Glutathione transferase-A2 S112T polymorphism predicts survival, transplant-related mortality, busulfan and bilirubin blood levels after allogeneic stem cell transplantation

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Supplementary Table 1. Genotype frequency distributions in the Busulfan and in the Comparator cohort.

						Busulfan color (n=185)			Comparator cohort (n=146)			
Gene/Locus	Polymorphism	Nucleotide change	MAF	Region	Protein	Genotypes N (%)			Genotypes N (%)			HW (p)
ABCB1	rs1045642	T>A	0.43	coding	I1145I	TT 62 (34)	TA 87 (47)	AA 36 (19)	TT 38 (26)	TA 76 (52)	AA 32 (22)	>0.05
ABCC1	rs45511401	G>T	0.04	coding	G671V	GG 175 (95)	GT 10 (5)	TT 0 (0)	GG 131 (91)	GT 13 (9)	TT 0 (0)	>0.05
ABCC4	rs2274407	C>A	0.02	coding	N304K	CC 154 (84)	AC 28 (15)	AA 1(1)	AA 124 (86)	AC 21 (14)	AA 0 (0)	>0.05
ABCC4	rs11568658	G>T	0	coding	G187W	GG 167 (90)	GT 18 (10)	TT 0 (0)	GG 135 (94)	GT 8 (5)	TT 1 (1)	>0.05
ABCC4	rs9561778	G>T	0.18	intronic	---	GG 118 (64)	GT 63 (34)	TT 3 (2)	GG 106 (73)	GT 38 (26)	TT 2 (1)	>0.05
CBS	rs5742905	T>C	0.00	coding	I278T	TT 172 (93)	CT 13 (7)	CC 0 (0)	TT 134 (92)	CT 11 (8)	CC 0 (0)	>0.05
CBS	rs234706	C>T	0.33	coding	Y233Y	CC 87 (47)	CT 84 (45)	TT 14 (8)	CC 74 (51)	CT 54 (37)	TT 18 (12)	>0.05
CBS	rs72958776	ins68bp	0.03	intronic/coding	---	wt 156 (85)	wt/ins 27 (15)	-	wt 132 (92)	wt/ins 11 (8)	-	--
CTH	rs482843	G>A	0.41	upstream gene	---	GG 66 (36)	AG 96 (52)	AA 23 (12)	GG 49 (34)	AG 62 (43)	AA 34 (23)	>0.05
CYP2B6	rs8192719	C>T	0.28	intronic	---	CC 92 (50)	TC 77 (42)	TT 16 (8)	CC 79 (54)	TC 59 (40)	TT 8 (6)	>0.05
CYP2C9	rs1057910	A>C	0.06	coding	I359L	AA 177 (96)	CA 8 (4)	CC 0 (0)	AA 137 (94)	CA 9 (6)	CC 0 (0)	>0.05
CYP2C19	rs4244285	G>A	0.16	coding	P227P	GG 135 (73)	AG 46 (25)	AA 4 (2)	GG 97 (67)	AG 45 (31)	AA 3 (2)	>0.05
GCLM	rs2301022	G>A	0.40	intronic	---	GG 78 (42)	AG 87 (47)	AA 20 (11)	GG 55 (38)	AG 73 (50)	AA 18 (12)	>0.05
GCLC	rs17883901	C>T	0.09	upstream gene	---	CC 156 (85)	CT 27 (15)	TT 0 (0)	CC 118 (81)	CT 27 (18)	TT 1 (1)	>0.05
GGT1	rs17004876	A>G	0.11	coding	N419D	AA 166 (90)	AG 19 (10)	GG 0 (0)	AA 133 (91)	AG 13 (9)	GG 0 (0)	>0.05
GPX1	rs1050450	C>T	0.12	coding	P200L	CC 82 (44.5)	CT 82 (44.5)	TT 20 (11)	CC 62 (43)	CT 59 (41)	TT 22 (16)	>0.05
GPX2	rs17881652	C>T	0.01	coding	P126L	CC 180 (97)	CT 5 (3)	TT 0 (0)	CC 143 (98)	CT 3 (2)	TT 0 (0)	>0.05
GPX3	rs3763013	A>G	0.33	upstream gene	---	AA 80 (43)	AG 77 (42)	GG 27 (15)	AA 61 (42)	AG 70 (48)	GG 15 (10)	>0.05
GSTA1	rs4715332	T>G	0.41	upstream gene	---	TT 53 (29)	GT 97 (53)	GG 34 (18)	TT 47 (32)	GT 75 (51)	GG 24 (17)	>0.05
GSTA1	rs3957356	G>A	0.37	upstream gene	---	GG 54 (30)	GA 96 (52)	AA 33 (18)	GG 48 (33)	GA 73 (50)	AA 24 (17)	>0.05
GSTA1	rs1051775	A>G	0.31	coding	K125K	AA 60 (33)	GA 89 (49)	GG 34 (18)	AA 47 (32)	GA 76 (53)	GG 22 (15)	>0.05
GSTA2	rs2180314	C>G	0.43	coding	S112T	CC 57 (32)	CG 85 (47)	GG 38 (21)	CC 45 (33)	CG 63 (46)	GG 30 (23)	>0.05

GSTM1	null allele	gene deletion	0.47	coding	---	wt/wt or wt/null 77(44)	null 99 (56)	---	wt/wt or wt/null 67 (49)	null 71 (51)	---	---
GSTP1	rs1138272	C>T	0.097	coding	A114V	CC 160 (86)	TC 24 (13)	TT 1 (1)	CC 129 (89)	TC 16 (11)	TT 0 (0)	>0.05
GSTP1	rs1695	A>G	0.41	coding	I105V	AA 101 (54)	AG 66 (36)	GG 18 (10)	AA 74 (51)	AG 56 (39)	GG 14 (10)	>0.05
GSTT1	null allele	gene deletion	0.2	coding	---	wt/wt or wt/null 136 (77)	null 40 (23)	---	wt/wt or wt/null 112 (81)	null 26 (19)	---	---
MGST1	rs7970208	G>A	0.49	upstream gene	---	AA 63 (34)	AG 89 (48)	GG 33 (18)	AA 40 (27)	AG 76 (52)	GG 30 (21)	>0.05
MGST1	rs2239676	C>G	0.08	intronic	---	CC 166 (89)	CG 18 (10)	GG 1 (1)	CC 128 (88)	CG 16 (11)	GG 2 (1)	>0.05
MGST1	rs11875	G>A	0.09	3' UTR	---	GG 156 (84)	AG 27 (15)	AA 2 (1)	GG 129 (88)	AG 16 (11)	AA 1 (1)	>0.05
MTHFR	rs1801131	A>C	0.36	coding	E429A	AA 95 (51)	CA 77 (42)	CC 13 (7)	AA 73 (50)	CA 57 (39)	CC 15 (10)	>0.05
MTR	rs1805087	A>G	0.16	coding	D919G	AA 129 (70)	GA 51 (28)	GG 4 (2)	AA 103 (71)	GA 41 (28)	GG 2 (1)	>0.05
MTRR	rs1532268	C>T	0.31	coding	S175L	CC 75 (40)	CT 83 (45)	TT 27 (15)	CC 70 (48)	CT 62 (42)	TT 14 (10)	>0.05
MTRR	rs1801394	A>G	0.45	coding	I22M	AA 63 (34)	GA 91 (49)	GG 31 (17)	AA 48 (33)	GA 60 (41)	GG 37 (26)	>0.05
NAT1	rs4986782	G>A	0.01	coding	R187Q	GG 180 (98)	GA 4 (2)	AA 0 (0)	GG 138 (95)	GA 7 (5)	AA 0 (0)	>0.05
NAT2	rs1801280	T>C	0.44	coding	I114T	TT 67 (36)	CT 88 (48)	CC 30 (16)	TT 47 (32)	CT 71 (49)	CC 28 (19)	>0.05
NAT2	rs1799930	G>A	0.30	coding	R197Q	GG 94 (51)	AG 71 (38)	AA 20 (11)	GG 73 (50)	AG 59 (40)	AA 14 (10)	0.013
PON1	rs854560	T>A	0.38	coding	L55M	AA 76 (41)	TA 77 (42)	TT 32 (17)	AA 60 (41)	TA 59 (41)	TT 26 (18)	0.021
TCNI	rs34324219	G>T	0.125	coding	D301Y	GG 141 (77)	GT 38 (21)	TT 4 (2)	GG 113 (77)	GT 30 (21)	TT 3 (2)	>0.05
TCN2	rs1801198	C>G	0.45	coding	P259R	CC 67 (36)	GC 88 (48)	GG 30 (16)	CC 58 (40)	GC 62 (42)	GG 26 (18)	>0.05
TCN2	rs4820889	G>A	0.042	coding	R399Q	GG 174 (94)	AG 11 (6)	AA 0 (0)	GG 136 (93)	AG 10 (7)	AA 0 (0)	>0.05

Footnote: MAF: minor allele frequency in Caucasian European (www.ncbi.nlm.nih.gov/snp); HW: Hardy-Weinberg; ins: insertion; wt: wild-type.

Supplementary Table 2. List of primers for Sequenom^{TM} analysis.

Gene/Locus	Polymorphism	First Primer	Second Primer	Extension Primer	Multiplex
ABCB1	rs1045642	**ACGTTGGATG**ACTGCAGCATTGCTGAGAAC	**ACGTTGGATG**TATGTTGGCCTCCTTTGCTG	CTCCTTTGCTGCCCTCAC	1
ABCC1	rs45511401	**ACGTTGGATG**CGTTTCAGCATCACCTTCTC	**ACGTTGGATG**TGAGAGCAGGGACGACTTTC	ccaACGGCCACCAAAGCA	2
ABCC4	rs2274407	**ACGTTGGATG**TATCTGGTTGACATCACTGC	**ACGTTGGATG**GGCAGGAACTTCTCAGAATC	ctaAGAATCTTGGAAATCTCCTT	1
ABCC4	rs11568658	**ACGTTGGATG**TTTCAGGCACTTCGTCTTAG	**ACGTTGGATG**CAGCAGATTGACTATCTGGC	GGCCTGTGGTTGTCTTCC	2
ABCC4	rs9561778	**ACGTTGGATG**AGTAGGAAGCATAGAGAACG	**ACGTTGGATG**AGCCATAACTGTACTTGGTC	CATTCTCCTTCCCTTCC	3
CBS	rs234706	**ACGTTGGATG**ACGGGCTCTGCTCTCTTTC	**ACGTTGGATG**GGCAGGAACTTCTCAGAATC	gagaATCAGCGGTGGTGTC	1
CBS	rs5742905	**ACGTTGGATG**TCTGCGAGGATGGACCCTTC	**ACGTTGGATG**TTTTGCTGGCCTTGAGCCCT	CTGAAGCCGCGCCCTCTGCAGATCA	3
CTH	rs482843	**ACGTTGGATG**GCAATTGAAAAGCTCTTGAC	**ACGTTGGATG**AACATGGAGAATTGCTCCCC	CCCCTAAAATGTTTTCTCTCTGATAT	4
CYP2B6	rs8192719	**ACGTTGGATG**TAAGCTGGACCCACAATTTC	**ACGTTGGATG**GTATCTCTCGTTGTTTTTCTC	ccCTCGTTGTTTTTCTCAAGTTG	4
CYP2C19	rs4244285	**ACGTTGGATG**CACTTTCCATAAAAGCAAGG	**ACGTTGGATG**GCAATAATTTTCCCACTATC	CCCACTATCATTGATTATTTCCC	4
CYP2C9	rs1057910	**ACGTTGGATG**GGCAGGCTGGTGGGGAGAA	**ACGTTGGATG**ACATGCCCTACACAGATGCT	ttTGGTGCACGAGGTCCAGAGATAC	5
GCLC	rs17883901	**ACGTTGGATG**AGGCGTGTGCAAGGGTGAT	**ACGTTGGATG**TTTGCGTAAAGCGAGGCCGA	gTCTCGCGAGCTGCTCCCCTCAACTG	3
GCLM	rs2301022	**ACGTTGGATG**GAAGCACCCTAAATAAAACAC	**ACGTTGGATG**GAGTCACACACCACAGTTTG	gggcAAACATTGTTCAAAGGACTA	5
GGT1	rs17004876	**ACGTTGGATG**ATGCTGGGAGAGCTGAAGTC	**ACGTTGGATG**TCTACTTTGGCTCCAAGGTC	ggGCGGGATCCTGTTCAAT	1
GPX2	rs17881652	**ACGTTGGATG**TCTTCGCCTACCTGAAGGAC	**ACGTTGGATG**AATGATGAGCTTGGGATCGG	GGGAAAATGGGTCATCATAA	3
GPX3	rs3763013	**ACGTTGGATG**GTGGACAACTGAGATCAGAG	**ACGTTGGATG**CCAGAGACCTGAGATGCTAC	acattCTACCCCTGGATTGCTAC	5
GSTA1	rs1051775	**ACGTTGGATG**CCACCTGAGGAAAAAGATGC	**ACGTTGGATG**TTCAAAGGCAGGGAAGTAGC	AGTAGCGATTTTTTATTTTCTC	6
GSTA1	rs4715332	**ACGTTGGATG**GAGTGACGCAAAGAGGATAG	**ACGTTGGATG**ACATTTAGGTGGGTATCCTG	ttTATCCTGTATTTTATCTGACAAATC	5
GSTA1	rs3957356	**ACGTTGGATG**GCTTTTCCCTAACTTGACTC	**ACGTTGGATG**ATAAGCTCTTTGTTCCTCTC	CTTTGTTCCTCTCAATAGTTC	7
GSTA2	rs2180314	**ACGTTGGATG**GAAGGTATAGCAGATTTGGG	**ACGTTGGATG**GCAAGCTTGGCATCTTGTTC	gaATCTTGTTCCTCAGGTTGA	8
GSTP1	rs1138272	**ACGTTGGATG**TGATACATGGTGGTGTCTGG	**ACGTTGGATG**TCAAAAGGCTTCAGTTGCCC	ttccCATAGTCATCCTTGCCC	8
GSTP1	rs1695	**ACGTTGGATG**TGGTGCAGATGCTCACATAG	**ACGTTGGATG**TGGTGGACATGGTGAATGAC	ACCTCCGCTGCAAATAC	2
MGST1	rs2239676	**ACGTTGGATG**CCAAACCCCTCCTCTAAATC	**ACGTTGGATG**AGAAGGGCTCAAAGGGAATC	tttgtAATCAGCAGGCGATGGTTACT	5
MGST1	rs11875	**ACGTTGGATG**GTACAGAATTCTTAAAAAGCC	**ACGTTGGATG**GCTTACAGGTTGCTGAAAAG	CCTGTAAAGAAAATCATACAACTCA	5
MGST1	rs7970208	**ACGTTGGATG**ATGGATCTATCTTTCATGGG	**ACGTTGGATG**GAGATATAGCACTAGGAGAG	gagACAGAAATCCTTAAACATTTCTC	4
MTHFR	rs1801131	**ACGTTGGATG**TCTCCCGAGAGGTAAAGAAC	**ACGTTGGATG**AGGAGCTGCTGAAGATGTGG	ggaGAGCTGACCAGTGAAG	6

MTR	rs1805087	**ACGTTGGATG**CTTTGAGGAAATCATGGAAG	**ACGTTGGATG**TACCACTTACCTTGAGAGAC	CCTTGAGAGACTCATAATGG	8
MTRR	rs1532268	**ACGTTGGATG**TGTAGCAGCTCTGACTTCAC	**ACGTTGGATG**ACAAGAGGAGATAAGTGGCG	CATCACCTGCATCCT	1
MTRR	rs1801394	**ACGTTGGATG**CTATATGCTACACAGCAGGG	**ACGTTGGATG**GCAGAAAATCCATGTACCAC	CACAGCTTGCTCACA	1
NAT1	rs4986782	**ACGTTGGATG**CTGATCTCCTAGAAGACAGC	**ACGTTGGATG**AATCTTCAATTGTTCGAGGC	gTAAGAGTAAAGGAGTAGATTTTT	8
NAT2	rs1801280	**ACGTTGGATG**TCTGGGAGGAGCTTCCAGAC	**ACGTTGGATG**CATGGTTCACCTTCTCCTGC	TCCTGCAGGTGACCA	8
NAT2	rs1799930	**ACGTTGGATG**TCATAGACTCAAAATCTTC	**ACGTTGGATG**CCTGCCAAAGAAGAAACACC	tcatcTACTTATTTACGCTTGAACCTC	3
PON1	rs854560	**ACGTTGGATG**GAGCTAATGAAAGCCAGTCC	**ACGTTGGATG**TTTCTGGCAGAAACTGGCTC	cagcAACTGGCTCTGAAGAC	6
TCN2	rs1801198	**ACGTTGGATG**CCTCACTCTATCACCAGTTC	**ACGTTGGATG**GCCTTGAGACATGCTGTTCC	CCCAGTTCTGCCCCA	8
TCN2	rs4820889	**ACGTTGGATG**CATGACTCACCTTGCAACAG	**ACGTTGGATG**TACTTAACCTCCGTGATGGG	ccacGTTCTGGCAGCTTCTCC	1
TCNI	rs34324219	**ACGTTGGATG**AGGTCTTACCTGCCCTGATG	**ACGTTGGATG**TATACCTGAAGCAGAGACGC	GACGCAAGAAGAGTCTTTGTTAATAT	1

Supplementary Table 3. Multivariate Cox analysis of TRM and OS in busulfan and comparator cohorts.

		busulfan color (n=185)		Comparator color (n=146)	
GENE	**LOCUS**	**TRM** p	**OS** p	**TRM** p	**OS** p
ABCB1	rs1045642	ns	ns	ns	ns
ABCC1	rs45511401	Ns	ns	ns	ns
ABCC 4	rs2274407	ns	ns	ns	ns
ABCC 4	rs11568658	ns	ns	ns	0.018
ABCC 4	rs9561778	ns	ns	ns	0.013
CBS	rs5742905	ns	ns	ns	ns
CBS	rs234706	ns	ns	ns	ns
CBS	ins 68bp	ns	ns	ns	ns
CTH	rs482843	ns	ns	ns	ns
CYP2B6	rs8192719	ns	ns	ns	ns
CYP2C9	rs1057910	ns	ns	ns	ns
CYP2C19	rs4244285	0.05	ns	ns	ns
GCLM	rs2301022	ns	ns	ns	ns

GCLC	rs17883901	ns	ns	ns	ns
GGT 1	rs17004876	ns	ns	0.014	ns
GPX 1	rs1050450	ns	ns	ns	ns
GPX2	rs17881652	ns	ns	ns	0.014
GPX3	rs3763013	ns	ns	ns	ns
GSTA1	rs1051775	0.04	ns	ns	ns
GSTA1	rs4715332	0.05	ns	ns	ns
GSTA1	rs3957356	0.05	ns	ns	ns
GSTA 2	rs2180314	**0.001**	**0.005**	ns	ns
GSTM 1	rs1065410	ns	0.04	ns	ns
GSTM 1	rs366631	ns	ns	ns	ns
GSTP 1	rs1138272	ns	ns	ns	ns
GSTP 1	rs1695	ns	ns	ns	0.014
GSTT 1	rs2266637	ns	0.02	ns	ns
mGST1	rs7970208	0.01	0.05	ns	ns
mGST1	rs2239676	ns	ns	ns	ns
MGST1	rs11875	ns	ns	ns	ns
MTHFR	rs1801131	ns	ns	ns	ns
MTR	rs1805087	ns	ns	ns	ns
MTRR	rs1532268	ns	ns	ns	ns

MTRR	rs1801394	ns	ns	ns	ns
NAT1	rs4986782	ns	ns	ns	ns
NAT2	rs1801280	ns	ns	ns	ns
NAT2	rs1799930	ns	ns	ns	ns
PON1	rs854560	ns	ns	ns	ns
TCN I	rs34324219	ns	0.04	ns	ns
TCN2	rs1801198	ns	ns	ns	ns
TCN2	rs4820889	ns	ns	ns	ns

Footnote: all p-values are referred to multivariate Cox analysis: for each polymorphism as covariate age, sex mismatch, disease phase, type of donor, interval to transplant and intensity of conditioning were included with covariates. Adjustment for multiple comparisons was made, leading to significant p-value threshold = 0.00125.

Supplementary Table 4. GSTA2 S112T-GSTA1 two loci haplotypes frequency estimates and linkage disequilibrium coefficients (D').

GSTA2-GSTA1	Haplotype	Estimated frequency	Linkage Disequilibrium	
			D'	p
S112T-rs1051775	Thr-A	0.478	0.70	<0.0001
	Thr-G	0.072		
	Ser-A	0.092		
	Ser-G	0.358		
S112T-rs3957356	Thr-G	0.485	0.72	<0.0001
	Thr-A	0.067		
	Ser-G	0.093		
	Ser-A	0.355		
S112T-rs4715332	Thr-T	0.475	0.69	<0.0001
	Thr-G	0.076		
	Ser-T	0.077		
	Ser-G	0.372		

Supplementary Table 5. **GSTA2 S112T-GSTA1*A/B haplotype frequency estimation.**

Haplotype	**Estimated frequency**
Thr-GSTA1*A	0.485
Thr-GSTA1*B	0.062
Ser-GSTA1*A	0.057
Ser-GSTA1*B	0.354
Others	0.042

Footnote: GSTA1*A haplotype is set up by the G allele at rs3957356 locus and the T allele at rs4715332 locus; GSTA1*B haplotype is set up by the A allele at rs3957356 locus and the G allele at rs4715332 locus, as previously reported[26].

Supplementary Table 6 Multivariate Cox analysis of TRM and OS according to two loci GSTA2-GSTA1 haplotypes.

		TRM			OS		
GSTA2-GSTA1	**Haplotype**	**RR**	**[95% CI]**	**p**	**RR**	**[95% CI]**	**p**
S112T-rs1051775	Thr-A	1	/	/	1	/	/
	Thr-G	2.271	[0.635-8.116]	0.206	1.529	[0.724-3.232]	0.265
	Ser-A	3.076	[1.305-7.248]	**0.010**	2.320	[1.312-4.104]	**0.003**
	Ser-G	2.187	[1.163-4.113]	**0.015**	1.630	[1.129-2.354]	**0.009**
S112T-rs3957356	Thr-G	1	/	/	1	/	/
	Thr-A	1.936	[0.563-6.654]	0.297	1.454	[0.693-3.053]	0.321
	Ser-G	3.083	[1.387-6.851]	**0.006**	2.502	[1.268-3.787]	**0.006**
	Ser-A	1.884	[1.016-3.492]	**0.044**	1.569	[1.063-2.221]	**0.022**
S112T-rs4715332	Thr-T	1	/	/	1	/	/
	Thr-G	2.271	[0.635-8.117]	0.206	1.525	[0.722-3.220]	0.268
	Ser-T	3.076	[1.305-7.248]	**0.010**	2.433	[1.403 -4.217]	**0.001**
	Ser-G	2.187	[1.163-4.113]	**0.015**	1.529	[1.058 -2.211]	**0.023**

Supplementary Table 7. Multivariate Cox analysis of Relapse in Busulfan cohort.

Variables	**RR**	**[95% CI]**	**p**
Age	0.986	0.959-1.013	0.312
Interval diagnosis- transplant	0.989	0.972-1.007	0.233
Sex donor/recipient (female/male vs others)	0.939	0.472-1.867	0.857
Type of donor (unrelated vs sibling)	0.708	0.381-1.317	0.276
Conditioning regimen (myeloablative vs reduced-intensity)	3.315	0.436-25.219	0.247
Phase at transplant (advanced vs early*)	3.3976	2.111-7.491	**0.0001**
GSTA2 S112T (ser/ser vs thr+)	1.332	0.672-2.641	0.411

Supplementary Table 8. Multivariate analysis of GSTA2 S112T locus on liver function tests.

Liver function tests	**Anova for repeated measures**	
	F-statistics	p
Aspartate transaminase (AST)	0.002	0.957
Alanine transaminase (ALT)	0.095	0.759
Alkaline phosphatase (ALP)	1.050	0.309
Gamma-glutamyl transferase (GGT)	0.118	0.732
Cholinesterase (AChE)	0.285	0.598

Footnote: ANOVA for repeated measures, adjusted for age, phase at transplant, intensity of conditioning, interval between diagnosis and transplant and sex-mismatch. Time points for plasma liver function tests were: baseline (day of admittance at BMT Unit), day 0, +7, +14, +21, +28 and +35 after transplant.