Physiol. Res. 55 (Suppl. 2): S119-S136, 2006

May 2006 Update in Porphobilinogen Deaminase Gene Polymorphisms and Mutations Causing Acute Intermittent Porphyria. Comparison with the Situation in Slavic Population

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Received June 16, 2006
Accepted September 4, 2006

Summary

Acute intermittent porphyria (AIP) is an autosomal dominant disorder of heme biosynthesis caused by molecular defects in the porphobilinogen deaminase (PBGD) gene. This paper reviews published mutations, their types, and polymorphisms within the PBGD gene. To date, 301 different mutations and 21 polymorphisms have been identified in the PBGD gene in AIP patients and individuals from various countries and ethnic groups. During the search for mutations identified among Slavic AIP patients we found 65 such mutations and concluded that there is not a distinct predominance of certain mutations in Slavs.

Key words

Acute intermittent porphyria • Polymorphisms • Mutations • PBGD gene • MIM 176000

Introduction

Heme is produced in the mitochondrion by a complex cellular machinery comprising eight enzymes that are evolutionarily conserved from bacteria to humans. Mutations in genes encoding the heme biosynthetic pathway enzymes lead to diseases broadly classified as porphyrias. Porphobilinogen deaminase (PBGD, EC 4.3.1.8), also marked as hydroxymethylbilan synthase, is the third enzyme in the heme biosynthetic pathway. Deficiency of this enzyme results in the low-penetrant autosomal dominant disorder, acute intermittent porphyria (AIP, MIM 176000). Clinically, AIP is characterized by life-threatening acute neurovisceral attacks that can be provoked by various factors such as drugs, hormones and alcohol. Numerous mutations within PBGD have been identified. The probability of a life-threatening porphyric attack in AIP is a significant personal burden and creates a challenge for counseling and medical management. Introducing molecular biology techniques to the diagnosis and heme arginate to the treatment of acute attacks increase our chances for effective patients care.

This paper reviews published defects and polymorphisms in the PBGD gene. Careful investigation of published bibliography revealed 301 mutations in the PBGD gene described so far. We hope this review will help in molecular screening for AIP. A special attention was given to the defects described in Slavic AIP population in which 65 different mutations found did not show specific hot spots in their distribution.

Table 1. Reported Mutations in the PBGD Gene Responsible for Acute Intermittent Porphyria

Position	Nucleotide change	Type of mutation	Mutation consequence	Reference (first report)
Promoter				
-154	del G	other	Transcription impairment	*Whatley et al. 2000*
Exon 1				
3	G>A*	MS	M1I	*Chen et al. 1994*
33	G>A	SD	(?)	*Luchinina et al. 2005*
33	G>T*	SD	IVS1 67 bp retention , FS → Stop + 41	*Grandchamp et al. 1989a*
IVS 1				
33+1	G>A*	SD	IVS1 67 bp retention , FS → Stop + 41	*Grandchamp et al. 1989b*
33+1	G>T	SD	IVS1 67 bp retention , FS → Stop + 41	*Yu et al. 2000*
33+2	T>A	SD	IVS1 67 bp retention , FS → Stop + 41	*Puy et al. 1998*
33+2	T>C	SD	IVS1 67 bp retention , FS → Stop + 41	*Brasch et al. 2004*
33+3	G>T	SD	IVS1 67 bp retention , FS → Stop + 41	*Mustajoki et al. 1998*
33+5	G>A	SD	(?)	*Luchinina et al. 2005*
33+5	G>C	SD	IVS1 67 bp retention , FS → Stop + 41	*Puy et al. 1998*
IVS 2				
34-2	A>G	SA	Exon 3 deletion	*Gouya et al. 2004*
Exon 3				
41	del A	FS	FS → Stop + 3	*Whatley et al. 2000*
53	del T	FS	FS → Stop + 2	*Surin et al. 2001*
64	C>T*	MS	R22C	*Ong et al. 1998*
66	C>G	SD	Exon 3 deletion	*Llewellyn et al. 1996*
70	G>A	MS	G24S	*Rosipal et al. 1997*
72	G>A	MS	G24D	*Luchinina et al. 2005*
76	C>T*	MS	R26C	*Kauppinen et al. 1995*
77	G>A*	MS	R26H	*Llewellyn et al. 1993*
83	G>A	MS	S28N	*Puy et al. 1997*
86	A>T	MS	Exon 3 deletion	*Mustajoki et al. 1998*
IVS 3				
87+1	G>A*	SD	Exon 3 deletion	*Lundin et al. 1995*
87+2	T>G	SD	Exon 3 deletion ?	*Schneider-Yin et al. 2006*
87+5	G>T	SD	Exon 3 deletion ?	*Luchinina et al. 2005*
88-2	A>G	SA	Exon 4 deletion	*Floderus et al. 2002*
Exon 4				
88	C>A	SA	Exon 4 deletion	*Gouya et al. 2004*
91	G>A*	MS	A31T	*Gu et al. 1994*
91	G>C*	MS	A31P	*Whatley et al. 1999*
92	C>T	MS	A31V	*Luchinina et al. 2005*
97	del A*	FS	FS → Stop + 10	*Kauppinen et al. 1995*
100	C>A*	MS	Q34K	*Mgone et al. 1992*
100	C>T	MS	Q34X	*Kauppinen et al. 1995*
101	A>C*	MS	Q34P	*De Siervi et al. 1999a*
101	A>G	MS	Q34R	*Gouya et al. 2004*
104	C>T	MS	T35M	*De Siervi et al. 2000*
108_109	ins T	FS	FS → Stop + 16	*Solis et al. 1999*
125	T>A*	NS	L42X	*Puy et al. 1996*
125	T>C*	MS	L42S	*Whatley et al. 1999*
134	C>A	NS	S45X	*Martinez di Montemuros et al. 2000*
138	C>A	NS	Y46X	*Gregor et al. 2002*

148	C>T	NS	Q50X	*Floderus et al. 2002*
158_159	ins A	FS	FS → Stop + 12	*Rosipal et al. 1997*
IVS 4				
160+1	G>T	SD	Exon 4 deletion	*Puy et al. 1997*
160+1	G>A	SD	Exon 4 deletion	*Whatley et al. 1999*
161-6	C>G*	SD	Exon 5 deletion	*Whatley et al. 1999*
161-3_5	del CTC	SA	Exon 5 deletion ?	*Schneider-Yin et al. 2006*
161-2	A>C	SA	Exon 5 deletion	*Whatley et al. 1999*
161-1	G>C	SA	Exon 5 deletion	*Petersen et al. 1998*
Exon 5				
163	G>T*	MS	A55S	*Gu et al. 1994*
168_169	del GT	FS	FS → Stop + 8	*Schreiber et al. 1995a*
174	del C*	FS	FS → Stop + 40	*Gu et al. 1994*
178_179	ins G	FS	FS → Stop + 5	*Gouya et al. 2004*
180_181	ins Alu (333 bp)	FS	FS → Stop + 18	*Mustajoki et al. 1999*
181	G>A	MS	D61N	*Whatley et al. 1999*
181	G>T	MS	D61Y	*Gregor et al. 2002*
181	G>C	MS	D61H	*Brasch et al. 2004*
181	del G	FS	FS → Stop + 37	*Di Pierro et al. 2005*
182_183	ins G*	FS	FS → Stop + 5	*Gu et al. 1994*
182	del A	FS	FS → Stop + 36	*Martinez di Montemuros et al. 2000*
182_183	ins GA	FS	FS → Stop + 37	*Martinez di Montemuros et al. 2001*
184_185	del AA	FS	FS → Stop + 3	*Whatley et al. 1999*
202_203	del CT	FS	FS → Stop + 2	*Luchinina et al. 2005*
206_207	del CT*	NS	S69X	*Puy et al. 1997*
207	del T	FS	FS → Stop + 28	*Floderus et al. 2002*
207_208	ins T	FS	FS → Stop + 1	*Gouya et al. 2004*
210	G>A	SD	Exon 5 deletion (?)	*Floderus et al. 2002*
IVS 5				
210+1	G>A*	SD	Exon 5 deletion	*Gu et al. 1994*
210+2_3	ins G*	SD	Exon 5 deletion	*Puy et al. 1997*
210+2	T>C	SD	Exon 5 deletion	*Whatley et al. 1999*
211-1	G>A	SA	Exon 6 deletion	*Di Pierro et al. 2005*
211-1	G>C	SA	Exon 6 deletion	*Surin et al. 2001*
Exon 6				
215_216	del GA	FS	FS → Stop + 10	*Gross et al. 1999*
218_219	del AG*	FS	FS → Stop + 9	*Gu et al. 1994*
232	A>C	MS	T78P	*Ramdall et al. 2000*
239	A>G	MS	E80G	*Ramdall et al. 2000*
242	T>C	MS	L81P	*Hesslels et al. 2004*
254	T>G*	MS	L85R	*Whatley et al. 1999*
257	A>T	MS	E86V	*Floderus et al. 2002*
IVS 6				
266+1	G>C	SD	Exon 6 deletion	*Lundin et al. 1997*
267-54_61	del GAAGGGGT	SA (?)	Exon 7 deletion (?)	*Brasch et al. 2004*
Exon 7				
269	T>G	MS	V90G	*Whatley et al. 1999*
275	T>C	MS	L92P	*Floderus et al. 2002*
277	G>T	MS	V93F	*Chen et al. 1994*
278	T>A	MS	V93D	*Luchinina et al. 2005*
278_280	del TTG	IFD	del V93	*Gregor et al. 2002*
287	C>T	MS	S96F	*De Rooij et al. 1995*
291	del G	FS	FS → Stop + 37	*Puy et al. 1997*
293	A>G	MS	K98R	*Kauppinen et al. 1995*
295	G>C	MS	D99H	*De Rooij et al. 1995*
295	G>A	MS	D99N	*Martinez di Montemuros et al. 2001*
296	A>G	MS	D99G	*Floderus et al. 2002*
308_309	del TG	FS	FS → Stop + 18	*Martinez di Montemuros et al. 2000*
314_315	ins C	FS	FS → Stop + 15	*Schreiber et al. 1995a*

315	del T	FS	FS → Stop + 15	*Gregor et al. 2002*
323_324	ins T	FS	FS → Stop + 13	*Whatley et al. 1999*
331	G>A*	MS	G111R	*Gu et al. 1993a*
335	C>A	MS	A112D	*Luchinina et al. 2005*
338	T>C	MS	I113T	*Floderus et al. 2002*
339_340	ins T	FS	FS → Stop + 7	*Solis et al. 2004*
340_341	ins T*	FS	FS → Stop + 7	*Whatley et al. 1999*
342	C>A	NS	C114X	*Puy et al. 1997*
IVS 7				
344+1	G>A	SD	Exon 7 deletion	*Robreau-Fraolini et al. 2000*
344+1	G>C	SD	Exon 7 deletion	*Cappellini et al. 2002*
344+2	T>C	SD	IVS 7 15 bp retention	*Martinez di Montemuros et al. 2000*
344+2_5	del TAAG	SD	Exon 7 deletion	*Surin et al. 2001*
344+33	G>T	SD	Exon 7 deletion	*Whatley et al. 1999*
345-2	A>G	SA	Exon 8 deletion	*Floderus et al. 2002*
345-1	G>C	SA	Exon 8 deletion	*Brasch et al. 2004*
345-1	G>A	SA	Exon 8 deletion	*Schreiber et al. 1994a*
Exon 8				
346	C>T*	MS	R116W	*Gu et al. 1993*
347	G>A	MS	R116Q	*Mgone et al. 1994*
356	C>T	MS	P119L	*Lundin et al. 1995*
361	G>T	MS	D121Y	*Schneider-Yin et al. 2006*
371	T>A	MS	V124D	*Puy et al. 1997*
415	G>T	NS	E139X	*Luchinina et al. 2005*
416_417	ins CA	FS	FS → Stop + 116	*Mustajoki et al. 1998*
422	del G	SD	Exon 8 deletion	*Whatley et al. 1999*
IVS 8				
422+1	G>T*	SD	Exon 8 deletion	*Lundin et al. 1995*
423-1	G>A	SA	(?)	*Luchinina et al. 2005*
423-1	G>T	SA	Deletion 15 bp Exon 9	*De Siervi et al. 1999*
Exon 9				
445	C>T*	NS	R149X	*Kauppinen et al. 1995*
446	G>A*	MS	R149Q	*Delfau et al. 1991*
446	G>T*	MS	R149L	*Gu et al. 1994*
453_455	del AGC	IFD	del A152	*De Siervi et al. 1999*
463	C>T	NS	Q155X	*Scobie et al. 1990a*
469_470	del AA	FS	FS → Stop + 52	*Di Pierro et al. 2004a*
470_471	ins A	FS	FS → Stop + 53	*Schreiber et al. 1994*
489_490	ins TCCT	FS	FS → Stop + 1	*Whatley et al. 1999*
IVS 9				
498+1	G>A	SD	Exon 9 deletion	*Nielsen 1997*
498+15	G>T	SD (?)	Exon 9 deletion (?)	*Brasch et al. 2004*
498+22	G>A	SD	?	*Martinez di Montemuros et al. 2001*
499-13	del 14 ins 3	SA (?)	Exon 10 deletion (?)	*Brasch et al. 2004*
499-1	G>A*	SA	Exon 10 deletion	*Lundin et al. 1994*
Exon 10				
499	C>T*	MS	R167W	*Gu et al. 1992*
500	G>A*	MS	R167Q	*Delfau et al. 1990*
500	del G	FS	FS → Stop + 98	*Puy et al. 1997*
503_504	ins A	FS	FS → Stop + 40	*Schuurmans et al. 2001*
508_510	del CTC	IFD	del L170	*Schuurmans et al. 2001*
517_533	del 17 bp	FS	FS → Stop + 30	*Puy et al. 1997*
517	C>T*	MS	R173W	*Lee 1991*
518	G>A*	MS	R173Q	*Delfau et al. 1990*
530	T>G*	MS	L177R	*Mgone et al. 1992*
532	G>A*	MS	D178N	*Puy et al. 1997*
541	C>T*	NS	Q181X	*Whatley et al. 1999*
552	del T	FS	FS → Stop + 5	*Gregor et al. 2002*
569	C>T	MS	T190I	*Schuurmans et al. 2001*

576_595	del 19 bp	FS	FS → Stop + 58	*Puy et al. 1997*
580	C>T	NS	Q194X	*Martinez di Montemuros et al. 2001*
583	C>T*	MS	R195C	*Kauppien et al. 1995*
593	G>A*	NS	W198X	*Lee and Anvret 1991*
600	del C	FS	FS → Stop + 55	*Luchinina et al. 2005*
601	C>T*	MS	R201W	*Lundin et al. 1994*
604	G>T	MS	V202F	*Gross et al. 1999*
604	del G	FS	FS → Stop + 53	*Schreiber et al. 1994*
609_610	ins G	FS	FS → Stop + 5	*Schneider-Yin et al. 2006*
610	C>A	MS	Q204K	*Ulbrichova, unpubl. data*
610	C>T*	NS	Q204X	*Mgone et al. 1994*
612	G>T*	SD	del 3 aa	*Delfau et al. 1991*
IVS 10				
612+2	T>C	SD	Exon 10 deletion	*Puy et al. 1997*
612+2	inv TAGGG >CCCTA	SD	Exon 10 deletion	*Petersen et al. 1998*
613-1	G>A	SA	Exon 11 deletion	*Gouya et al. 2004*
613-1	G>T*	SA	Exon 11 deletion	*Robreau-Fraolini et al. 2000*
Exon 11				
623	del C	FS	FS → Stop + 47	*Lam et al. 2001*
625	G>A*	MS	E209K	*Puy et al. 1997*
629	del A	FS	FS → stop + 45	*Lee et al. 1995*
634	A>G	MS	M212V	*Solis-Villa et al. 1997*
639	T>G	NS	Y213X	*Puy et al. 1997*
647	G>A	MS	G216D	*Lundin et al. 1997*
646_647	ins A	FS	FS → stop + 51	*Luchinina et al. 2005*
650	A>G	MS	Q217R	*Schneider-Yin et al. 2006*
650	A>T	MS	Q217L	*Schneider-Yin et al. 2000*
651	G>T	MS	Q217H	*Puy et al. 1997*
IVS 11				
651+1	G>C	SD	Exon 11 retention	*Petersen et al. 1998*
651+2	T>C	SD	Exon 11 retention	*Whatley et al. 1999*
652-5_4	del ins AT>TC	SA	(?)	*Luchinina et al. 2005*
652-3	C>G*	SA	Exon 12 deletion	*Llewellyn et al. 1996*
652-2	A>G	SA	Exon 12 deletion	*Petersen et al. 1998*
652-2	A>C	SA	Exon 12 deletion	*Bor et al. 2003*
652-2	del A	SA	Exon 12 deletion	*Martinez di Montemuros et al. 2001*
652-1	del G*	SA	Exon 12 deletion	*Puy et al. 1997*
652-1	G>C*	SA	Exon 12 deletion	*Puy et al. 1997*
Exon 12				
654_655	ins G	FS	FS → Stop + 33	*Di Pierro et al. 2004b*
656	C>A	MS	A219D	*Whatley et al. 1999*
664	G>A	MS	V222M	*Mustajoki et al. 1998*
665_666	ins A	FS	FS → Stop + 28	*De Siervi et al. 1999a*
666_667	del GG	FS	FS → Stop + 28	*De Siervi et al. 1997*
667	G>A*	MS	E223K	*Gu et al. 1994*
669_698	del 30 bp*	IFD	del 11 aa	*Guillen-Navarro et al. 2004*
673	C>G*	MS	R225G	*Kauppinen et al. 1995*
673	C>T*	NS	R225X	*Kauppinen et al. 1995*
674	G>A	MS	R225Q	*Floderus et al. 2002*
675	del A	FS	FS → Stop + 29	*Ulbrichová, unpubl. data*
680_681	ins AA	FS	FS → Stop + 28	*Whatley et al. 1999*
691_721	del 30 bp	IFD	del aa 231_241	*Puy et al. 1997*
706	G>A	MS	G236S	*Gouya et al. 2004*
713	T>G*	MS	L238R	*Kauppinen et al. 1995*
715_716	del CA*	FS	FS → Stop + 9	*Puy et al. 1996*
716	ins C	FS	FS → Stop + 10	*Puy et al. 1997*
721	C>T	MS	P241S	*Schuurmans et al. 2001*
723_744	dupl 21 bp	IFI	Repeat 7 aa	*Puy et al. 1997*
723	del C	FS	FS → Stop + 13	*Whatley et al. 1999*

728	del C	FS	FS → Stop + 12	*De Siervi et al. 1997*
728_729	del CT	FS	FS → Stop + 6	*De Siervi et al. 1999a*
730_731	del CT*	FS	FS → Stop + 6	*Mgone et al. 1993*
731	T>C	MS	L244P	*Gouya et al. 2004*
731_732	ins T	FS	FS → Stop + 6	Schneider-Yin et al. 2006
734	T>G*	MS	L245R	*Delfau et al. 1991*
739	T>C*	MS	C247R	*Mgone et al. 1993*
740	G>T*	MS	C247F	*Chen et al. 1994*
741_742	ins 13 bp	FS	FS → Stop + 7	*Gouya et al. 2004*
742_743	ins TTCGCTGC*	FS	FS → Stop + 10	*Gu et al. 1994*
744_751	del CGCTGAAA	FS	FS → Stop + 40	*Bor et al. 2003*
748	G>C*	MS	E250Q	*Lundin et al. 1995*
748	G>A*	MS	E250K	*Gu et al. 1994*
748_749	ins CATCGCTG	FS	FS → Stop + 7	*Whatley et al. 1999*
749	A>T	MS	E250V	*Puy et al. 1997*
749	A>C	MS	E250A	*Puy et al. 1997*
749	del A	FS	FS → Stop + 12	*Gouya et al. 2004*
754	G>A	MS	A252T	*Mgone et al. 1993*
754	G>C	MS	A252P	*Nissen et al. 1997*
755	C>T*	MS	A252V	*Mgone et al. 1993*
766	C>T*	MS	H256Y	*Puy et al. 1997*
766	C>A	MS	H256N	*Mgone et al. 1992*
770	T>C	MS+FS	L257P + Exon11/12 del.	*Pischik et al. 2005*
771_772	ins T	FS	FS → Stop + 33	*Ong et al. 1996*
771	G>A*	SD	Exon 12 deletion	*Grandchamp et al. 1989*
771	G>C	SD	Exon 12 deletion	*Diamon et al. 1993*
IVS 12				
771+1	G>C	SD	Exon 12 deletion	*De Siervi et al. 1999a*
771+1	G>A*	SD	Exon 12 deletion	*Puy et al. 1996*
771+1	G>T	SD	Exon 12 deletion	*Rosipal et al. 1997*
771+2	T>C	SD	Exon 12 deletion	*Martinez di Montemuros et al. 2001*
772-17	A>G	SA	(?)	*Luchinina et al. 2005*
772-2	A>G	SA	Exon 13 retention	*Mustajoki et al. 1998*
772-1	G>A*	SA	Exon 13 deletion	*Puy et al. 1997*
Exon 13				
779	G>A	MS	G260D	*Floderus et al. 2002*
798_799	ins AGCC	FS	FS → Stop + 24	*Whatley et al. 1999*
799	G>A	MS	V267M	*Rosipal et al. 1997*
806	C>T*	MS	T269I	*Mgone et al. 1994*
809	C>A	MS	A270D	*Puy et al. 1997*
809	C>G	MS	A270G	*Robreau-Fraolini et al. 2000*
815_818	del AGGA	FS	FS → Stop + 6	*De Siervi et al. 1999a*
820	G>A	MS	G274R	*Mgone et al. 1994*
823	C>T	NS	Q275X	*Puy et al. 1997*
IVS 13				
825+1	G>C	SD	Exon 13 deletion	*Brasch et al. 2004*
825+1	G>A	SD	Exon 13 deletion	*Llewellyn et al. 1996*
825+2	T>C	SD	Exon 13 deletion	*Brasch et al. 2004*
825+2	T>A	SD	Exon 13 deletion	*Gross et al. 1999*
852+2_6	T>G	SD	Exon 13 deletion ?	*Luchinina et al. 2005*
825+5	G>C	SD	Exon 13 del 2 aa + FS	*Pischik et al. 2005*
825+3_6	del AAGT	SD	Exon 13 deletion	*Pischik et al. 2005*
826-2	A>G*	SA	IVS 13 retention	*Mustajoki et al. 1998*
826-1	G>A	SA	IVS 13 retention	*Martinez di Montemuros et al. 2001*
Exon 14				
833	T>C	MS	L278P	*Mustajoki et al. 1998*
835_837	del ACT ins G	FS	FS → Stop + 10	*Solis et al. 1999*
838	G>A	MS	G280R	*Kauppinen et al. 1995*
841_843	del GGA*	IFD	del G281	*De Siervi et al. 2000*
847_848	del TG	FS	FS → Stop + 7	*Lundin et al. 1997*

848	G>A*	NS	W283X	*Mgone et al. 1994*
849	G>A*	NS	W283X	*Schreiber et al. 1995a*
854_855	del TA	FS	FS → Stop + 4	*Puy et al. 1997*
863	C>A	NS	S288X	*Puy et al. 1997*
863	C>G	NS	S288X	*Petersen et al. 1998*
863_864	ins T	FS	FS → Stop + 29	*Floderus et al. 2002*
866_869	del ATAG	FS	FS → Stop + 26	*Whatley et al. 1999*
874	C>T*	NS	Q292X	*Schneider-Yin et al. 2000*
886_887	ins A	FS	FS → Stop + 10	*Gross et al. 1999*
886	C>T	NS	Q296X	*Kauppinen et al. 1995*
900_901	ins T	FS	FS → Stop + 6	*Schreiber et al. 1995*
900	del T*	FS	FS → Stop + 15	*Delfau et al. 1991*
911	del A	FS	FS → Stop + 13 (?)	*Bor et al. 2003*
IVS 14				
912+1	G>A*	SD	Exon 14 deletion	*Gu et al. 1993a*
912+1	G>T	SD	Exon 14 deletion	*Whatley et al. 1999*
912+2	T>C	SD	Exon 14 deletion (?)	*Luchinina et al. 2005*
913-2	A>G	SA	Exon 15 deletion	*Floderus et al. 2002*
Exon 15				
913_914	ins C*	FS	FS → Stop + 1	*Puy et al. 1996*
940	C>T	NS	Q314X	*Di Pierro et al. 2004*
948	del A	FS	FS → Stop + 27	*De Siervi et al. 1999a*
950_951	ins G	FS	FS → Stop + 5	*Flachsová et al. 2003*
962	G>A	MS	R321H	*Schuurmans et al. 2001*
965_966	ins A	FS	FS → Stop + 36	*Ulbrichová, unpubl. data*
973	C>T*	NS	R325X	*Petersen et al. 1996*
980_986	del CCCAGTT	FS	FS → Stop + 14	*De Siervi et al. 1997*
982	del C	FS	FS → Stop + 16	*Whatley et al. 1999*
982_983	del CA	FS	FS → Stop + 30	*Maeda et al. 2000*
985_996	del 12 bp	IFD	del LAAQ	*De Siervi et al. 1999a*
986_987	ins T	FS	FS → Stop + 30	*Petersen et al. 1998*
992_...	del 131 bp	IFD	del 31 aa	*Gregor et al. 2002*
1000_1018	del 19 bp	FS	FS → Stop + 9	*Kauppinen et al. 2005*
1002	del G	FS	FS → Stop + 8	*Ong et al. 1998*
1003	G>A	MS	G335S	*De Siervi et al. 1999a*
1004	G>A*	MS	G335D	*Puy et al. 1997*
1004	del G	FS	FS → Stop + 9	*Robreau-Fraolini et al. 2000*
1013	T>G	MS	L338R	*Luchinina et al. 2005*
1024_1071	del 67 bp	FS	(?)	*Luchinina et al. 2005*
1028	T>C	MS	L343P	*Floderus et al. 2002*
1029_1033	del GAGCA	FS	FS → Stop + 13	*Luchinina et al. 2005*
1062_1063	ins C	FS	FS → Stop + 4	*Daimon et al. 1994*
1067	del A	FS	?	*Brasch et al. 2004*
1067_1068	ins CGGCA	FS	FS → Stop + 90	*Brasch et al. 2004*
1073	del A*	FS	(?)	*Kauppinen et al. 1995*

Nucleotide positions are numbered according to human PBGD cDNA deduced from GenBank sequences (Accession No. M95623 and X04808, ATG initiation codon for the housekeeping isoform is +1). Amino acids (aa) and nucleotides – standard one-letter abbreviations, X – nonsense codon, SD – donor site splice defect, SA –acceptor site splice defect, NS – nonsense mutation, MS – missense mutation, FS – frameshift mutation, IFD – in-frame deletion, IFI – in-frame insertion, IVS – Intervening Sequence (intron), ins – insertion, del – deletion, delins – deletion followed by insertion, inv - inversion, dupl - duplication, (?) - predicted consequence / not tested / data not available, * – found in more than one subject (*Cappellini et al. 2002*)

Table 2. Reported Mutations in the PBGD Gene Responsible for Acute Intermittent Porphyria in Slavic Populations

Position	Nucleotide change	Type of mutation	Mutation consequence	Country	Reference (first report)
Exon 1					
33	G>A	SD	(?)	Russia	*Luchinina et al. 2005*
IVS 1					
33+5	G>A	SD	(?)	Russia	*Luchinina et al. 2005*
Exon 3					
70	G>A	MS	G24S	Czech Rep.	*Rosipal et al. 1997*
72	G>A	MS	G24D	Russia	*Luchinina et al. 2005*
76	C>T	MS	R26C	Czech Rep., Russia	*Kauppinen et al. 1995*
77	G>A	MS	R26H	Czech Rep., Poland, Russia	*Llewellyn et al. 1993*
IVS 3					
87+2	T>G	SD	Exon 3 deletion (?)	Poland	*Schneider-Yin et al. 2006*
87+5	G>T	SD	Exon 3 deletion (?)	Poland, Russia	*Luchinina et al. 2005*
Exon 4					
92	C>T	MS	A31V	Russia	*Luchinina et al. 2005*
138	C>A	NS	Y46X	Poland	*Gregor et al. 2002*
158_159	ins A	FS	FS → Stop + 12	Czech Rep.	*Puy et al. 1997*
IVS 4					
161-3_5	del CTC	SA	Exon 5 deletion (?)	Poland	*Schneider-Yin et al. 2006*
Exon 5					
181	G>T	MS	D61Y	Poland	*Gregor et al. 2002*
202_203	del CT	FS	FS → Stop + 2	Russia	*Luchinina et al. 2005*
206_207	del CT	NS	S69X	Russia	*Puy et al. 1997*
210	G>A	SD	Exon 5 deletion (?)	Poland	*Floderus et al. 2002*
IVS 5					
211-1	G>C	SA	Exon 6 deletion	Russia	*Surin et al. 2001*
Exon 7					
278_280	del TTG	IFD	del V93	Poland	*Gregor et al. 2002*
315	del T	FS	FS → Stop + 15	Poland	*Gregor et al. 2002*
331	G>A	MS	G111R	Czech Rep., Poland, Russia	*Gu et al. 1993a*
335	C>A	MS	A112D	Russia	*Luchinina et al. 2005*
IVS 7					
344+1	G>A	SD	Exon 7 deletion	Poland	*Robreau-Fraolini et al. 2000*
344+2_5	del TAAG	SD	Exon 7 deletion	Russia	*Surin et al. 2001*
Exon 8					
415	G>T	NS	E139X	Russia	*Luchinina et al. 2005*
361	G>T	MS	D121Y	Poland	*Schneider-Yin et al. 2006*
IVS 8					
423-1	G>A	SA	Deletion 15 bp Exon 9 (?)	Russia	*Luchinina et al. 2005*
Exon 9					
445	C>T	NS	R149X	Poland, Russia	*Kauppinen et al. 1995*
Exon 10					
499	C>T	MS	R167W	Russia	*Gu et al. 1992*
517	C>T	MS	R173W	Russia	*Lee 1991*
518	G>A	MS	R173Q	Czech Rep., Poland	*Delfau et al. 1990*
552	del T	FS	FS → Stop + 5	Poland	*Gregor et al. 2002*
583	C>T	MS	R195C	Russia	*Kauppien et al. 1995*
600	del C	FS	FS → Stop + 55	Russia	*Luchinina et al. 2005*
609_610	ins G	FS	FS → Stop + 5	Poland	*Schneider-Yin et al. 2006*
610	C>T	NS	Q204X	Russia	*Mgone et al. 1994*
610	C>A	MS	Q204K	Czech Rep.	*Ulbrichová, unpubl. data*
Exon 11					

647	G>A	MS	G216D	Russia	*Lundin et al. 1997*
646_647	ins A	FS	FS → stop + 51	Russia	*Luchinina et al. 2005*
650	A>G	MS	Q217R	Poland	*Schneider-Yin et al. 2006*
IVS 11					
652-1	G>C	SA	Exon 12 deletion	Russia	*Puy et al. 1997*
652-5_4	del ins AT>TC	SA	(?)	Russia	*Luchinina et al. 2005*
Exon 12					
673	C>T	NS	R225X	Poland, Russia	*Kauppinen et al. 1995*
675	del A	FS	FS → Stop + 29	Czech Rep.	*Ulbrichová, unpubl. data*
730_731	del CT	FS	FS → Stop + 6	Poland	*Mgone et al. 1993*
731_732	ins T	FS	FS → Stop + 6	Poland	Schneider-Yin et al. 2006
739	T>C	MS	C247R	Russia	*Mgone et al. 1993*
748	G>C	MS	E250Q	Russia	*Lundin et al. 1995*
770	T>C	MS+FS	L257P + Exon 11/12 deletion	Russia	*Pischik et al. 2005*
IVS 12					
771+1	G>T	SD	Exon 12 deletion	Czech Rep., Russia	*Rosipal et al. 1997*
771+1	G>C	SD	Exon 12 deletion	Russia	*De Siervi et al. 1999a*
771+2	T>C	SD	Exon 12 deletion	Poland	*Martinez di Montemuros et al. 2001*
772-17	A>G	SA	(?)	Russia	*Luchinina et al. 2005*
Exon 13					
799	G>A	MS	V267M	Czech Rep.	*Rosipal et al. 1997*
IVS 13					
825+1	G>A	SD	Exon 13 deletion	Russia	*Llewellyn et al. 1996*
825+2	T>A	SD	Exon 13 deletion	Russia	*Gross et al. 1999*
825+3_6	del AAGT	SD	Exon 13 deletion	Poland, Russia	*Pischik et al. 2005*
825+5	G>C	SD	Exon 13 del 2 aa + FS	Russia	*Pischik et al. 2005*
852+2_6	T>G	SD	Exon 13 deletion ?	Russia	*Luchinina et al. 2005*
IVS 14					
912+2	T>C	SD	Exon 14 deletion ?	Russia	*Luchinina et al. 2005*
Exon 15					
965_966	ins A	FS	FS → Stop + 36	Czech Rep.	*Ulbrichová, unpubl. data*
982_983	del CA	FS	FS → Stop + 30	Poland	*Maeda et al. 2000*
992_...	del 131 bp	IFD	del 31 aa	Poland	*Gregor et al. 2002*
1013	T>G	MS	L338R	Russia	*Luchinina et al. 2005*
1024_	del 67 bp	FS	(?)	Russia	*Luchinina et al. 2005*
1029_1033	del GAGCA	FS	FS → Stop + 13	Russia	*Luchinina et al. 2005*

Nucleotide positions are numbered according to human PBGD cDNA deduced from GenBank sequences (Accession No. M95623 and X04808, ATG initiation codon for the housekeeping isoform is +1). Amino acids (aa) and nucleotides – standard one-letter abbreviations, bp – base pairs, X – nonsense codon, SD – donor site splice defect, SA – acceptor site splice defect, NS – nonsense mutation, MS – missense mutation, FS – frameshift mutation, IFD – in-frame deletion, IFI – in-frame insertion, IVS – Intervening Sequence (intron), ins – insertion, del – deletion, delins – deletion followed by insertion, inv – inversion, dupl - duplication, ? – predicted consequence/not tested/data not available

Table 3. Reported PBGD Gene Polymorphisms and Variants

Nucleotide change	Screening method	Population studied	Frequency reported	No. studied	References
Promoter					
-235 A>T	Sequencing	Swedish	A: 0,67, T: 0,33	33	*Lundin and Anvret 1997*
		Caucasians	A: 0,65; T: 0,35	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	A: 0,75; T: 0,25	30	*Robreau-Fraolini et al. 2000*
		Africans	A: 0,67, T: 0,33	68	*Robreau-Fraolini et al. 2000*
5´UTR					
-64 C>T	RFLP (ApaI)	Euro. Caucasians	C: 0,63; T: 0,37	35	*Picat et al. 1991*
		Canadians	C: 0,52; T: 0,48	100	*Schreiber et al. 1992*
		Caucasians	C: 0,63; T: 0,37	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	C: 0,63; T: 0,37	30	*Robreau-Fraolini et al. 2000*
		Africans	C: 0,71; T: 0,29	68	*Robreau-Fraolini et al. 2000*
IVS 1					
245 G>A	RFLP (MspI)	Euro. Caucasians	G: 0,53; A: 0,47	20	*Llewellyn et al. 1987*
		Finnish	G: 0,41; A: 0,59	66	*Kauppinen et al. 1990*
		European	G: 0,54; A: 0,46	96	*Scobie et al. 1990*
		Swedish	G: 0,60; A: 0,40	98	*Lee et al. 1991*
		N. A Caucasians	G: 0,58; A: 0,42	104	*Yoo et al. 1993*
		Caucasians	G: 0,58; A: 0,42	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	G: 0,53; A: 0,47	30	*Robreau-Fraolini et al. 2000*
		Africans	G: 0,64; A: 0,36	68	*Robreau-Fraolini et al. 2000*
400 T>C	RFLP (PstI)	European	T: 0,58; C: 0,42	37	*Lee and Anvret 1987*
		European	T: 0,55; C: 0,45	137	*Scobie et al. 1990*
		Finnish	T: 0,74; C: 0,26	66	*Kauppinen et al. 1990*
		Swedish	T: 0,60; C: 0,40	98	*Lee et al. 1991*
		N. A. Caucasians	T: 0,62; C: 0,38	106	*Yoo et al. 1993*
		Caucasians	T: 0,62; C: 0,38	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	T: 0,65; C: 0,35	30	*Robreau-Fraolini et al. 2000*
		Africans	T: 0,68; C: 0,32	68	*Robreau-Fraolini et al. 2000*
1277 C>A	RFLP (ApaLI)	Swedish	C: 0,60; A: 0,40	98	*Lee et al. 1991*
		N. A. Caucasians	C: 0,54; A: 0,46	100	*Yoo et al. 1993*
		Caucasians	C: 0,54; A: 0,46	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	C: 0,55; A: 0,45	30	*Robreau-Fraolini et al. 2000*
		Africans	C: 0,59; A: 0,41	68	*Robreau-Fraolini et al. 2000*
2478 A>G	RFLP (BstNI)	Finnish	A: 0,25; G: 0,75	66	*Kauppinen et al. 1990*
		European	A: 0,53; G: 0,47	100	*Scobie et al. 1990*
		Swedish	A: 0,55; G: 0,45	34	*Lee et al. 1991*
		N. A. Caucasians	A: 0,62; G: 0,38	104	*Yoo et al. 1993*
		Caucasians	A: 0,62; G: 0,38	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	A: 0,62; G: 0,38	30	*Robreau-Fraolini et al. 2000*
		Africans	A: 0,66; G: 0,34	68	*Robreau-Fraolini et al. 2000*
IVS 2					
3119 G>T	DGGE	Japanese	G: 0,95; T: 0,05	31	*Daimon et al. 1993a*
		Caucasians	G: 0,95; T: 0,05	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	G: 0,97; T: 0,03	30	*Robreau-Fraolini et al. 2000*
		Africans	G: 0,97; T: 0,03	68	*Robreau-Fraolini et al. 2000*
3167 del G	DGGE	Caucasians	G: 1,00; delG: 0,00	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	G: 0,83; delG: 0,17	30	*Robreau-Fraolini et al. 2000*
		Africans	G: 0,91; delG: 0,09	68	*Robreau-Fraolini et al. 2000*
IVS 3					
3581 A>G	RFLP (BsmAI)	Japanese	A: 0,21; G: 0,79	31	*Daimon et al. 1993*
		N. A. Caucasians	A: 0,59; G: 0,41	100	*Yoo et al. 1993*
		Argentinean	A: 0,56; G: 0,44	64	*De Siervi et al. 1999a*
		Caucasians	A: 0,75; G: 0,25	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	A: 0,79; G: 0,21	30	*Robreau-Fraolini et al. 2000*
		Africans	A: 0,85; G: 0,15	68	*Robreau-Fraolini et al. 2000*
Exon 4					

3615 C>T	DGGE	French	?	(?)	*Puy et al. 1997*
IVS 4					
3982 T>C	RFLP	British	T: 0,58; C: 0,42	20	*Whatley et al. 1999*
	(HhaI)	Caucasians	T: 0,58; C: 0,42	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	T: 0,60; C: 0,40	30	*Robreau-Fraolini et al. 2000*
		Africans	T: 0,67; C: 0,33	68	*Robreau-Fraolini et al. 2000*
Exon 7					
4679 C>T	Sequencing	German	(?)	(?)	*Brasch et al. 2004*
Exon 10					
6479 G>T	DGGE	Euro. Caucasians	G: 0,65; T: 0,35	43	*Gu et al. 1991*
		N. A Caucasians	G: 0,69; T: 0,31	100	*Yoo et al. 1993*
		Argentinean	G: 0,81; T: 0,19	74	*De Siervi et al. 1999a*
		Caucasians	G: 0,69; T: 0,31	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	G: 0,76; T: 0,24	30	*Robreau-Fraolini et al. 2000*
		Africans	G: 0,70; T: 0,30	68	*Robreau-Fraolini et al. 2000*
		German	G: 0,73; T: 0,27	22	*Brasch et al. 2004*
IVS 10					
6589 A>G	Sequencing	German	?	(?)	*Brasch et al. 2004*
6761 A>G	Sequencing	German	?	(?)	*Brasch et al. 2004*
7052 A>G	DGGE	Caucasians	A: 1,00; G: 0,00	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	A: 0,60; G: 0,40	30	*Robreau-Fraolini et al. 2000*
		Africans	A: 0,54; G: 0,46	68	*Robreau-Fraolini et al. 2000*
7064 C>A	RFLP	N. A Caucasians	C: 0,75; A: 0,25	92	*Yoo et al. 1993*
	(HinfI)	Chinese	C: 0,50; A: 0,50	50	*Lam et al. 2001*
		Caucasians	C: 0,75; A: 0,25	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	C: 0,69; A: 0,31	30	*Robreau-Fraolini et al. 2000*
		Africans	C: 0,70; A: 0,30	68	*Robreau-Fraolini et al. 2000*
IVS 12					
7539 C>T	Sequencing	British	C: 0,87; T: 0,13	19	*Whatley et al. 1999*
		Caucasians	C: 0,87; T: 0,13	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	C: 0,94; T: 0,06	30	*Robreau-Fraolini et al. 2000*
		Africans	C: 0,98; T: 0,02	68	*Robreau-Fraolini et al. 2000*
IVS 14					
7998 G>A	RFLP	N. A Caucasians	G: 0,97; A: 0,03	96	*Yoo et al. 1993*
	(MnlI)	Caucasians	G: 0,97; A: 0,03	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	G: 0,94; A: 0,06	30	*Robreau-Fraolini et al. 2000*
		Africans	G: 0,95; A: 0,05	68	*Robreau-Fraolini et al. 2000*
8003 G>A	Sequencing	Chinese	G: 0,99; A: 0,01	50	*Lam et al. 2001*
3´ UTR					
8578 G>A	RFLP	Chinese	G: 0,64; A: 0,36	48	*Law et al. 1999*
	(BsrI)	Caucasians	G: 0,65; A: 0,35	78	*Robreau-Fraolini et al. 2000*
		Afro-Caribbeans	G: 0,65; A: 0,35	30	*Robreau-Fraolini et al. 2000*
		Africans	G: 0,58; A: 0,42	68	*Robreau-Fraolini et al. 2000*

Position of nucleotide change is numbered relative to the translation initiation codon in Exon 1 in genomic DNA sequence (GenBank Accession No. M95623, A in the ATG initiation codon for the housekeeping isoform is +1). Nucleotides – standard one-letter abbreviations, DGGE – Denaturing Gradient Gel Electrophoresis, RFLP – Restriction Fragment Length Polymorphism, name of restriction enzyme in parentheses, IVS – Intervening Sequence (intron), UTR – Untranslated Region, N. A Caucasians – North American Caucasians, Euro. Caucasians – European Caucasians, ? – not tested / data not available

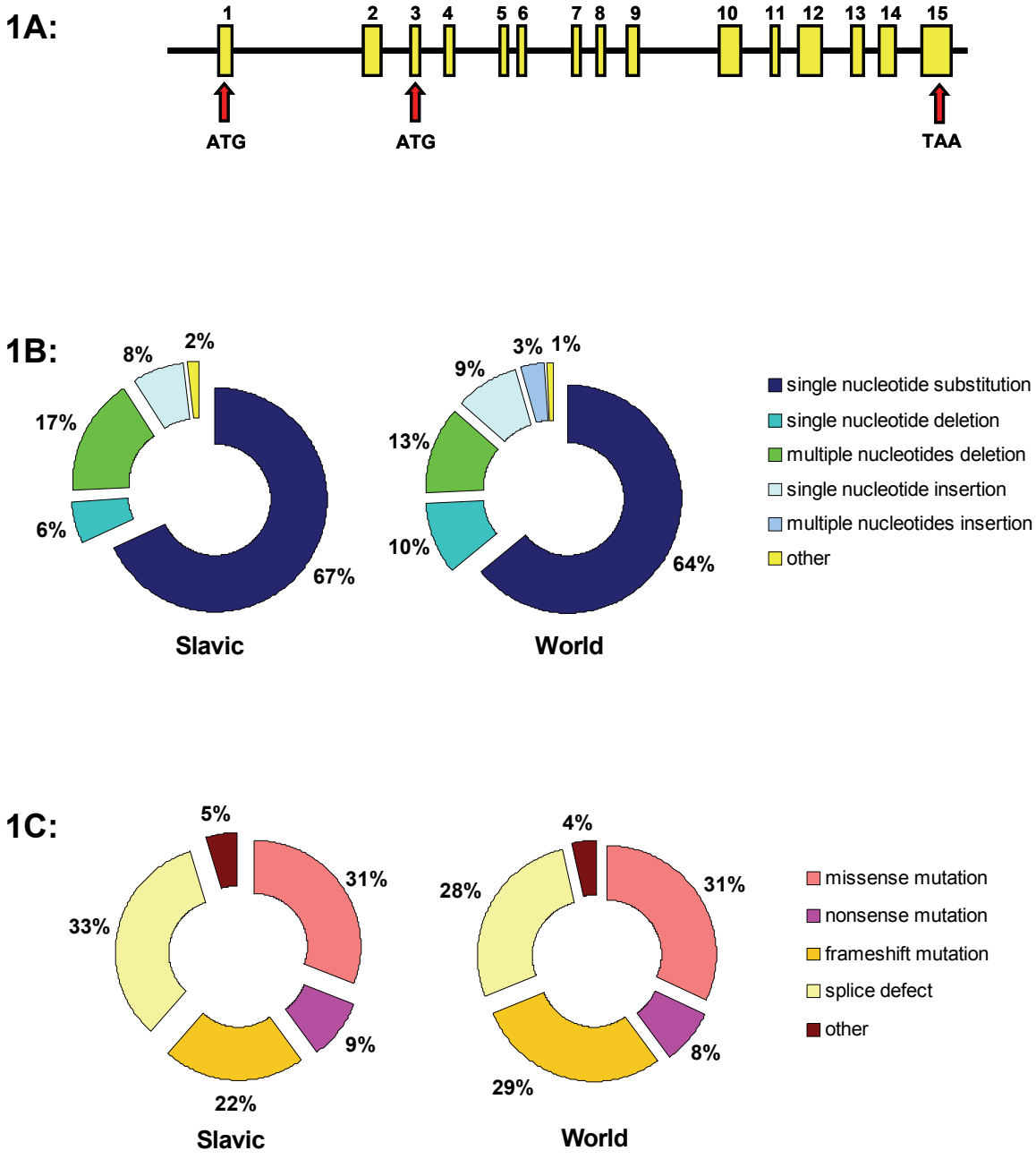
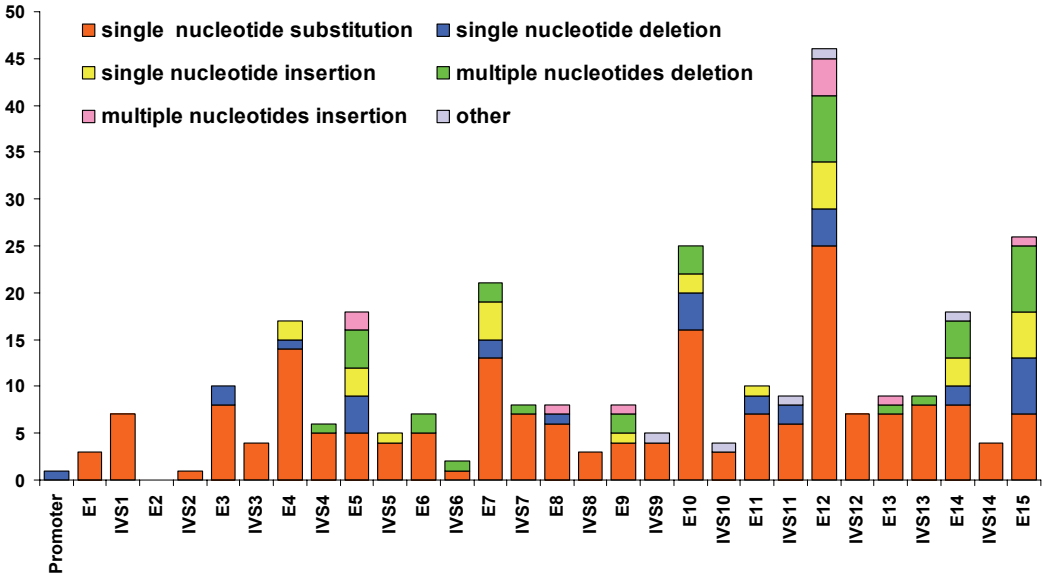
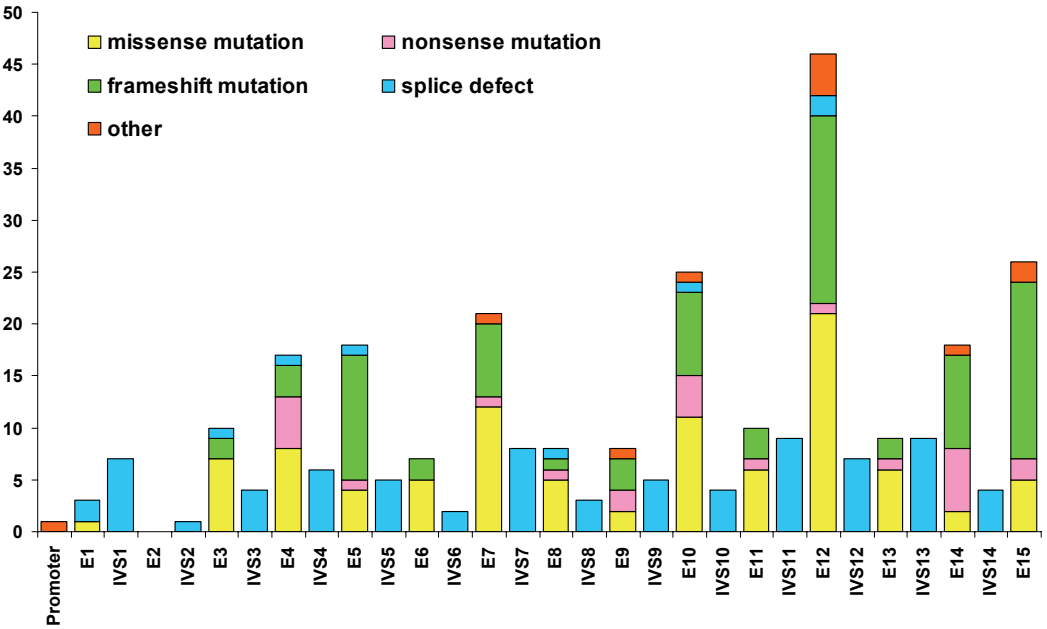


Fig. 1A: Exon / intron organisation of the PBGD gene, ATG – translation initiation codon, TAA – translation termination codon. **1B:** Graphical representation of mutations in the PBGD gene at DNA level. **1C:** Graphical representation of mutations in the PBGD gene at protein level.

2A:



2B:



2C:

Fig. 2A. Location, number and type of mutations in the PBGD gene at DNA level. **2B.** Location, number and type of mutations in the PBGD gene at protein level. **2C.** The number of mutations found in exons divided by the length of each exon (i.e. number of mutations per base pair) of the PBGD gene expressed as relative percentage. Intronic mutations are not included.

Acknowledgements

This work was supported by grants from the Grant Agency of Charles University (GAUK 10/2004) and Grant Barrande 2006-06-040, and grant MSM 0021620806.

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