HEMOGLOBIN DIAGNOSTIC REFERENCE LABORATORY

BOSTON MEDICAL CENTER

GLOBIN GENE MUTATIONS identified, May 2003 to December 2008

α-Globin variant mutations … 30

Name	Codon	Nucleotide	Amino acid	No. of chromosome	Comments
Hb Swan River	α2 6	GAC>G*G*C	Asp→Gly	1	Unstable
Hb Chad	α2 23	GAG>*A*AG	Glu→Lys	1	
Hb G-Honolulu	α2 30	GAG>*C*AG	Glu→Gln	1	
Hb Hasharon	α2 47	GAC>*C*AC	Asp→His	5	Unstable
Hb Montgomery	α2 48	CTG>C*G*G	Leu→Arg	3	Elutes like Hb S on HPLC
Hb J-Rovigo	α2 53	GCC>G*A*C	Ala→Asp	1	
Hb Adana	α2 59	GGC>G*A*C	Gly→Asp	2	Highly unstable; severe hemolytic anemia
Hb Waimanalo	α2 64	GAC>*A*AC	Asp→Asn	2	
Hb J-Habana	α2 71	GCG>G*A*G	Ala→Glu	2	
Hb Stanleyville II	α2 78	AAC>AA*A*	Asn→Lys	5	
Novel **Hb New Hampshire**	**α2 88**	**GCG>*A*CG**	**Ala→Thr**	**1**	**Likely high O_2 affinity**
Novel **Hb Delaware**	**α2 91**	**CTT>*G*TT**	**Leu→Val**	**1**	**Likely low O_2 affinity**
Hb Titusville	α2 94	GAC>*A*AC	Asp→Asn	3	Low O_2 affinity
Hb Oleander	α2 116	GAG>*C*AG	Glu→Gln	3	
Hb Westmead	α2 122	CAC>CA*G*	His→Gln	2	
Hb Policoro	α2 124	TCC>*C*CC	Ser→Pro	1	Unstable; Heinz body; microcytic anemia
Hb Chicago	α2 136	CTG>*A*TG	Leu→Met	1	
Hb La Lamentin	α1 20	CAC>CA*A*	His→Gln	1	
Novel **Hb Hekinan II**	**α1 27**	**GAG>GA*T***	**Glu→Asp**	1	
Hb Q-India	α1 64	GAC>*C*AC	Asp→His	9	
Hb Stanleyville II	α1 78	AAC>AA*A*	Asn→Lys	2	
Hb M-Iwate	α1 87	CAC>*T*AC	His→Tyr	1	Methemoglobin
Hb Buffalo	α1 89	CAC>CA*G*	His→Gln	1	
Hb Titusville	α1 94	GAC>*A*AC	Asp→Asn	3	Low O_2 affinity
Hb St. Luke's	α1 95	CCG>C*G*G	Pro→Arg	1	Increased O_2 affinity
Hb Twin Peaks	α1 113	CTC>C*A*C	Leu→His	1	
Hb Phnom Penh	α1 between 117-118	Insertion of ATC	Insertion of Isoleucine	2	
Hb Owari	α1 121	GTG>*A*TG	Val→Met	1	
Hb G-Philadelphia	$-\alpha^{3.7}$ 68	AAC>AA*G*	Asn→Lys	9	
Hb Q-Thailand	$-\alpha^{4.2}$ 74	GAC>*C*AC	Asp→His	1	

α-Thalassemia deletions and α-globin gene triplication … 8

Mutation	No. of chromosome	Comments
(– α $^{3.7}$) single α-globin gene deletion	**> 250**	
(– α $^{4.2}$) single α-globin gene deletion	**15**	
(– – ^{SEA}) two α-globin genes deletion	**197**	All can cause Hb Barts hydrops fetalis
(– – ^{FIL}) two α-globin genes deletion	4	
(– – ^{THAI}) two α-globin genes deletion	1	
(– – ^{MED}) two α-globin genes deletion	6	
– (α)$^{20.5}$ two α-globin genes deletion	2	
Anti-3.7 ααα triplication	**11**	

Non-deletional α-thalassemia mutations … 20

Mutation	No. of chromosome	Comments
α2 initiation codon ATG>A<u>C</u>G	1	Causes α-thalassemia
α2 initiation codon ATG>AG	2	Causes α-thalassemia
α2 codon 19 GCG>GC–	1	Frame-shift α-thalassemia mutation
Novel **α2 codon 22 GGC>GG–**	**3**	**Frame-shift α-thalassemia mutation**
Novel **α2 codon 24 TAT>TA<u>G</u> or Tyr→Term**	**1**	**Non-sense α-thalassemia mutation**
Novel **α2 IVSI-1 G>A**	**1**	**Causes α-thalassemia**
α2 IVS I donor splice site 5 bp deletion (–TGAGG)	**12**	**α^{Hph}**
α2 codon 35 TCC>C<u>C</u>C or Ser→Pro (Hb Evora)	3	Highly unstable; causes α-thalassemia
α2 codon 108 ACC>A<u>A</u>C or Thr→Asn (Hb Bleuland)	2	Highly unstable; causes α-thalassemia
Novel **α2 codon 122 CAC>C<u>T</u>C or His→Leu (Hb NS)**	**2**	**Likely highly unstable; causes α-thalassemia**
α2 codon 125 CTG>C<u>C</u>G or Leu→Pro (Hb Quong Sze)	2	Highly unstable; causes α-thalassemia
α2 codons 113/114 (–C)	3	Frame-shift α-thalassemia mutation
α2 codons 131 TCT>C<u>C</u>T or Ser→Pro	2	Causes α-thalassemia
α2 codon 142 TAA><u>C</u>AA Term→Gln Hb Constant Spring	**29**	**Causes α-thalassemia**
α2 codon 142 TAA>G<u>G</u>AA Term→Glu (Hb Seal Rock)	1	Causes α-thalassemia
α2 codon 142 TAA>TA<u>T</u> Term→Tyr (Hb Pakse)	1	Causes α-thalassemia
α2 poly-A signal AATAAA>AATAA<u>G</u>	1	α^{TSaudi}
α1 initiation codon ATG>G<u>G</u>TG	1	Causes α-thalassemia
Novel **α1 codon 61 AAG>AA–**	**1**	**Frame-shift α-thalassemia mutation**
Novel **α1 codon 62 GTG>–TG**	**1**	**Frame-shift α-thalassemia mutation**

β-Globin variant mutations … 42

Name	Codon	Nucleotide	Amino acid	No. of chromosome	Comments
Hb Raleigh	1	GTG>G<u>C</u>G	Val→ Ac-Ala	2	
Hb S	**6**	**GAG>G<u>T</u>G**	**Glu→Val**	**> 250**	**Sickle cell hemoglobin**
Novel **Hb S - South End**	**6** **132**	**GAG>G<u>T</u>G** **AAA>AA<u>C</u>**	**Glu→Val** **Lys→Asn**	**1**	**Elutes as Hb A on HPLC; Sickles**
Hb C	**6**	**GAG>G<u>A</u>AG**	**Glu→Lys**	**95**	**Sickles with Hb S**
Hb Leiden	6 / 7	del GAG	del Glu	2	Unstable Hb
Hb G-San Jose	7	GAG>G<u>G</u>G	Glu→Gly	1	
Hb Saki	14	CTG>C<u>C</u>G	Leu→Pro	1	Heinz body hemolytic anemia
Hb J-Baltimore	16	GGC>G<u>A</u>C	Gly→Asp	2	More variant than Hb A in heterozygote
Hb D-Iran	22	GAA><u>C</u>AA	Glu→Gln	3	
Hb E-Saskatoon	22	GAA><u>A</u>AA	Glu→Lys	2	
Hb E	**26**	**GAG>G<u>A</u>AG**	**Glu→Lys**	**134**	**Causes β-thalassemia**
Hb Volga	27	GCC>G<u>A</u>C	Ala→Asp	4	Hemolytic anemia
Hb Knossos	27	GCC>T<u>C</u>C	Ala→Ser	1	Causes β-thalassemia
Hb Perth	32	CTG>C<u>C</u>G	Leu→Pro	1	Severe hemolytic anemia
Hb Athens-GA	40	AGG>A<u>A</u>G	Arg→Lys	2	
Hb Hammersmith	42	TTT>T<u>C</u>T	Phe→Ser	1	Severe hemolytic anemia
Hb Zurich-Langstrasse	50	ACT>T<u>C</u>T	Thr→Ser	1	Elutes as Hb A on HPLC
Hb Osu-Christiansborg	52	GAT>A<u>A</u>T	Asp→Asn	1	
Hb M-Saskatoon	63	CAT>T<u>A</u>T	His→Tyr	1	Methemoglobin; hemolytic anemia
Hb Mizuho	68	CTC>C<u>C</u>C	Leu→Pro	1	Severe hemolytic anemia
Hb City of Hope	69	GGT>A<u>G</u>T	Gly→Ser	1	Elutes as Hb A on HPLC
Hb Korle-Bu	73	GAT>A<u>A</u>T	Asp→Asn	4	
Hb Shepherds Bush	74	GGC>G<u>A</u>C	Gly→Asp	2	Heinz body hemolytic anemia
Hb Quebec-Chori	87	ACA>A<u>T</u>A	Thr→Ile	1	Sickles with Hb S; elutes as Hb A
Hb N-Baltimore	95	AAG>G<u>A</u>G	Lys→Glu	3	More variant than HbA in heterozygote
Hb Regina	96	CTG>G<u>T</u>G	Leu→Val	1	Increased O_2 affinity; elutes as Hb A
Hb Köln	98	GTG>A<u>T</u>G	Val→Met	2	Heinz body hemolytic anemia
Hb Kempsey	99	GAT>A<u>A</u>T	Asp→Asn	1	High oxygen affinity
Hb Southampton	106	CTG>C<u>C</u>G	Leu→Pro	1	Severe hemolytic anemia
Hb Showa-Yakushiji	110	CTG>C<u>C</u>G	Leu→Pro	1	Hemolytic anemia and β-thalassemia
Hb New York	113	GTG>G<u>A</u>G	Val→Glu	2	Mildly unstable
Hb D-Los Angeles	**121**	**GAA><u>C</u>AA**	**Glu→Gln**	**13**	**Sickles with Hb S**
Hb O-Arab	121	GAA>A<u>A</u>A	Glu→Lys	3	Sickles with Hb S
Hb Bushey	122	TTC>C<u>T</u>C	Phe→Leu	1	
Hb Khartoum	124	CCA>C<u>G</u>A	Pro→Arg	2	Mildly unstable
Hb La Desirade	129	GCC>G<u>T</u>C	Ala→Val	1	Unstable and low oxygen affinity
Hb Wien	130	TAT>G<u>A</u>T	Tyr→Asp	1	Heinz body hemolytic anemia
Hb Shelby	131	CAG>A<u>A</u>G	Gln→Lys	4	Mildly unstable
Hb Camden	131	CAG>G<u>A</u>G	Gln→Glu	1	
Hb Hope	**136**	**GGT>G<u>A</u>T**	**Gly→Asp**	**14**	**Mildly unstable**
Hb Little Rock	143	CAC>CA<u>G</u>	His→Gln	1	High oxygen affinity
Hb Bethesda	145	TAT>CA<u>T</u>	Tyr→His	1	High oxygen affinity

Non-deletional β -Thalassemia mutations … 56

Position	Mutation	No. of chromosome	Comments
Nt – 101	C>T	1	β^+
Nt – 88	**C>T**	**26**	**β^+**
Nt – 87	C>A	2	β^+
Nt – 87	C>G	6	β^+
Nt – 87	C>T	1	β^+
Nt – 31	A>G	1	β^+
Nt – 29	**A>G**	**47**	**β^+**
Nt – 28	A>C	1	β^+
Nt – 28	**A>G**	**14**	**β^+**
***Novel* Nt –26 to –29**	**(– AA)**	**3**	**β^+**
Cap +1	A>C	1	β^+
Nt +20	C>T	2	β^+
Initiation codon	ATG>AGG	1	β^0
Initiation codon	ATG>ACG	1	β^0
Codon 5	(– CT)	2	β^0
Codon 8	(– AA)	3	β^0
Codons 8/9	(+ G)	7	β^0
Codon 10	GCC>GCA	1	β^+
Codons 14/15	(+ G)	5	β^0
Codon 15	TGG>TAG	6	β^0
Codon 16	(– C)	2	β^0
Codon 17	**AAG>TAG**	**21**	**β^0**
Codon 24	GGT>GGA	4	β^+
Codons 27/28	(+ C)	1	β^0
IVS I (–1)	G>A	2	β^0
IVS I (–1) / Hb Monroe	G>C (AGG>ACG or Arg→Thr)	3	β^0
IVS I-1	**G>A**	**15**	**β^0**
IVS I-1	**G>T**	**34**	**β^0**
IVS I-5	**G>C**	**35**	**β^+**
IVS I-5	G>T	4	β^+
IVS I-6	**T>C**	**22**	**β^+**
IVS I-110	**G>A**	**29**	**β^+**
IVS I-130	G>A	2	β^0
IVS I-130	G>C	3	β^0
Codon 37	TGG>TAG	1	β^0
Codon 39	**CAG>TAG**	**47**	**β^0**
Codons 41/42	**(– CTTT)**	**85**	**β^0**
Codon 43	GAG>TAG	3	β^0
Codon 44	(– C)	3	β^0
Codon 47	(+ A)	1	β^0
Codon 67	(– TG)	1	β^0
Codons 71/72	(+ A)	3	β^0
Codons 82/83	(– G)	1	β^0
***Novel* Codon 91**	**(– T)**	**4**	**Dominant β^0-thalassemia**
IVS II-1	G>A	9	β^0
IVS II-2	T>C	1	β^0

Non-deletional β -Thalassemia mutations ……

Position	Mutation	No. of chromosome	Comments
IVS II-654	**C>*T***	**40**	**β^+**
IVS II-745	**C>*G***	**16**	**β^+**
IVS II-837	T > *G*	1	β^+ / β^0
IVS II-848	C > *A*	1	β^+
IVS II-849	A > *C*	1	β^0
IVS II-849	A>*G*	6	β^0
***Novel* Codon 125**	**CCA>*TG*A**	**1**	**Non-sense β^0-thalassemia**
Termination codon + 6	C > *G*	1	β^+
Poly-A signal	**AATAAA>AA*C*AAA**	**10**	**β^+**
Poly-A signal	AATAAA>AATAA*G*	1	β^+

β -Thalassemia deletions … 8

Name	Deletion	No. of chromosome	Comments
***Novel* LCR deletion, removing HS 1, 2, and 3.**	**Deletion of 11,889 bp**	**1**	**β^0 with normal Hb A_2**
***Novel* LCR deletion, removing HS 1, 2, 3, 4 and 5..**	**Deletion of 22,529 bp**	**1**	**β^0 with normal Hb A_2**
Filipino β^0-thalassemia deletion	Deletion of 45 kb	3	β^0
***Novel* Romanian 5' end deletion**	**Deletion of 1,517 bp**	**1**	**β^0 with elevated Hb A_2 and Hb F**
Black 5' end deletion	Deletion of 1,393 bp	3	β^0 with elevated Hb A_2
3' end of IVS I	Deletion of 25 bp	1	β^0
3' end	**Deletion of 619 bp**	**10**	**β^0**
***Novel* Cape Verde deletion**	**Deletion of 7,733 bp**	**1**	**β^0**

(δβ)-Thalassemia deletions … 6

Name	Deletion	No. of chromosome	Comments
Hb Lepore Boston-Washington	**δ - β hybrid (codon 88 - IVSII-7)**	**15**	**$(\delta\beta)^0$ thalassemia**
Black $(\delta\beta)^0$ thalassemia	12 kb deletion	1	**$(\delta\beta)^0$ thalassemia**
Sicilian $(\delta\beta)^0$ thalassemia	**13.4 kb deletion**	**17**	
Black $^{G}\gamma\,(^{A}\gamma\delta\beta)^0$ thalassemia	35 kb deletion	3	$^{G}\gamma\,(^{A}\gamma\delta\beta)^0$ thalassemia
Chinese $^{G}\gamma\,(^{A}\gamma\delta\beta)^0$ thalassemia	100 kb deletion	2	
Asian Indian $^{G}\gamma\,(^{A}\gamma\delta\beta)^0$ thalassemia	Complex deletion/inversion	1	

δ-Globin variant mutations … 4

Name	Codon	Nucleotide	Amino acid	No. of chromosome	Comments
Hb A_2'	16	GGC>CGC	Gly→Arg	2	Found mainly in African-Americans
Hb A_2 – Puglia	26	GAG>GAC	Glu→Asp	1	
Hb A_2 – Yialousa	27	CGC>TGC	Arg→Cys	1	
Hb A_2 – Troodos	116	GCC>TCC	Ala→Ser	1	

γ-Globin gene mutations … 13

Position	Mutation	No. of chromosome
Hb Kenya	$^{A}\gamma$ - β hybrid (codons 81-86)	1
$^{G}\gamma$ codon 41	TTC>TCC or Phe→Ser (Hb F-Cincinnati)	1
$^{A}\gamma$ codon 75 ($^{A}\gamma^{T}$)	ATA>ACA or Ile→Thr (Hb F-Sardinia)	12
$^{A}\gamma$ codon 121	GAA>AAA or Glu→Lys (Hb F-Hull)	6
Novel $^{A}\gamma$ **codon 131**	**CAG>CAT or Glu→His**	**2**
Novel $^{G}\gamma$ **– 567**	**T>G ; possibly leads to HPFH**	**3**
$^{G}\gamma$ – 202	C>G Hereditary persistence of fetal hemoglobin	1
$^{G}\gamma$ **– 158**	**C>T polymorphism (*Xmn I*) associated with ↑ Hb F**	**164**
$^{A}\gamma$ – 196	C>T Hereditary persistence of fetal hemoglobin	1
Hereditary persistence of fetal hemoglobin deletion – 1 of the Black type		6
Hereditary persistence of fetal hemoglobin deletion – 2 of the Ghanaian type		**33**
Hereditary persistence of fetal hemoglobin deletion – 3 of the Indian type		2
Hereditary persistence of fetal hemoglobin deletion of the Vietnamese/SEA type		5