Differences in the erythropoiesis-hepcidin-iron store axis between hemoglobin H disease and β-thalassemia intermedia

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Supplementary data

Table 1. Demographic, hematological and genetic characteristics of A. β-Thalassemia Intermedia. B. Hemoglobin H disease.

Table 1A. β-Thalassemia Intermedia.

Sex	**Age (years)**	**Hb g/dl**	**MCV fl**	**MCH pg**	**Reticulocytes**		**β-globin genotype**		**α-globin genotype clinical severity classification**	**α-globin genotype**	
					%	**Absolute number (per μL)**	**Conventional name**	**HGVS nomenclature**		**Conventional name**	**HGVS nomenclature**
M	32	9.6	97.8	30.4	3.6	112100	Codon 39 (C>T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	αα/αα	[=];[=]
M	40	9.6	79.5	23.9	3.6	135600	Codon6(-A)/IVS-I-6(T>C)	HBB:c.[20delA];HBB:c.[92+6T>C]	mild	$-\alpha^{3.7}/\alpha\alpha$	NG_000006.1:g.[34164_37967del3804];[=]
F	31	7.1	81.9	24.3	4.7	136000	Codon 39 (C >T)/	HBB:c.[118C>T];[=]	mild	αα/αααα	[=];HGVS not attributable
M	17	8.8	59.2	18.7	1.9	77900	Codon 39 (C >T)/	HBB:c.[118C>T];[=]	mild	αα/ααα	[=];HGVS not attributable
M	37	8.9	74.8	23.1	2.5	95300	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	αα/αα	[=];[=]
M	56	9.3	84.2	24.7	4.1	170100	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	αα/αα	[=];[=]
G	50	5.5	82.7	23.6	1.6	37600	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	$\alpha\alpha/\alpha^{\mathrm{Ncol}}\alpha$	[=];HBA2:c.[2T>C]
M	36	8.1	90.5	28	2.6	75000	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	αα/αα	[=];[=]
F	19	10.1	61.9	20.0	2.9	150000	Codon 39 (C >T)/	HBB:c.[118C>T];[=]	mild	αα/ααα	[=];HGVS not attributable
M	33	8.3	79.4	23.6	0.7	24300	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	$\alpha\alpha/\alpha^{\mathrm{Ncol}}\alpha$	[=]; HBA2:c.[2T>C]
F	9	8.8	81.8	27.7	1.4	50600	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	$-\alpha^{3.7}/\alpha\alpha$	NG_000006.1:g.[34164_37967del3804];[=]
M	39	8.1	91.6	30.0	2.9	89500	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	αα/αα	[=];[=]
F	74	7.8	67.7	20,5	4.7	186700	Codon 39 (C >T)/HbShelby	HBB:c.[118C>T];HBB:c.[394C>A]	moderate	αα/αα	[=];[=]
F	30	6.6	89.2	26.4	8.0	210000	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	$-\alpha^{3.7}/\alpha\alpha$	NG_000006.1:g.[34164_37967del3804];[=]
F	38	8.2	93.9	26.8	1.9	57000	Deltabeta0/Codon39(C>T)	HBB:c.[118C>T];HBG1:c.[-249C>T];HBB:c.[118C>T]	moderate	αα/αα	[=];[=]
F	43	8.0	113.2	31.9	9.2	231200	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	αα/αα	[=];[=]
M	48	7.5	72.4	22.1	0.7	27200	Codon 39 (C >T)/Codon6(-A)	HBB:c.[118C>T];HBB:c.[20delA]	moderate	$-\alpha^{3.7}/\alpha\alpha$	NG_000006.1:g.[34164_37967del3804];[=]
M	40	8.0	86.9	27.2	1.8	53300	Codon 39 (C >T)/Codon6(-A)	HBB:c.[118C>T];HBB:c.[20delA]	moderate	$-\alpha^{3.7}/\alpha\alpha$	NG_000006.1:g.[34164_37967del3804];[=]
M	40	9.7	62.8	20.9	3.0	13380	Codon 39 (C >T)/	HBB:c.[118C>T];[=]	mild	$-\alpha^{3.7}/\alpha\alpha$	NG_000006.1:g.[34164_37967del3804];[=]
F	43	6.4	83.0	26.1	2.4	58800	Codon 39 (C >T)/Codon 39 (C>T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	αα/αα	[=];[=]

F	35	8.6	82.1	25.3	3.7	125500	Codon 39 (C >T)/Codon6(-A)	HBB:c.[118C>T];HBB:c.[20delA]	moderate	$-\alpha^{3.7}/\alpha\alpha$	NG_000006.1:g.[34164_37967del3804];[=]
F	46	6.9	69.5	20.8	1.0	33300	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	$-\alpha^{3.7}/\alpha\alpha$	NG_000006.1:g.[34164_37967del3804];[=]
F	17	8.8	88.2	27.3	3.5	111400	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	αα/αα	[=];[=]
F	62	7.0	78.9	24.5	0.5	13200	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	$-\alpha^{3.7}/-\alpha^{3.7}$	NG_000006.1:g.[34164_37967del3804];NG_000006.1:g.[34164_37967del3804]
F	33	8.3	78.0	23.2	4.6	162000	Codon 39 (C >T)/-87(C>A.G.T)	HBB:c.[118C>T];HBB:c.[-137C>A,G,T]	severe	NA	NA
M	43	7.2	84.2	25.1	1.4	40800	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	$-\alpha^{3.7}/\alpha^{3.7}$	NG_000006.1:g.[34164_37967del3804];NG_000006.1:g.[34164_37967del3804]
M	38	10.4	78.0	22.6	5.0	241000	Deltabeta0/Codon39(C>T)	HBB:c.[118C>T];HBG1:c.[-249C>T];HBB:c.[118C>T]	moderate	$-\alpha^{3.7}/\alpha\alpha$	NG_000006.1:g.[34164_37967del3804];[=]
M	22	10	64.3	20.8	1.6	77400	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	$\alpha\alpha/\alpha^{\mathrm{NcoI}}\alpha$	[=]; HBA2 :c.[2T>C]
M	3	10.2	76.6	22.5	5.5	272000	Deltabeta0/Codon39(C>T)	HBB:c.[118C>T];HBG1:c.[-249C>T];HBB:c.[118C>T]	moderate	NA	NA
F	56	10.4	68.0	22.4	2.0	91700	Codon 39 (C>T)/	HBB:c.[118C>T];[=]	mild	αα/ααα	[=]; HGVS not attributable
F	54	8.7	62.1	20.0	2.4	116000	Codon 39 (C >T)/	HBB:c.[118C>T];[=]	mild	$-\alpha^{3.7}/\alpha\alpha\alpha\alpha$	NG_000006.1:g.[34164_37967del3804];HGVS not attributable
F	58	7.4	80.3	25.3	2.7	82000	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	αα/αα	[=];[=]
M	29	9.3	87.7	27.6	2.5	80200	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	$-\alpha^{3.7}/\alpha\alpha$	NG_000006.1:g.[34164_37967del3804];[=]
F	64	8.0	78.2	24.0	1.2	38700	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	$-\alpha^{3.7}/-\alpha^{3.7}$	NG_000006.1:g.[34164_37967del3804];NG_000006.1:g.[34164_37967del3804]
F	18	9.4	62.8	20.9	1.2	50000	Codon 39 (C >T)/Codon 39 (C >T)	HBB:c.[118C>T];HBB:c.[118C>T]	severe	$-\alpha^{3.7}/-\alpha^{3.7}$	NG_000006.1:g.[34164_37967del3804];NG_000006.1:g.[34164_37967del3804]
M	34	7.3	90.3	28.9	1.2	34500	Codon 39 (C >T)/Codon6(-A)	HBB:c.[118C>T];HBB:c.[20delA]	moderate	αα/αα	[=];[=]
M	48	10.3	82.2	26.0	3.7	143000	Codon 39 (C >T)/Codon6(-A)	HBB:c.[118C>T] ;HBB:c.[20delA]	moderate	αα/αα	[=];[=]
M	49	7.9	94.2	27.5	2.3	66100	Deltabeta0/Codon39(C>T)	HBB:c.[118C>T];HBG1:c.[-249C>T];HBB:c.[118C>T]	moderate	αα/αα	[=];[=]

NA, not available

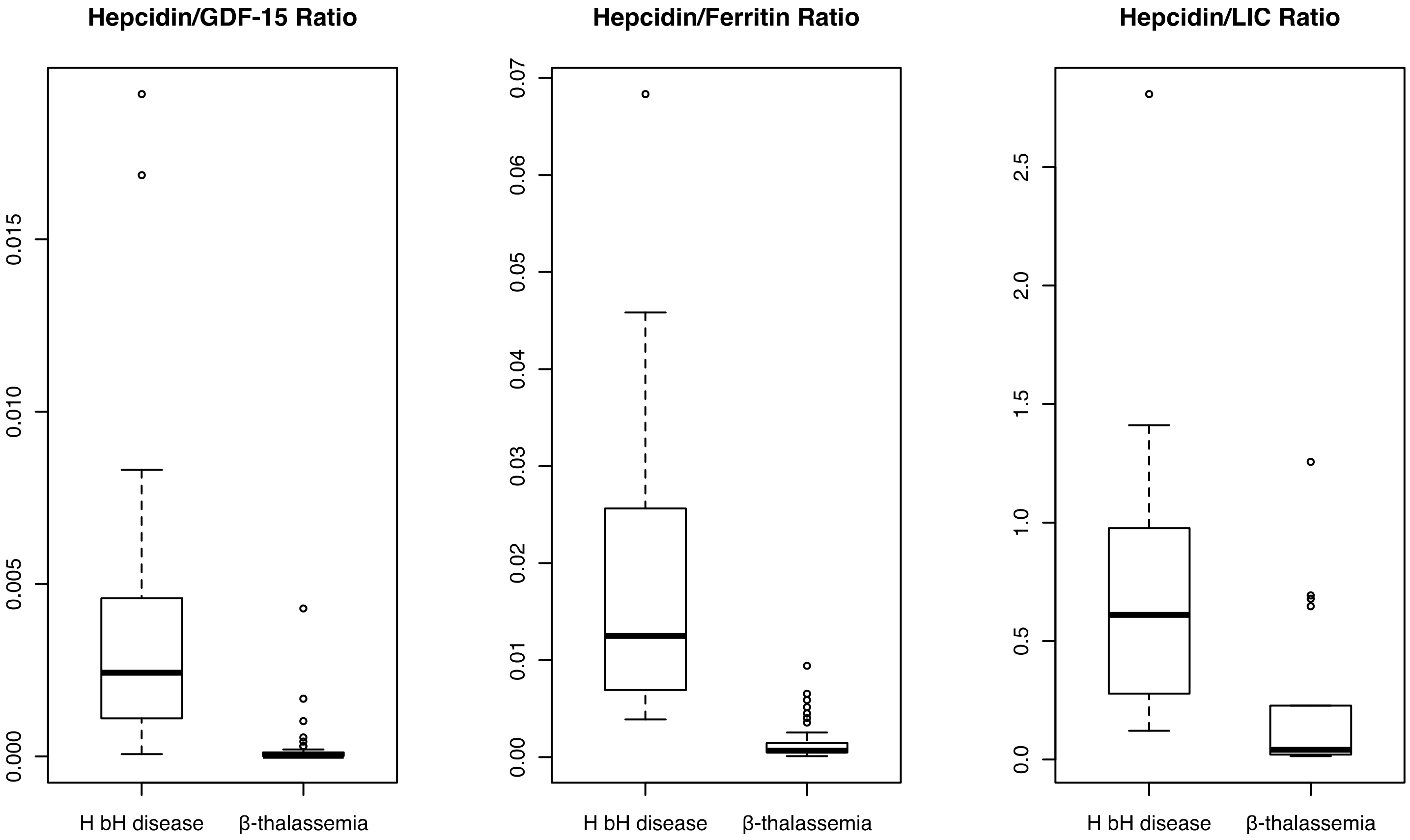
Table 1B. Hemoglobin H disease.

Sex	Age (years)	Hb g/dl	MCV fl	MCH pg	Reticulocytes		α-globin genotype	
					%	Absolute number (per µl)	Conventional name	HGVS nomenclature
F	63	7.4	57.1	17.6	3.0	128400	––(MED)/$\alpha^{HphI}\alpha$	NG_000006.1 :g.[24664_41064del16401];HBA2:c.[95+2_95+6delTGAGG]
F	38	8.5	67.5	19.6	6.1	264000	––(MED)/$\alpha^{NcoI}\alpha$	NG_000006.1 :g.[24664_41064del16401]; HBA2:c.[2T>C]
M	62	9.3	63.9	19.4	2.7	127400	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401]; NG_000006.1:g.[34164_37967del3804]
F	72	9.0	65.7	18.7	4.0	193200	––(MED)/$\alpha^{HphI}\alpha$	NG_000006.1 :g.[24664_41064del16401]; HBA2 :c.[95+2_95+6delTGAGG]
F	44	9.1	58.9	18.4	2.4	116300	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	75	6.9	70.0	21.8	3.6	122600	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	50	8.9	61.0	19.5	4.0	179300	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
M	22	9.9	60.0	18.9	3.3	176100	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	35	10.4	60.8	18.8	2.6	141900	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
M	49	9.6	60.8	18.8	2.5	126100	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	52	8.2	59.6	19.4	2.9	121000	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	74	7.8	67.5	20.0	3.8	147500	––(MED)/$\alpha^{NcoI}\alpha$	NG_000006.1 :g.[24664_41064del16401]; HBA2:c.[2T>C]
F	33	8.2	58.3	18.8	4.0	175400	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
M	16	8.6	56.9	17.0	3.8	194500	––(MED)/$\alpha^{NcoI}\alpha$	NG_000006.1 :g.[24664_41064del16401]; HBA2:c.[2T>C]
F	78	7.2	74.0	23.1	2.7	82400	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	22	8.8	59.3	18.0	2.1	100300	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
M	36	9.1	62.9	19.8	2.2	99900	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
M	5	8.6	52.4	16.2	1.2	58700	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	13	8.8	61.0	18.5	3.0	142700	––(MED)/$\alpha^{NcoI}\alpha$	NG_000006.1 :g.[24664_41064del16401]; HBA2:c.[2T>C]
M	58	10.1	65.9	20.3	2.7	134400	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
M	24	9.2	61.3	18.9	2.9	140300	––(MED)/$-\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]

F	19	8.4	59.7	18.4	2.4	107100	−−(MED/−$\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	17	9.2	58.4	18.4	2.3	36400	−−(MED)/−$\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
M	15	7.3	67.3	19.0	1.0	117900	NA	NA
M	33	9.3	57.6	17.4	1.7	89300	−−(MED)/−$\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
M	21	10.3	65.5	20.8	1.7	85000	−−(MED)/−$\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	63	9.2	66.1	20.1	4.4	198800	−−(MED)/−$\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	21	9.1	55.2	17.5	1.6	85200	--(SEA)/-$\alpha^{3.7}$	NG_000006.1 :g.[26264_45564del19301];NG_000006.1:g.[34164_37967del3804]
F	8	9.1	59.4	18.1	3.0	150200	−−(MED)/−$\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	42	8.9	61.8	19.1	3.3	152000	−−(MED)/−$\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	15	9.1	61.3	19.0	2.8	134000	−−(MED)/−$\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
F	47	8.7	62.2	19.1	2.7	125100	−−(MED)/−$\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]
M	45	7.6	57.9	19.1	3.7	150100	−−(MED)/−$\alpha^{4.2}$	NG_000006.1 :g.[24664_41064del16401]; −$\alpha^{4.2}$(HGVS not attributable)
F	41	6.8	54.6	17.6	4.6	178000	--$^{(20.5)}$/-$\alpha^{3.7}$	NG_000006.1:g.[15164_37864del22701];NG_000006.1:g.[34164_37967del3804]
M	16	8.4	69.9	20.3	3.9	162000	--(MED)/$\alpha^{\text{Constant Spring}}\alpha$	NG_000006.1 :g.[26264_45564del19301];HBA2:c.[427 T>C]
F	50	8.8	64.6	20.1	4.0	176800	−−(MED)/−$\alpha^{3.7}$	NG_000006.1 :g.[24664_41064del16401];NG_000006.1:g.[34164_37967del3804]

NA, not available

Supplementary Figure 1. Hepcidin/GDF-15 (µmol/ng), Hepcidin/Ferritin (pmol/µg) and Hepcidin/LIC ratio (µmol x d.w./L) in patients with untransfused β-thalassemia Intermedia (TI) and with Hemoglobin H disease (HbH). Figures are based on 38 patients for TI and 36 for HbH, except for the hepcidin/LIC ratio that is based on 18 and 12 patients, respectively. Central band characterizes the median, box boundaries indicate interquartile range (IQR), whiskers represent 1.5 IQR, whereas outliers are symbolized with circles. Five out of 6 patients who are outliers within the TI group with more elevated ratios had the HBB:c.[118C>T];[=] plus αα/ααα genotype associated with a milder phenotype. The 3 patients who are outliers with elevated ratios within the HbH group do not have clearly recognizable special features in terms of genotype but they have a combination of high hepcidin and relatively low GDF15, ferritin and LIC.



Supplementary Figure 2. Distribution of biochemical data in patients with β-Thalassemia Intermedia and Hemoglobin H disease. A, Erythropoietin; B, GDF15; C, sTfR; D, serum hepcidin; E, serum ferritin; F, Liver Iron Concentration (LIC). Central band characterizes the median, box boundaries indicate interquartile range (IQR), whiskers represent 1.5 IQR, whereas outliers are symbolized with circles and extremes (>3 IQRs) with a star. The dotted lines represent the upper and lower limit of the reference range of the parameters.