Supplementary Table 1: Univariable hemoglobin, bilirubin and creatinine increments after RBC transfusion

	Hemoglobin	Hb (RBC-Omics)	Bilirubin	Creatinine
N (RBC transfusion episodes)	102,043	6,168	19,205	64,051
Blood Donor Characteristics				
Sex, male (ref: female)	0.07 (0.06, .08)	0.05 (0.00, .10)	0.03 (.01, 0.4)	NS
Age in years by decade	-0.01 (-.01, -.00)	NS	NS	NS
(+) Rh status	0.03 (-.02, .05)	NS	-0.01 (-.03, -0.01)	NS
ABO, O (vs. all others)	NS	NS	-0.03 (-.04, -0.02)	NS
Donor hemoglobin level	0.03 (.02, .04)	0.06 (.04, .08)	0.01 (.01, .02)	NS
History of tobacco use	0.04 (.02, .07)	NS	0.03 (.01, .05)	NS
Race (ref: White)				
Black/African American	NS	NS	NS	NS
Asian	NS	NS	0.05 (.02, .09)	NS
Other	0.04 (.00, .08)	NS	NS	NS
Unknown	NS	NS	0.05 (.03, .08)	NS
Blood Component Characteristics				
Gamma irradiation	0.05 (.03, .06)	NS	-0.08 (-.09, -.07)	0.02 (.01, .02)
RBC storage age in days	-0.01 (-.01, -.00)	-0.02 (-.03, -0.00)	0.03 (.02, .03)	-0.00
Apheresis-derived	-0.06 (-.08, -.04)	-0.14 (-.25, -.03)	NS	NS
Storage solution, AS-3 (ref: AS-1)	0.09 (.08, .11)	0.06 (.00, .11)	0.06 (.00, .11)	NS
Leukoreduction	-0.13 (-.15, -.11)	-0.08 (-.16, .00)	-0.08 (-.16, .00)	0.02 (.01, .03)
Transfusion Recipient Characteristics				

Sex, Male	-0.27 (-.28, -.26)	-0.30 (-.28, -.25)	-0.02 (-.03, -.01)	-0.00
Age (per decade)	0.03 (.02, .03)	0.02 (.00, .04)	0.01 (.01, .02)	0.00
Body mass index (per unit)	-0.02 (-.02, -.01)	-0.02 (-.02, -.01)	-0.00	0.00
(+) Rh status	0.04 (.02,.06)	NS	NS	NS
ABO, O (vs. all others)	NS	NS	-0.03 (-.04, -.02)	NS
Race (ref: White)				
Black/African American	0.10 (.08, .12)	0.14 (.06, .21)	-0.02 (-.04, -.00)	0.01 (.00, .02)
Asian	0.24 (.20, .29)	0.31 (0.12, .51)	0.16 (.12, .19)	0.02 (.00, .03)
Other	NS	NS	NS	NS
Concomitant plasma	-0.51 (-.55, -.48)	-0.27 (-.40, -.13)	0.41 (.38, .45)	0.05 (.04, .06)
Concomitant platelets	-0.34 (-.37, -.32)	-0.24 (-.35, -.12)	0.03 (.01, .05)	0.04 (.03, .05)
Issue location (ref: ward)				
Emergency department	NS	NS	0.10 (.08, .13)	-0.05 (.07, .04)
Intensive care	-0.11 (-.13, -.10)	-0.15 (-.21, -.09)	0.03 (.02, .05)	0.03 (.02, .03)
Operating room	-0.28 (-.32, -.24)	-0.38 (-.52, -.24)	-0.03 (-.06, -.00)	NS
Outpatient	NS	-0.97 (-1.09, -.85)	0.37 (.34, .40)	NS
Pre-TX laboratory measure	-0.53 (-.53, -.52)	-0.50 (-.52, -.48)	.04 (.03, .06)	-0.09 (-.10, -.08)
Time Pre-TX to TX (per hour)	-0.005 (-.006, -.003)	-0.004 (-.01,-.002)	NS	0.00
Time TX to Post-TX (per hour)	-0.008 (-.009,-.007)	-0.008 (-.01, -.003)	-0.01 (-.01, -.01)	0.00
Count of prior RBC Tx	-0.002 (-.003,-.002)	-0.002 (-.004,-.000)	-0.003 (-.003, -.002)	0.00

RBC=red blood cell; Hb=hemoglobin; TX = transfusion
Linear model estimates and 95% confidence intervals.
All presented outcomes were statistically significant ($p<0.05$) except where indicated (NS)

Supplementary Table 2: Mean allele frequency for single nucleotide polymorphisms associated with hemolysis in genotyped blood donors and single RBC unit transfusion events from genotyped blood donors									
				Genotyped blood donor; n (%)			Single RBC unit transfusions from genotyped blood donor; n (%)		
chromosome	**Nearest gene**	**Hemolysis**	**Single nucleotide polymorphism**	**Homozygous Major**	**Heterozygous**	**Homozygous Minor**	**Homozygous Major**	**Heterozygous**	**Homozygous Minor**
1	*SPTA1*	Osmotic	rs857725	6,875 (54.4)	4,729 (37.4)	1044 (8.3)	3428 (55.6)	2276 (36.9)	459 (7.5)
1	-	Oxidative	rs17661899	9353 (74.7)	2865 (22.9)	305 (2.4)	4363 (71.6)	1571 (25.8)	163 (2.7)
1	*TFB2M*	Osmotic	rs35558093	7579 (60.3)	4272 (34.0)	710 (5.7)	3492 (57.1)	2274 (37.2)	349 (5.7)
2	*MFSD2B*	Osmotic	rs55707417	10073 (79.6)	2423 (19.2)	156 (1.2)	4868 (78.9)	1218 (19.8)	81 (1.3)
5	*GLRX*	Oxidative	rs6871404	7009 (55.5)	4775 (37.8)	853 (6.8)	3387 (55.1)	2316 (37.7)	444 (7.2)
6	*EYS*	Osmotic	rs78484557	12040 (95.6)	540 (4.3)	8 (0.1)	5791 (94.4)	337 (5.5)	5 (0.1)
7	*AQP1*	Osmotic	rs1859838	8642 (68.3)	3485 (27.5)	532 (4.2)	4209 (68.3)	1741 (28.3)	213 (3.5)
7	*IKZF1*	Osmotic	rs12718598	3414 (27.0)	6114 (48.4)	3100 (24.5)	1613 (26.3)	2967 (48.3)	1564 (25.5)
8	*ANK1*	Osmotic	rs4737009	6319 (49.8)	5028 (39.6)	1339 (10.6)	3251 (52.6)	2411 (39.0)	524 (8.5)
9	*MIR4289*	Osmotic	Chr 9:91408347	11507 (91.6)	1024 (8.2)	32 (0.2)	5519 (90.2)	589 (9.6)	13 (0.2)
10	*HK1*	Osmotic	rs16926246	9958 (78.4)	2567 (20.2)	170 (1.3)	4755 (76.9)	1340 (21.7)	90 (1.5)
11	*HBB*	Osmotic	rs3345248	12367 (99.2)	97 (0.8)	2 (0)	6044 (99.6)	22 (0.4)	0 (0)
11	*SWAP70*	Osmotic	rs93139	3898 (30.7)	6176 (48.7)	2608 (20.6)	2030 (32.8)	2985 (48.3)	1168 (18.0)
11	*ARHGAP42*	Osmotic	rs11606890	9961 (79.0)	2423 (19.2)	224 (1.8)	4866 (79.2)	1178 (19.2)	101 (1.6)
12	*ALDH2*	Osmotic	rs4646777	8577 (67.8)	3676 (29.0)	402 (3.2)	4173 (67.8)	1792 (29.1)	191 (3.1)
13	-	Osmotic	rs118149920	11946 (96.1)	471 (3.8)	10 (0.1)	5910 (96.9)	182 (3.0)	5 (0.1)
16	*HBA2*	Osmotic	Chr 16:226229	11975 (96.6)	403 (3.2)	21 (0.2)	5924 (97.6)	140 (2.3)	10 (0.1)
16	*PIEZO1*	Osmotic	rs837763	3956 (31.2)	6231 (49.2)	2476 (19.6)	1930 (31.3)	3058 (49.5)	1185 (19.2)
17	*SLC4A1*	Osmotic	rs7222349	4034 (31.9)	5460 (43.1)	3172 (25.0)	2159 (34.9)	2737 (44.3)	1285 (20.8)
19	*GPX4*	Oxidative	rs8178962	3806 (32.4)	5622 (48.0)	2293 (19.6)	1852 (32.0)	2843 (49.1)	1092 (18.9)
19	*MYO9B*	Osmotic	rs35365035	4388 (34.7)	5948 (47.0)	2321 (18.3)	2118 (34.7)	2879 (47.1)	1113 (18.2)
22	*SEC14L4*	Oxidative	rs9606739	8280 (65.5)	3845 (30.4)	510 (4.0)	3837 (62.9)	2016 (33.1)	247 (4.0)
23	*G6PD*	Oxidative	rs1050828	12421 (97.8)	169 (1.3)	104 (0.8)	6042 (98.5)	46 (0.8)	43 (0.7)

Supplementary Table 3: Hemoglobin increments after single unit RBC transfusion by SNP allele – g/dL [95% Confidence Interval]					
Hemolysis	**Single nucleotide polymorphism**	**Gene**	**Homozygous dominant**	**Heterozygous dominant**	**Homozygous recessive**
Osmotic	rs857725	*SPTA1*	0.95 [0.92-0.98]	0.98 [0.95-1.02]	0.96 [0.87-1.04]
Oxidative	rs17661899	-	0.96 [0.93-0.99]	0.97 [0.93-1.02]	0.93 [0.78-1.07]
Osmotic	rs35558093	*TFB2M*	0.97 [0.94-1.00]	0.95 [0.91-0.99]	1.00 [0.90-1.10]
Osmotic	rs55707417	*MFSD2B*	0.95 [0.93-0.98]	0.99 [0.94-1.05]	0.99 [0.79-1.19]
Oxidative	rs6871404	*GLRX*	0.95 [0.92-0.98]	0.99 [0.94-1.02]	0.93 [0.84-1.02]
Osmotic	rs78484557	*EYS*	0.96 [0.94-0.98]	1.01 [0.91-1.12]	0.98 [0.21-1.76]
Osmotic	rs1859838	*AQP1*	0.96 [0.93-0.99]	0.97 [0.92-1.01]	0.98 [0.86-1.11]
Osmotic	rs12718598	*IKZF1*	0.97 [0.92-1.01]	0.97 [0.93-1.00]	0.95 [0.91-1.00]
Osmotic	rs4737009	*ANK1*	0.94 [0.90-0.97]	0.99 [0.95-1.03]	1.00 [0.92-1.08]
Osmotic	Chr 9:91408347	*MIR4289*	0.97 [0.94-0.99]	0.92 [0.85-1.00]	1.00 [0.51-1.49]
Osmotic	rs16926246	*HK1*	0.94 [0.90-0.97]	0.99 [0.95-1.03]	0.87 [0.68-1.06]
Osmotic	rs3345248	*HBB*	0.96 [0.94-0.99]	0.90 [0.52-1.27]	-
Osmotic	rs93139	*SWAP70*	0.98 [0.94-1.02]	0.95 [0.92-0.99]	0.95 [0.89-1.00]
Osmotic	rs11606890	*ARHGAP42*	0.97 [0.95-1.00]	0.92 [0.87-0.98]	0.97 [0.79-1.16]
Osmotic	rs4646777	*ALDH2*	0.95 [0.93-0.98]	0.98 [0.93-1.02]	1.04 [0.91-1.17]
Osmotic	rs118149920	-	0.96 [0.94-098]	0.97 [0.83-1.10]	1.13 [0.23-2.02]
Osmotic	Chr 16:226229*	*HBA2*	0.96 [0.94-0.98]	0.84 [0.68-1.00]	0.53 [0.11-1.16]
Osmotic	rs837763	*PIEZO1*	0.99 [0.94-1.03]	0.95 [0.92-0.98]	0.96 [0.91-1.01]
Osmotic	rs7222349	*SLC4A1*	0.96 [0.92-1.00]	0.96 [0.92-0.99]	0.97 [0.92-1.02]
Oxidative	rs8178962	*GPX4*	0.94 [0.90-0.98]	0.97 [0.94-1.01]	0.95 [0.89-1.01]
Osmotic	rs35365035*	*MYO9B*	0.98 [0.94-1.02]	0.96 [0.93-1.00]	0.92 [0.87-0.98]
Oxidative	rs9606739*	*SEC14L4*	0.97 [0.94-1.00]	0.96 [0.92-1.00]	0.84 [0.72-0.96]
Oxidative	rs1050828*	*G6PD*	0.97 [0.94-0.99]	0.85 [0.58-1.13]	0.70 [0.43-0.96]

RBC=red blood cell; SNP=single nucleotide polymorphism; CI=confidence interval

* Outcomes statistically significant ($p<0.05$)

Supplementary Table 4. Hemoglobin increments after single unit RBC transfusion by SNP allele & irradiation status – g/dL [95% Confidence interval]					
Gene	**Single nucleotide polymorphism**	**Modification**	**Homozygous dominant**	**Heterozygous dominant**	**Homozygous recessive**
SEC14L4	rs9606739	Unirradiated	1.01 [0.97-1.04]	0.97 [0.93-1.02]	0.93 [0.79-1.06]
		Irradiated	0.88 [0.82-0.93]	0.93 [0.86-1.01]	0.72 [0.52-0.93]
HK1	rs16926246	Unirradiated	0.99 [0.96-1.03]	0.99 [0.93-1.05]	0.97 [0.73-1.21]
		Irradiated	0.90 [0.85-0.95]	0.86 [0.77-0.95]	0.67 [0.37-0.98]
No Gene	rs176618991	Unirradiated	0.99 [0.96-1.02]	1.00 [0.95-1.06]	1.02 [0.85-1.20]
		Irradiated	0.89 [0.84-0.94]	0.90 [0.81-0.98]	0.71 [0.45-0.97]
AQP1	rs1859838	Unirradiated	0.93 [0.90-0.96]	0.92 [0.88-0.97]	1.01 [0.88-1.15]
		Irradiated	0.83 [0.78-0.88]	0.84 [0.76-0.92]	0.74 [0.50-0.98]

Supplementary Table 5a: Donor, component, & patient characteristics for transfusion recipients of single RBC units by *SECL414* alleles			
N (episodes)	Homozygous dominant (n=3,837)	Heterozygote (n=2,016)	Homozygous recessive (n=247)
Blood Donor Characteristics			
Sex (% male)	56	58	61
Age in years (median, (IQR))	56 (43-63)	56 (45-64)	57 (42-65)
Hemoglobin level (mean, (SD))	14.3 (1.2)	14.4 (1.1)	14.4 (1.3)
Blood Component Characteristics			
Apheresis-derived (%)	6	7	4
Gamma irradiation (%)	27	27	27
RBC storage age -days (median (IQR))	27 (16-36)	27 (16-36)	27 (15-36)
Transfusion Recipient Characteristics			
Sex (% male)	54	54	53
Age (median, (IQR))	64 (56-74)	64 (52-74)	64 (54-72)
Body mass index (median, (IQR))	28 (24-33)	28 (24-33)	27 (23-31)
Pre-transfusion Hb in g/dL (mean, (SD))	7.5 (1.0)	7.5 (1.0)	7.5 (0.8)

Supplementary Table 5b: Donor, component, & patient characteristics for transfusion recipients of single RBC units by *MYO9B* alleles			
N (episodes)	Homozygous dominant (n=2,365)	Heterozygote (n=3,163)	Homozygous recessive (n=1,219)
Blood Donor Characteristics			
Sex (% male)	59	55	58
Age in years (median, (IQR))	56 (43-64)	56 (44-64)	54 (43-62)
Hemoglobin level (mean, (SD))	14.4 (1.2)	14.3 (1.1)	14.4 (1.2)
Blood Component Characteristics			
Apheresis-derived (%)	6	6	6
Irradiation (%)	26	27	27
RBC storage age -days (median, (IQR))	27 (15-36)	27 (16-36)	27 (17-36)
Transfusion Recipient Characteristics			
Sex (% male)	55	53	52
Age (median, (IQR))	64 (53-75)	63 (53-73)	64 (53-74)
Body mass index (median, (IQR))	28 (24-33)	28 (24-33)	27 (23-33)
Pre-transfusion Hb in g/dL (mean, (SD))	7.5 (1.0)	7.5 (1.0)	7.5 (0.9)

Supplementary Table 6: Sample size estimates for SNP allele frequency and estimated effect size

Power	**Allele Frequency**	**Effect Size**	**N (∆Hemoglobin; *mu* = 1.0, SD = 0.9)**	**N (∆Bilirubin; *mu* = 0.0, SD = 0.4)**
80%	50%	0.05	5,082	1,001
		0.10	1,268	247
		0.15	561	108
		0.20	314	59
	20%	0.05	7,943	1,566
		0.10	1,983	389
		0.15	879	170
		0.20	493	94
	10%	0.05	14,124	2,787
		0.10	3,528	694
		0.15	1,566	306
		0.20	879	170
	1%	0.05	128,432	25,366
		0.10	32,105	6,339
		0.15	14,267	2,815
		0.20	8,023	1,582

SNP=single nucleotide polymorphism

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