	3		31,052, G → A	311, G → R		Koeberl et al (1989)
UK 11	<1	<2	31,059–60, Δ 2	313	Frameshift	Green et al (1989)
Toronto 7	<1	90	31,080, C → A	320, A → D		Koeberl et al (1990a)
Oxford h5	4	4	31,103, G → T	328, V → F		Winship (1990)
Ursem	1	<1	31,103, G → A	328, V → I	Double (see 6,492–5), N	Poort et al
HB29	<1	<1	31,118, C → T[4]	333, R → Stop		Koeberl et al (1990b)
HB30	<1	1	31,118, C → T[4]	333, R → Stop		Koeberl et al (1990b)
UK 34	6		31,118, C → T[4]	333, R → Stop	Female	Green et al (1990)
Unnamed	<1	1	31,118, C → T[4]	333, R → Stop		Chen et al (1990)
UK 2	<1	135	31,119, G → A[4]	333, R → Q		Tsang et al (1988)
Heerde	1	122	31,119, G → A[4]	333, R → Q		Poort et al (1989a)
Iceland 1	3	119	31,119, G → A[4]	333, R → Q	Double (see 30,800)	Green et al (1990)
UK 5	1–2	75	31,119, G → A[4]	333, R → Q		Green et al (1989)
UK 18	1	130	31,119, G → A[4]	333, R → Q		Green et al (1990)
Unnamed	2	32	31,119, G → A[4]	333, R → Q		Wang et al (1990a)
UK 8	2	2	31,127, T → C	336, C → R		Green et al (1989)
Bonn 1	<1	<1	31,133, C → T[4]	338, R → Stop		Ludwig et al (1989)
New York	<1	<1	31,133, C → T[4]	338, R → Stop		Driscoll et al (1989)
UK 20	2	<1	31,133, C → T[4]	338, R → Stop		Green et al (1990)
UK 31	<1		31,133, C → T[4]	338, R → Stop		Green et al (1990)
Unnamed	<1	<1	31,133, C → T[4]	338, R → Stop		Freedenberg et al (1989)
Gladbeck	4	87	31,151, A → T	344, I → F		Ludwig et al
Unnamed	3	103	31,163, A → G	348, M → V		Chen et al (1990)
Unnamed	2	130	31,200, C → T	360, S → L		Chen et al (1990)
Eagle Rock	1–5	100	31,209, G → T	363, G → V		Spitzer et al (1988b)
Mechtal	<1	100	31,211, G → C	364, D → H		Ludwig et al
Toronto 4	1	90	31,216, T → A	365, S → R		Koeberl et al (1990a)
Unnamed	<1	14	31,220, G → A	367, G → R		Chen et al (1990)
Bergamo	<1	156	31,223, C → A	368, P → T	B_m	Bertina et al (1989)
Unnamed	<1	<1	31,253, T → C	378, F → L		Chen et al (1990)
Lake Elsinore	<1	100	31,290, C → T	390, A → V	B_m	Spitzer et al (1988a)
Niigata	1–4	140	31,290, C → T	390, A → V	B_m	Sugimoto et al (1988)
Unnamed	2	30	31,290, C → A	390, A → E		Wang et al (1990a) Chen et al (1990)
Angers	<1	90	31,307, G → A	396, G → R	B_m^6	Attree et al (1989)
Angers	<1	110	31,307, G → A	396, G → R	B_m^6	Vidaud et al (1988)
HB11,12,14, 16,18	<1–6		31,311, T → C	397, I → T		Koeberl et al (1989)
Long Beach	<1	100	31,311, T → C	397, I → T		Ware et al (1988)
Los Angeles	<1	100	31,311, T → C	397, I → T		Spitzer et al (1990)
Toronto 3	2	55	31,311, T → C	397, I → T		Bottema et al (1990b)
Toronto 9	2	65	31,311, T → C	397, I → T		Bottema et al (1990b)
Toronto 10	1	73	31,311, T → C	397, I → T		Bottema et al (1990b)
Toronto 12	4	61	31,311, T → C	397, I → T		Bottema et al (1990b)
Vancouver	3	62	31,311, T → C	397, I → T		Geddes et al (1989)
Vancouver, Fr	2	62	31,311, T → C	397, I → T	B_m^6	Attree et al (1989)
Vancouver, Fr	3	70	31,311, T → C	397, I → T	B_m^6	Attree et al (1989)
Vancouver, Fr	4	52	31,311, T → C	397, I → T	B_m^6	Attree et al (1989)
Lincoln Park	3	9	31,327–8, Δ2 Ins AAGGTACCAA	402	Rao et al (1990)	
HB20	1		31,340, T → C	407, W → R		Koeberl et al (1989)
Bordeaux	<1	<1	31,352, A → T	411, K → Stop		Attree et al (1989)

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

[2] Nucleotide change predicted from amino acid sequence.

[3] The following comments or abbreviations are used:
(i) *Inhibitor*–patients developing anti-factor IX antibodies in response to therapeutic factor IX.
(ii) *Frameshift*–caused by the addition (symbol *Ins*) or deletion (symbol Δ) affecting nucleotides corresponding to the *stated amino acid number* and terminating at a new stop codon shortly after.
(iii) *Double*–a double mutant, entered twice in the data base and cross-referenced.
(iv) *N*–indicates the mutation, usually a double mutant, is probably a normal variant–not causing the disease.
(v) the exon (a-h) immediately adjacent to *donor* or *acceptor splice* sites is noted.
(vi) *Gla* refers to glutamic acid residues normally γ-carboxylated, and β-hydroxyaspartate to the single modified aspartate residue.
(vii) B_m–patients with a prolonged bovine prothrombin time (Hougie & Twomey, 1967).

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

[5] % varies with age, rising after puberty.

[6] Bovine prothrombin time is moderately prolonged.

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

database that 45% (or 97 of the total of 216 mutations) occur at CG residues. However this figure may over-estimate the proportion of cases involving CG mutations, because of the inclusion of the Green et al (1990) paper which selectively reports on a large number of patients with such mutations. If we exclude this paper, the proportion of CG to total mutations decreases to about 35%. A few repeat mutations do not involve CG residues, and with regard to the repeat at nucleotide 31,311, it has been proposed from a haplotype analysis that they are separate observations of the same 'founder' mutant (Thompson et al, 1990).

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 except the signal peptide and poly(A) site. Missense mutations within individual protein domains give valuable information as to the essential nature of specific amino acids and are a significant aid to structural studies of domains (e.g. see Handford et al, 1990). Similarly, promoter mutations are invaluable in studying gene regulation (e.g. Crossley & Brownlee, 1990).

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

The data base was compiled from separate lists prepared by coordinators for the different countries as follows: Giannelli and Green representing the UK, Sweden and Iceland (60 entries); High and Lozier representing USA (60 entries); Lillicrap representing Canada (27 entries); Ludwig and Olek representing Germany (32 entries); Reitsma representing The Netherlands (18 entries); Goossens representing France (11 entries); Yoshioka representing Japan (10 entries); and Brownlee, the rest of the world (3 entries from Hong Kong) and central coordinator. Sommer is included, exceptionally, as his laboratory has made significant recent contributions to both the Canadian and USA list of entries. We plan to update this data base annually. New data or notification of errors or omissions should be sent to the individual country coordinators.

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REFERENCES

Anson D.S., Choo K.H., Rees D.J.G. et al (1984) EMBO J. 3: 1054–1064
Attree O., Vidaud D., Vidaud M., Amselem S., Lavergne J.M. and Goossens M. (1989) Genomics 4: 266–272
Bentley A.K., Rees D.J.G., Rizza C. and Brownlee G.G. (1986) Cell 45: 343–348
Bertina R.M., Van der Linden I.K., Mannucci P.M. et al (1989) Thromb. Haemostas. 62: 203
Bottema C.D.K., Koeberl D.D. and Sommer S.S. (1989) Lancet (ii), 526–529
Bottema C.D.K., Ketterling R.P., Koeberl D.D. et al (1990a) Nucleic Acids Research, in press
Bottema C.D.K., Koeberl D.D., Ketterling R.P. et al (1990b) Brit.J.Haematol. in press.
Brownlee G.G. (1988) in: Recent Advances in Haematology, ed. Hoffbrand A.V. (Churchill Livingstone) vol.5, pp. 251–264
Chan V. et al, Dept of Medicine, Univ. of Hong Kong, Queen Mary Hospital, Hong Kong, unpublished
Chen S.H., Scott C.R., Lovrien E.W. et al (1989a) Am. J. Hum. Genetics 44: 567–569
Chen S.H., Thompson A.R, Zhang M., and Scott C.R. (1989b) J. Clin. Invest. 84: 113–118
Chen S.H., Zhang M., Lovrien E.W. et al (1990) Genomics, in press
Crossley P.M. and Brownlee G.G. (1990) Nature 345: 444–446
Crossley P.M., Winship P.R., Black A., Rizza C. and Brownlee G.G. (1989) Lancet (i): 60
Crossley P.M. et al, Dunn School of Pathology, University of Oxford, South Parks Road, Oxford, UK, unpublished
Davis L.M, McGraw R.A., Ware J.L. et al (1987) Blood 69: 140–143
De la Salle C., INSERM U311, CRTS, 10 Rue Spielman, 67085 Strasbourg, France, unpublished
Denton P.H., Fowlkes D.M., Lord S.T., and Reisner H.M. (1988) 72: 1407–1411
Diuguid D.L., Rabiet M.J., Furie B.C. et al (1986) Proc. Natl. Acad. Sci. (USA) 83: 5803–5807
Diuguid D.L., Rabiet M.J., Furie B.C., and Furie B. (1989) Blood 74: 193–200
Driscoll M.C., Bouhassira E. and Aledort L.M. (1989) Blood 74: 737–742
Fahner J.B., Salier J.P., Landa L. et al (1988) Blood 72 (suppl): 295a (abstract)
Freedenberg D.L., Chen S.H., and Scott R. (1989) Am J. Hum. Genetics 45 (suppl): A186 (abstract)
Geddes V.A., LeBonniec B.F., Louie G.V., Brayer G.D., Thompson A.R., and MacGillivray R.T.A. (1989) J.Biol.Chem. 264: 4689–4697
Giannelli F., (1989) in: Baillière's Clinical Haematology, ed. Tuddenham E.G.D. (Baillière & Tindall, London) vol.2
Gispert S., Vidaud M., Vidaud D., Gazengel C., Boneu B. and Goossens M. (1989) Am.J.Hum.Genet. 45 Abstract 739
Green P.M., Paediatric Research Unit, Guy's Hospital Tower, London, UK, unpublished
Green P.M., Bentley D.R., Mibashan R.S., Nilsson I.M. and Giannelli F. (1989) EMBO J. 8: 1067–1072
Green P.M., Montandon A.J., Bentley D.R., Ljung R., Nilsson I.M. and Giannelli F. (1990) Nucleic Acids Research, 18: 3227–3231
Hamaguchi M., Matsushita T., Tanimoto M., Yamamoto K., Sugiura I., Takamatsu J., Saito H. and Kamiya T. (1990) Acta Haematol.Jpn. 53: 452 (abstract)
Handford P.A., Baron M., Mayhew M., Willis A., Beesley T., Brownlee G.G. and Campbell I.D. (1990) EMBO J. 9: 475–480
Hougie C. and Twomey J.J. (1967) Lancet i: 699
Huang M.N., Kasper C.K., Roberts H.R. et al (1989) Blood 73: 718–721
Jagadeeswaran P., Dept of Cellular & Structural Biology, Univ. of Texas, San Antonio, Texas, USA, unpublished
Koeberl D.D., Bottema C.D.K., Buerstedde J.M., and Sommer S.S. (1989) Am. J. Hum. Genetics 45: 448–457
Koeberl D.D., Bottema C.D.K., Ketterling R.P., et al. (1990a) Am.J.Hum.Genet. in press
Koeberl D.D, Bottema C.D.K., Sarkar G. et al (1990b) Hum. Genetics 84: 387–390
Liddell M.B., Lillicrap D.P., Peake I.R. and Bloom A.L. (1989a) Brit.J.Haematol. 72: 208–215
Liddell M.B., Peake I.R., Taylor S.A.M. et al (1989b) Brit.J.Haematol 72: 556–560
Lozier J.N., Monroe D.M., Stanfield-Oakley S.A. et al (1990) Blood 75: 1097–1104
Ludwig M., Schwaab R., Eigel A., Horst J., Egli H., Brackmann H-H and Olek K. (1989) Am.J.Hum.Genet. 45: 115–122
Ludwig M. et al, Inst. Exp. Hämatologie, Univ. of Bonn, 5300 Bonn 1, W.Germany, unpublished
Matsushita T., Tanimoto M., Yamamoto K., Sugiura I., Hamaguchi M., Takamatsu J., Kamiya T. and Saito H. (1990) Acta Haematol.Jpn. 53: 452 (abstract)
Monroe D.M., McCord D.M., Huang M.N. et al (1989) 73: 1540–1544
Montandon, A.J., Green, P.M., Giannelli, F. and Bentley, D.R. (1989) Nucl. Acids Res. 17: 3347–3358
Montandon, A.J., Green, P.M., Bentley, D.R., Ljung, R., Nilsson, I.M. and Giannelli, F. (1990) Hum. Gen., in press
Noyes C.M., Griffith M.J., Roberts H.R., and Lundblad R.L. (1983) Proc. Natl. Acad. Sci. (USA) 80: 4200–4202
Poort S.R., Briët E., Bertina R.M. and Reitsma P.H. (1989a) Nucl. Acids Res. 17: 3614
Poort S.R., Briët E., Bertina R.M. and Reitsma P.H. (1989b) Nucl. Acids. Res. 17: 5869
Poort S.R. et al, Hemostasis & Thrombosis Research Unit, 2300 RC Leiden, The Netherlands, unpublished
Rao K.J., Lyman G., Hamsabhushami K. et al (1990) Molecular & Cellular Probes, in press
Rees D.J.G., Rizza C.R. and Brownlee G.G. (1985) Nature 316: 643–645

Reitsma P.H., Bertina R.M., Ploos van Amstel J.K., Riemens A. and Briët E. (1988) Blood 72: 1074–1076
Reitsma P.H., Mandalaki T, Kasper C.K. and Briët E. (1989) Blood 73: 743–746
Reitsma P.H. et al, Hemostasis & Thrombosis Research Unit, 2300 RC Leiden, The Netherlands, unpublished
Ritchie D.B.C., Tam B.M. and MacGillivray R.T.A. (1989) Alberta Heritage Foundation for Medical Research Heritage Days. Abstract
Sakai T., Yoshioka A., Yamamoto K., Niinomi K., Fujimura Y., Fukui H., Miyata T. and Iwanaga S. (1989) J.Biochem. 105: 756–759
Schach B.G., Yoshitake S., Davie E.W. (1987) J. Clin. Invest. 80: 1023–1028
Siguret V., Amselem S., Vidaud M., Assouline Z., Kerbirou-Nabias D., Pietu G., Goossens M., Larrieu M.J., Bahnak B., Meyer D. and Lavergne J.M. (1988) Br.J.Haematol. 70: 411–416
Spitzer S.G., Pendurthi U.R., Kasper C.K., and Bajaj S.P. (1988a) J. Biol. Chem. 263: 10,545–10,548
Spitzer S.G., Warn-Cramer B.J., Kasper C.K. et al (1988b) Circulation 78 (suppl II): 118 (abstract)
Spitzer S., Katzman D., Kasper C.K., and Bajaj S.P. (1989) Thromb. Haemostasis 62 (suppl): 203 (abstract)
Spitzer S.G., Warn-Cramer B.J., Kasper C.K., and Bajaj S.P. (1990) Biochem. J. 265: 219–225
Suehiro K., Okamura T., Murakawa M., Niho Y., Takeya H., Nishimura H. and Iwanaga S. (1989a) Blood & Vessel 20: 397 (abstract)
Suehiro K., Kawabata S., Miyata T., Takeya H., Takamatsu J., Ogata K., Kamiya T., Saito H., Niho Y. and Iwanaga S. (1989b) J.Biol.Chem. 264: 21257–21265
Suehiro K., Miyata T., Takeya H., Takamatsu J., Saito H., Niho Y. and Iwanaga S. (1990) Acta Haematol.Jpn. 53: 452 (abstract)
Sugimoto M., Miyata T., Kawabata S., Yoshioka A., Fukui H., Takahashi H. and Iwanaga S. (1988) J. Biochem. 104: 878–880
Sugimoto M., Miyata T., Kawabata S., Yoshioka A., Fukui H. and Iwanaga S. (1989) Br.J.Haematol. 72: 216–221
Taylor S.A.M. (1990). Ph.D. Thesis, Queen's University, Kingston, Ontario.
Taylor S.A.M., Liddell M.B., Peake I.R., Bloom A.L. and Lillicrap D.P. (1990) Brit.J.Haematol. in press.
Thein S.L. and Weatherall D.J. (1988) in: Recent Advances in Haematology, ed. Hoffbrand A.V. (Churchill Livingstone) vol.5, pp. 43–74
Thompson A.R. (1990) Prog.Hemost.Thromb. 10: in press
Thompson A.R., Chen S.H., and Brayer G.D. (1989) Blood 74 (suppl): 134a (abstract)
Thompson A.R., Bajaj S.P., Chen S-H. and MacGillivray R.T.A. (1990) Lancet 335: 418
Toomey J.R., Stafford D., and Smith K. (1988) Blood 72 (suppl): 312a (abstract)
Tsang T.C., Bentley D.R., Mibashan R.S. and Giannelli F. (1988) EMBO J. 7: 3009–3015
Vidaud M., Attree O., Schaad O., Vidaud D., Edelstein S. and Goossens M. (1988) Blood 72 Suppl.1, Abstract 1161
Vidaud M. (1990) Thesis, Paris VII University
Wang N.S., Chen S.H., Thompson A.R. (1990a) Thromb. Haemostasis, submitted
Wang N.S., Zhang N.S., Thompson A.R., and Chen S.H. (1990b) Thromb. Haemostasis 63: 24–26
Ware J., Davis L., Frazier D. et al (1988) Blood 72: 820–822
Ware J., Diuguid D.L., Liebman H.A. et al (1989) J. Biol. Chem. 264: 11,401–11,406
Winship P.R. (1986) D.Phil thesis, Oxford University
Winship P.R. (1989) Thromb. Haemostasis (abstract) 62, 465
Winship P.R. (1990) Nucleic Acids Research 18: 1310
Winslow R.M. and Anderson W.F. (1983) in: The Metabolic Basis of Inherited Disease, eds. Stanbury J.B. et al., 5th edn. (McGraw-Hill, New York) pp. 1666–1710
Yoshitake S., Schach B.G., Foster D.C., Davie E.W. and Kurachi K. (1985) Biochemistry 24: 3736–3750
Zhang M., Chen S.H., Scott C.R., and Thompson A.R. (1989a) Hum. Genetics 82: 283–284
Zhang M., Chen S.H., Thompson A.R., and Lovrien E. (1989b) Am. J. Hum. Genetics 45 (suppl): A231 (abstract)