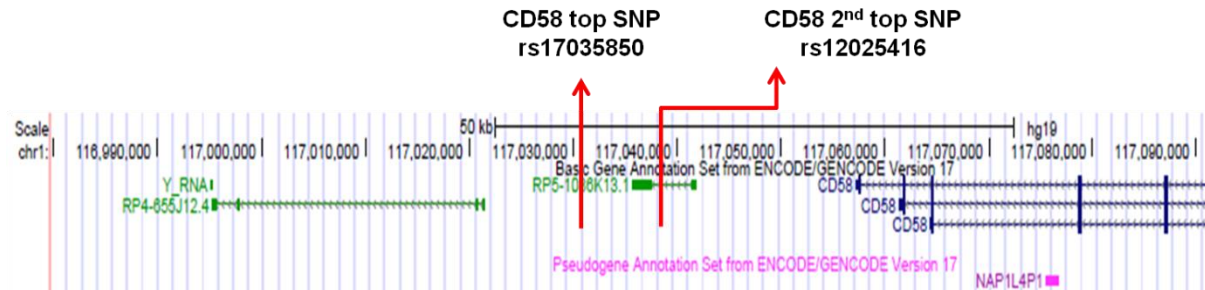
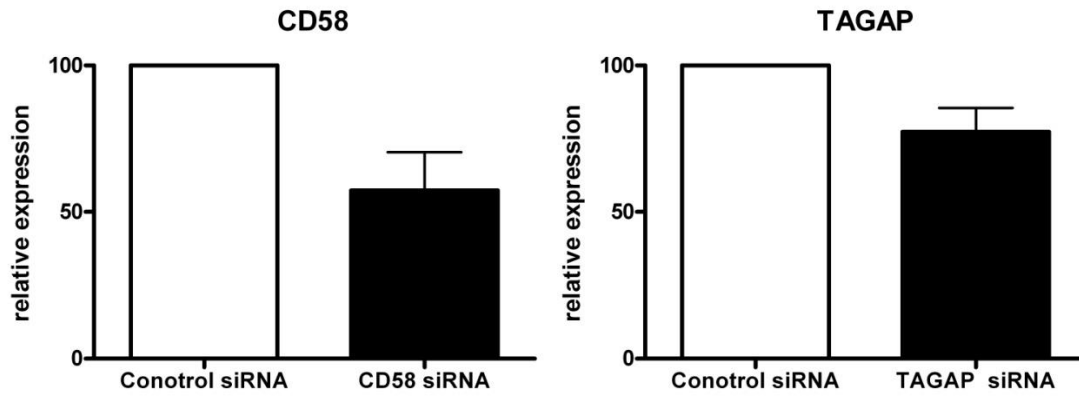


Supplementary Figures



Supplementary Fig. 1. Location of top two candidemia associated SNPs in *CD58* gene locus. The region encompass *CD58* and three long non-coding RNAs (RP4-655J12.4, RP5-1086K13.1 and NAP1L4P1). The top SNP rs17035850 is located in intergenic region 25kb 3' of *CD58* gene. The second SNP rs12025416 is located within intron of long non-coding RNA RP5-1086K13.1. The plot generated using UCSC genome browser, hg19 assembly (<http://genome.ucsc.edu>).

Supplementary Fig. 2



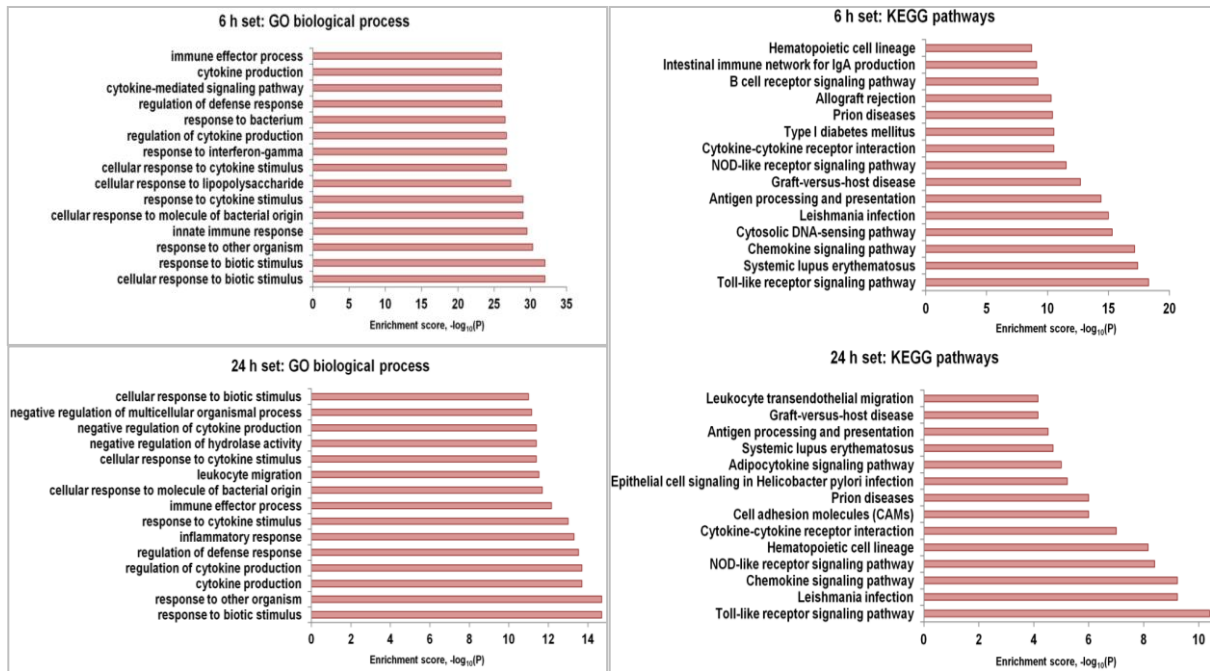
Supplementary Fig. 2. Human monocyte-derived macrophages were transfected with control, CD58, and TAGAP siRNA, respectively, for 48 hours. Total mRNA was collected for cDNA synthesis. Relative gene expression was determine by RT-PCR. The experiments were repeated for 4 different individuals. The error bars depicts SEM.

A. 6 hour data				B. 24 hour data				
	Up	Up	Down		Up	Down		
	IFIT1	2.111	SETDB2	1.260	HSPA1A	2.087		
	OAS1	1.758	RGS2	1.276	CD58_2	1.908		
	IFITM1	1.695	SDF2	1.272	HSP61	1.908		
	IFI6	1.597	IL6	1.270	CD58	1.881		
	HIST1H2BD	1.572	HIST2H2AC	1.270	HSPA1B	1.778		
	LY6E	1.564	MAP1LC3A	1.270	SERPINB2	1.771		
	ARL4A	1.502	TMEM43	1.269	CDAN1	1.638		
	IFIT3	1.495	CCDC115	1.268	CCL2	1.637		
	CCL5	1.490	FAM63A	1.268	ABHD12	1.485		
	CES1	1.481	HIST2H2BE	1.267	PNPT1	1.475		
	VNN2	1.474	MYL12A	1.267	FLJ43681	1.419		
	HLA-A29.1	1.470	DUSP10	1.264	SERPINS2_2	1.408		
	IFI6_2	1.470	IFI35	1.262	ARL2	1.406		
	ADA	1.460	CD72	1.262	TNFAIP3	1.401		
	HIST1H2AC	1.446	UNC93B1	1.262	SOC33	1.392		
	NCF1	1.442	OGFRL1	1.261	CCL4L2	1.391		
	PTGES	1.418	CXCR4	1.261	ARL16	1.374		
	H1FO	1.416	SERPING1	1.260	CXCL5	1.373		
	OAS1_2	1.407	CT1ORF48	1.260	ZC3H12A	1.372		
	MX1	1.399	OAS3	1.259	SRMS5	1.370		
	IFITM2	1.398	LY9	1.257	IRG1	1.368		
	C15	1.396	OAS2	1.257	LEP	1.365		
	HIST1H2BD_2	1.392	STAT1	1.257	NABP2	1.364		
	YFEL1	1.390	RHBD02	1.256	IGSF6	1.359		
	BRSK1	1.386	PLA2G7	1.256	PRKAR1A	1.353		
	NT5C3	1.385	DHRS9	1.254	DEI	1.343		
	GADD45G	1.384	GEP2	1.254	ZNF486	1.343		
	HIST2H2AA3	1.383	NCK1	1.254	RPS6P1	1.342		
	ANG	1.382	ACTA2	1.254	NFKBIZ	1.335		
	XAF1	1.365	BCL6	1.253	ANXA2P2	1.335		
	SILV	1.365	CMPY3	1.253	KLF6	1.331		
	RSAD2	1.360	AK2	1.252	RFWD2	1.328		
	CD38	1.353	PXYD5	1.252	ZNF738	1.327		
	NKG7	1.353	MDK	1.251	MFHAS1	1.326		
	NUPR1	1.351	ARL85P1	1.251	EIF1B	1.317		
	OAS1_3	1.350	RCAN1	1.250	DNAJA1	1.314		
	IFITM3	1.349			ID2	1.313		
	CCL5_2	1.349			UBB	1.312		
	MT1X	1.348			RNU6-1	1.310		
	CCR2L2	1.344			MMP12	1.304		
	ABHD5	1.344			DUXAP3	1.304		
	C21ORF7	1.343			FTHL16	1.300		
	PTGDS	1.342			MGC7895	1.292		
	CAMP	1.340			TSPAN13	1.285		
	P8	1.339			ATP5A1	1.284		
	CCL23	1.335			COL22A1	1.282		
	CD86	1.331			CLK1	1.281		
	ANG_2	1.327			CCL24	1.281		
	CES1_2	1.325			LSP1	1.280		
	HLA-DRB5	1.325			SLC22B1	1.280		
	SGLEC10	1.324			MGC10997	1.278		
	OLR1	1.324			SLC25A24	1.278		
	CCL8	1.318			PTTG1	1.277		
	EST2	1.318			FAM5A	1.276		
	RNASE4	1.317			HLA-F	1.272		
	NCF4	1.311			EIF3A	1.268		
	DEDD2	1.306			SDSL	1.267		
	IFI27	1.302			PDLA3P	1.267		
	LY6E	1.297			CRCP	1.267		
	PIRRA	1.295			GSTP1	1.266		
	FLJ10374	1.294			SLC38A2	1.265		
	GPR162	1.294			RPS9	1.262		
	PARP3	1.292			FTHL2	1.260		
	OR1L4	1.290			JUNB	1.258		
	ISG20	1.287			FKSG36	1.257		
	ERN1	1.286			ABCG1	1.256		
	FGL2	1.286			MCL1	1.256		
	IL4I1	1.285			NME1-NME2	1.255		
	BTG3	1.285			CREB1	1.254		
	SLC16A8	1.282			AMY1C	1.252		
	CAPZA2	1.281			PPA2	1.251		
					RSAD2	1.498	CD58	2.087
					IL6	1.452	CD58_2	1.828
					LY9	1.436	VCAN	1.554
					IFI27	1.421	S100A8	1.489
					HIST1H2BD	1.395	BLZF1	1.385
					SDC4	1.374	IL1R2	1.380
					CES1	1.368	ABHD12	1.372
					LY6E	1.366	HSPA1A	1.351
					PTGES	1.360	RNU1G2	1.346
					IFI6	1.347	ARL2	1.345
					HES4	1.347	CD163_2	1.335
					OGFRL1	1.346	CXCL5_2	1.335
					HIST1H2BD_2	1.339	CXCL5	1.329
					HIST3H2A	1.330	TPM2	1.324
					C1QC	1.322	COL22A1	1.318
					HIST2H2AA3	1.315	CD1B	1.317
					CYBASC3	1.315	FTHL11	1.314
					MUCL1	1.312	CDKN2AIPNL	1.313
					SMG5	1.311	CSORF28	1.311
					OGFRL1_2	1.311	C20ORF127	1.308
					WNT1	1.310	HCG2P7	1.306
					SILV	1.302	CD163	1.304
					RARRES3	1.299	RNU1-3	1.304
					AKR1B1	1.286	CREB1	1.302
					GZMB	1.286	RNU1A3	1.300
					SDS	1.282	SLC39A8	1.298
					HLA-DRB5	1.279	FCGR1B	1.296
					STAT3	1.276	BCAT1	1.294
					RB1CC1	1.271	STX4	1.293
					ETS2	1.271	CCL24	1.290
					NEU1	1.271	SDHC	1.286
					HIST2H2AA4	1.269	RTN1	1.285
					TMEM158	1.268	ANGPTL4	1.285
					LSS	1.267	ITGAM	1.284
					SP140	1.265	ZFP36L1	1.282
					IL23A	1.262	RNU1F1	1.277
					HLA-DRB6	1.262	CAT	1.276
					TNFSF14	1.262	NUMB_2	1.272
					SF3B1	1.260	HSPA7	1.269
					PLEKH2	1.260	TGM2	1.267
					CAMP	1.260	NDRG2	1.264
					CCR7	1.259	CMPK1	1.264
					TNFAIP6	1.258	COTL1	1.261
					SERPING1	1.256	SLC2A14	1.261
					EPAS1	1.256	ANXA2P1	1.259
					CXCR4	1.256	NUMB	1.259
					DPVSL3	1.254	STC1	1.252
					PPID	1.252	CAMK1	1.251
					OAS1	1.252		
					CHKA	1.251		
					ADIPOR2	1.250		

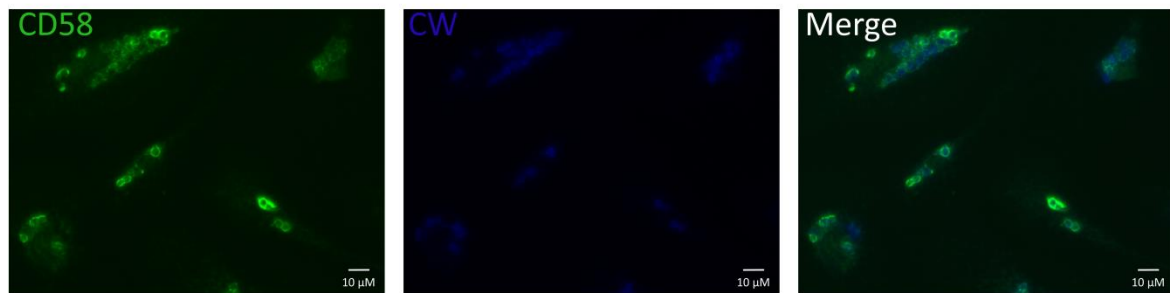
Supplementary Fig. 3. Transcriptomic analysis of macrophages transfected with control siRNA or CD58 siRNA and stimulated with live *C. albicans* for 6 hours or 24 hours.

Differentially expressed genes from control and CD58 siRNA cells were defined by at least 1.25-fold change at (A) 6 hours, and (B) 24 hours.

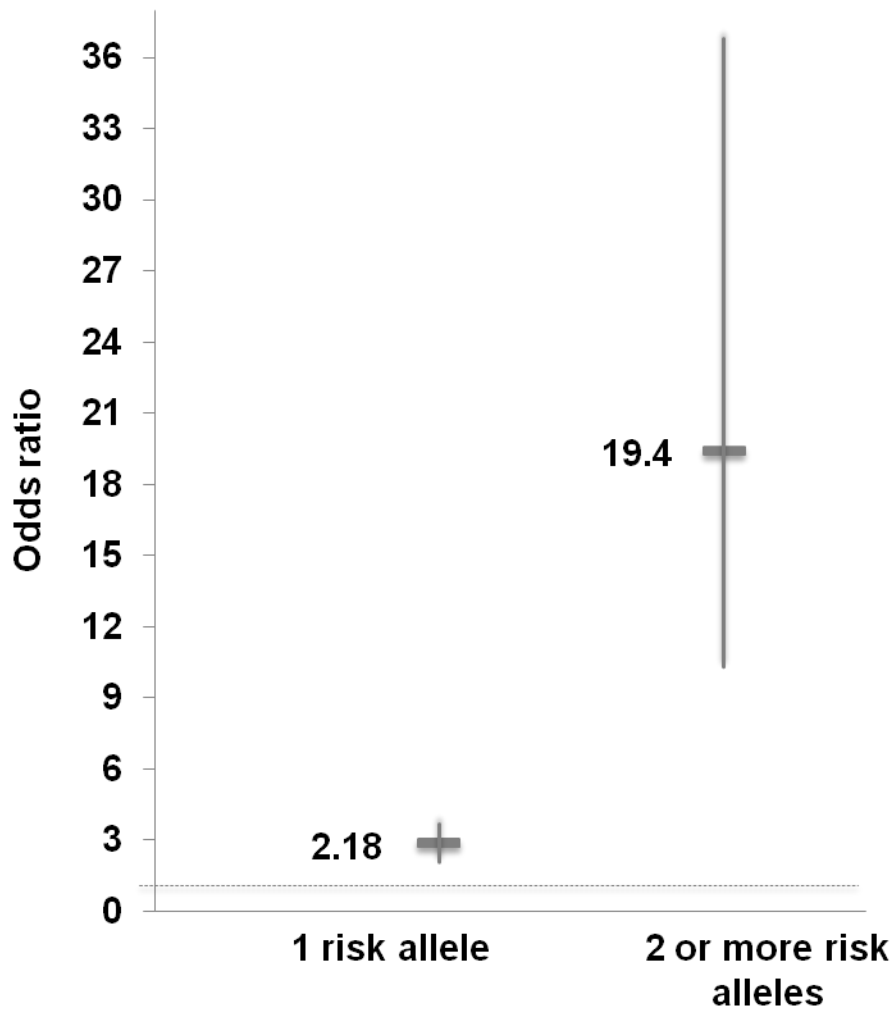
Supplementary Fig. 4



Supplementary Fig. 4. Transcriptomic analysis of macrophages transfected with control siRNA, CD58 siRNA, or TAGAP siRNA, and stimulated with live *C. albicans* for 6 hours or 24 hours. Differentially expressed genes between control and CD58 siRNA cells were defined by at least 1.25-fold change. GO enrichment and KEGG pathway enrichment analyses of the regulated genes by CD58 are shown respectively.

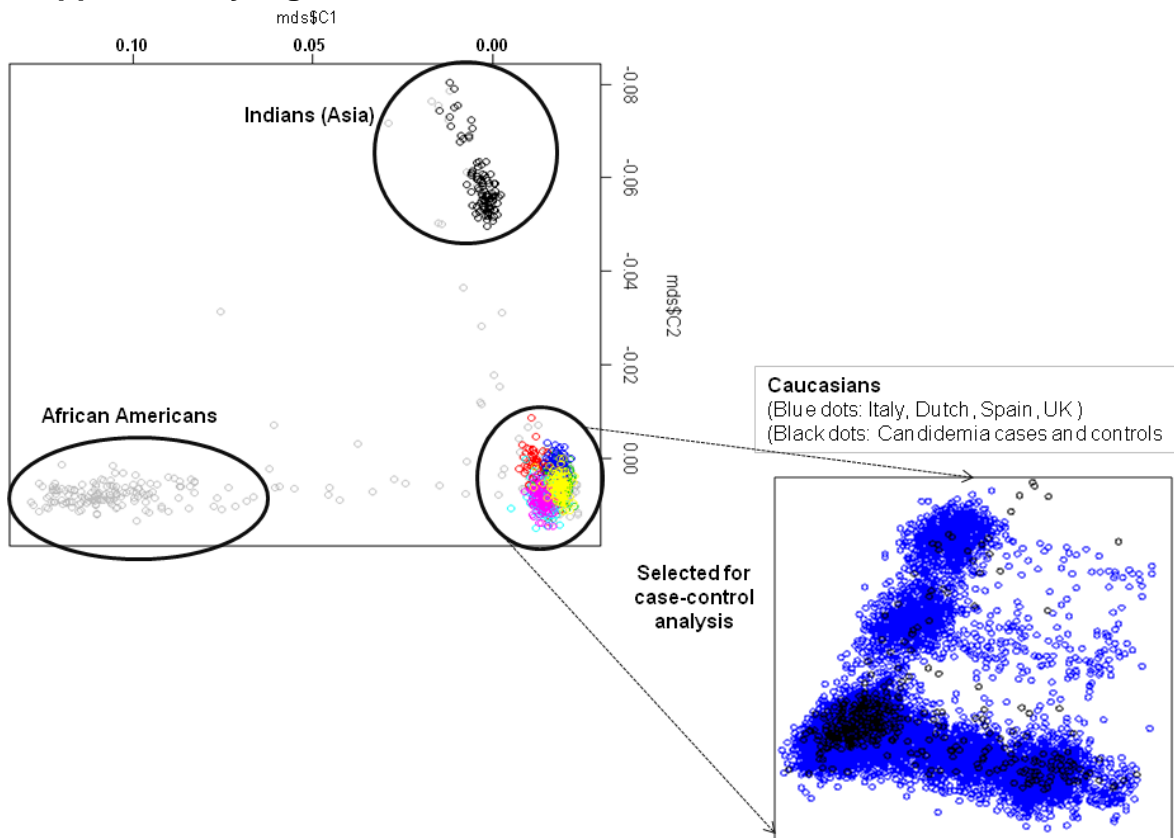


Supplementary Fig. 5. Immunofluorescence microscopic photos were taken after 1 hour incubation of live *Candida* with macrophages. CD58 (green) was co-localized with calcofluor white (blue, staining for the chitin of *Candida*).

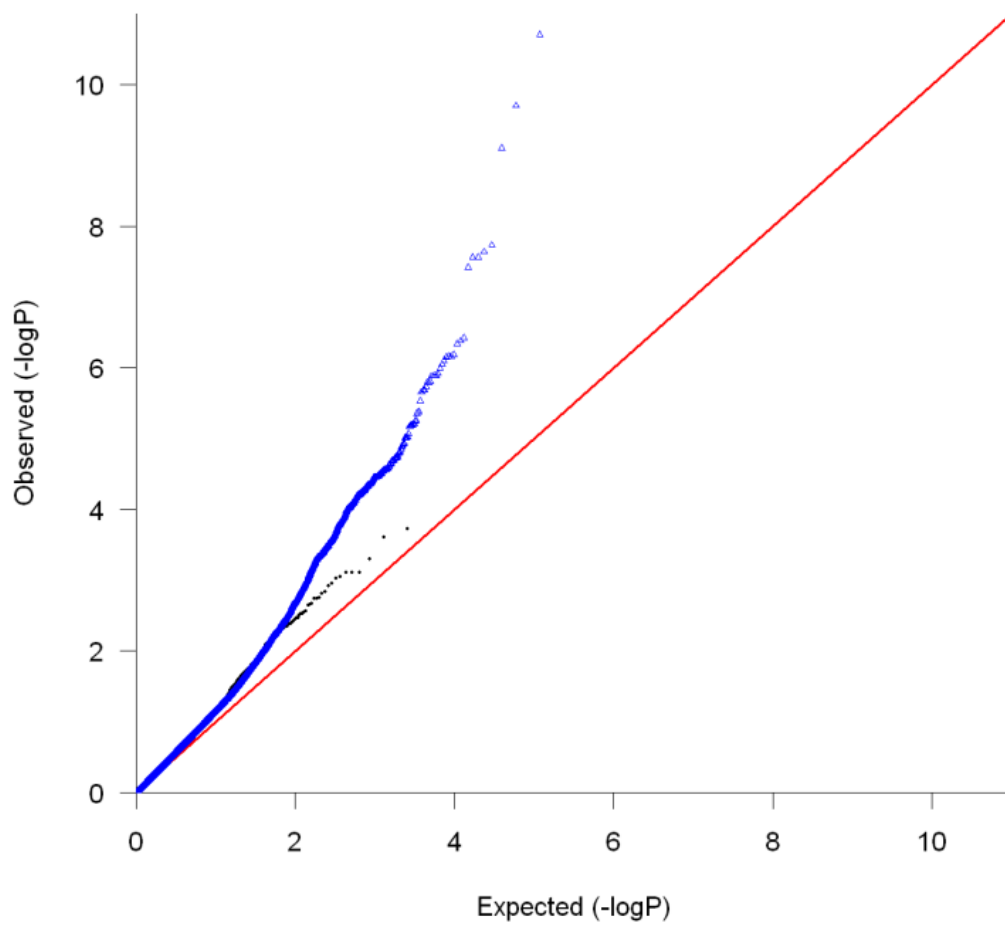


Supplementary Fig. 6. Odds ratio (OR) of cumulative effect of the three SNPs tested in the present study. The cumulative effects of three risk SNPs on candidemia risk among individuals carrying either 1 (OR = 2.18; CI = 1.50-3.16) or 2 and more risk alleles (OR = 19.40; CI = 10.24-36.75). The odds ratios were calculated relative to the individuals with no risk alleles for the three SNPs.

Supplementary Fig. 7



Supplementary Fig. 7. Multidimensional scaling (MDS) analysis (implemented in PLINK, MDS on the $N \times N$ matrix of genome-wide IBS pairwise distances) was performed on individuals from Candidemia cohort by including population based control samples of known ethnicity as reference. Caucasian samples were well separated from African-American candidemia samples as well as Indian candidemia samples. Only samples which overlap with the known European ethnic populations were included (in the second panel) for case-control analysis.



Supplementary Fig. 8. The Quantile-Quantile plot of association p values of all SNPs on the ImmunoChip array (blue points), and SNPs that are unrelated to immune-mediated traits (black points). The GWAS significant hits are circled using red dotted line. The genetic inflation factor λ for all SNPs was 1.22 and for non-immune SNPs was 1.102.

Supplementary Tables

Supplementary Table 1. Replication results at top 3 loci in African-American candidemia cohorts

rs ID	Chr	Position (hg19)	Case				Controls				P	Odds ratio (CI)	Protein-coding gene
			AA	AB	BB	MAF	AA	AB	BB	MAF			
rs17035850	1	117032022	6	30	39	0.280	2	24	22	0.370	0.837	1.06 (0.60-1.87)	CD58
rs12025416	1	117038287	7	30	38	0.293	7	23	24	0.342	0.411	1.26 (0.74-2.13)	CD58
rs4845320	1	152709896	0	18	57	0.120	0	8	46	0.074	0.203	0.59 (0.25-1.4)	LCE4A-C1orf68
rs3127214	6	159511488	4	20	50	0.189	0	11	43	0.101	0.062	1.996 (0.95-4.18)	TAGAP

Supplementary Table 2. Joint analysis at candidemia risk SNPs

rs ID	Chr	Position (hg19)	Replication cohorts	Case				Controls				p value	Odds ratio (CI)	Gene	p*
				AA	AB	BB	MAF	AA	AB	BB	MAF				
rs17035850	1	117032022	Validation cohort	3	16	198	0.051	0	8	138	0.027	0.15	1.58 (0.66-3.78)	CD58	0.168
			Switzerland candidiasis cohort	0	1	26	0.019	0	4	36	0.050	0.336	0.36 (0.04-3.3)		
			Joint analysis	3	17	224	0.0471	0	12	174	0.032	0.37	0.67 (0.32-1.39)		
rs12025416	1	117038287	Validation cohort	11	57	147	0.184	1	32	111	0.118	0.022	1.694 (1.08-2.56)	CD58	0.56
			Switzerland candidiasis cohort	2	8	17	0.222	0	13	27	0.163	0.376	1.47 (0.61-3.53)		
			Joint analysis	13	65	164	0.188	1	45	138	0.128	0.016	1.64 (1.11-2.42)		
rs4845320	1	152709896	Validation cohort	3	16	198	0.051	0	3	143	0.010	0.008	4.091 (1.21-13.85)	LCE	NA
			Switzerland candidiasis cohort	0	1	27	0.018	0	0	40	0.000	0.229	NA		
			Joint analysis	3	17	225	0.047	0	3	183	0.008	0.004	5.49 (1.64-18.35)		
rs3127214	6	159511488	Validation cohort	3	23	191	0.067	0	8	137	0.027	0.026	2.51 (1.13-5.55)	TAGAP	0.112
			Switzerland candidiasis cohort	0	1	25	0.019	0	4	36	0.050	0.356	0.37 (0.004-3.43)		
			Joint analysis	3	24	216	0.061	0	12	173	0.032	0.842	0.51 (0.25-1.03)		

Chr; Chromosome

*P value for heterogeneity calculated using Breslow-Day test

Supplementary Table 3(A) Functional annotation of CD58 SNP and its proxies with $r^2 \geq 0.8$ using HaploReg

Functional annotation of CD58 SNP, rs17035850 and variants with $r^2 \geq 0.8$												
chr	pos (hg19)	LD	LD	variant	Ref	Alt	Minor allele frequency in EUROPEANS	Promoter	Enhancer	DNase	Proteins	Motifs
		(r^2)	(D')				MAF	histone marks	histone marks		bound	changed
1	117031305	0.84	0.92	rs58830348	C	T	0.02		5 cell types			10 altered motifs
1	117032022	1	1	rs17035850	A	T	0.02		7 cell types	13 cell types	10 bound proteins	NRSF
1	117032630	1	1	rs17035853	C	T	0.02		6 cell types	HMVEC-LB1,NH-A		
1	117034860	1	1	rs74111604	G	C	0.02		K562, HepG2	5 cell types		NRSF,TCF12
1	117036111	1	1	rs148224339	C	T	0.02		HepG2, K562	CLL		ZEB1
1	117043713	0.92	1	rs76594009	G	T	0.02		K562			Hoxa5,TCF12
1	117048486	0.84	0.92	rs61789220	G	A	0.02		4 cell types			Foxa,GR,STAT
1	117087590	0.84	0.92	rs61789231	G	A	0.02		4 cell types	6 cell types	16 bound proteins	4 altered motifs

Supplementary Table 3(B) Functional annotation of LCE locus SNP and its proxies with $r^2 \geq 0.8$ using HaploReg

Functional annotation of LCE locus SNP, rs4845320 and variants with $r^2 \geq 0.8$												
chr	pos (hg19)	LD	LD	variant	Ref	Alt	Minor allele frequency in EUROPEANS	Enhancer	DNase	Motifs	changed	
		(r^2)	(D')				MAF	histone marks				
1	152625292	0.91	1	rs12048544	C	A	0.01				4 altered motifs	
1	152647240	0.91	1	rs12024423	G	C	0.01				GATA	
1	152666149	0.91	1	rs140940191	C	A	0.01				7 altered motifs	
1	152680720	0.91	1	rs12033945	A	G	0.01				4 altered motifs	
1	152681835	0.82	0.91	rs10888510	G	T	0.01				CTCF,HDAC2,Myc	
1	152682533	0.82	0.91	rs74130116	T	C	0.01				4 altered motifs	
1	152682708	0.82	0.91	rs12036739	T	C	0.01				MeF2,Msx-1,Nanog	
1	152687791	1	1	rs61281084	T	C	0.01				Nrf-2	
1	152688119	1	1	rs80154606	T	C	0.01				ERalpha,a,RORalpha1	
1	152689730	1	1	rs12040771	G	C	0.01				AP-2rep,Egr-1,Gcm1	
1	152690547	1	1	rs16834366	A	G	0.01		HMEC, NHEK		4 altered motifs	
1	152693043	1	1	rs16834376	C	T	0.01					
1	152693600	1	1	rs75063514	T	G	0.01					
1	152694501	1	1	rs6656896	T	G	0.01			T-47D	EWSR1-FLI1	
1	152696256	1	1	rs4845472	G	C	0.01				5 altered motifs	
1	152698168	1	1	rs12048867	G	A	0.01					
1	152698935	1	1	rs6661464	G	T	0.01			LNcaP	HNF4	
1	152702580	1	1	rs12045233	T	C	0.01				Foxp1,RREB-1	
1	152707760	1	1	rs78389247	G	T	0.01				GR,PU.1	
1	152709896	1	1	rs4845320	A	C	0.01				Bbx,Hbp1,Pax-4	

Supplementary Table 3(C) Functional annotation of TAGAP SNP and its proxies with $r^2 \geq 0.8$ using HaploReg

Functional annotation of TAGAP SNP, rs3127214 and variants with $r^2 \geq 0.8$												
chr	pos (hg19)	LD (r ²)	LD (D')	variant	Ref	Alt	Minor allele frequency in EUROPEANS	Enhancer	DNase	Proteins	Motifs	
							MAF	histone marks		bound	changed	
6	159498306	0.96	1	rs1572527	G	A	0.03	GM12878	10 cell types	BATF,BC L11A,EG R1	AP-1,Bach2,HNF1	
6	159501256	1	1	rs103418	G	A	0.03	HSM1, GM12878	CLL,Jurkat	EBF1	Arnt,GATA,My	
6	159504878	1	1	rs127210	A	G	0.03					
6	159507027	1	1	rs3127211	C	A	0.03	NHEK, K562			AhR::Arnt,Arnt	
6	159507971	1	1	rs3127212	A	G	0.03	K562			Foxp1	
6	159511488	1	1	rs3127214	C	T	0.03					

Supplementary Table 4. Co-regulation partners of RP5-1086K13.1 extracted using GeneNetwork database

Queried gene	coregulated genes	coregulated gene Ensembl ID	Chromosome	start	stop	strand	z score	P value
RP5-1086K13.1	<i>CD58</i>	ENSG00000116815	1	117057157	117113661	-	11.28	1.65E-29
RP5-1086K13.1	<i>SH2D4B</i>	ENSG00000178217	10	82297658	82406316	+	5.87	4.36E-09
RP5-1086K13.1	<i>CTC-436K13.5</i>	ENSG00000253792	5	157600609	157603430	-	5.78	7.47E-09
RP5-1086K13.1	<i>TMEM106A</i>	ENSG00000184988	17	41363894	41371589	+	4.86	1.17E-06
RP5-1086K13.1	<i>RP3-523C21.1</i>	ENSG00000228495	6	132453055	132490514	+	4.61	4.03E-06
RP5-1086K13.1	<i>ZNF674</i>	ENSG00000251192	23	46357162	46404892	-	4.56	5.12E-06
RP5-1086K13.1	<i>HCG27</i>	ENSG00000206344	6	31165537	31171745	+	4.44	9.00E-06
RP5-1086K13.1	<i>ANKHD1</i>	ENSG00000131503	5	139781399	139929163	+	4.39	1.13E-05
RP5-1086K13.1	<i>HMHB1</i>	ENSG00000158497	5	143191726	143200284	+	4.36	1.30E-05
RP5-1086K13.1	<i>AC135050.2</i>	ENSG00000249093	16	31052374	31054276	+	4.31	1.63E-05
RP5-1086K13.1	<i>AL096869.5</i>	ENSG00000233208	14	90921574	90925249	+	4.28	1.87E-05
RP5-1086K13.1	<i>RAG2</i>	ENSG00000175097	11	36597124	36619829	-	4.27	1.95E-05
RP5-1086K13.1	<i>RP11-290F20.1</i>	ENSG00000203999	20	48909257	48931459	+	4.24	2.24E-05
RP5-1086K13.1	<i>SIN3B</i>	ENSG00000127511	19	16940218	16991164	+	-4.16	3.18E-05
RP5-1086K13.1	<i>RP11-397G17.1</i>	ENSG00000226733	6	50061424	50066995	+	4.11	3.96E-05
RP5-1086K13.1	<i>TRAF1</i>	ENSG00000056558	9	123664671	123691451	-	4.11	3.96E-05
RP5-1086K13.1	<i>OR2B6</i>	ENSG00000124657	6	27925019	27925960	+	4.11	3.96E-05
RP5-1086K13.1	<i>RADIL</i>	ENSG00000157927	7	4836686	4923350	-	4.05	5.12E-05
RP5-1086K13.1	<i>CHRNA10</i>	ENSG00000129749	11	3686817	3692614	-	3.99	6.61E-05
RP5-1086K13.1	<i>GHRL0S</i>	ENSG00000240288	3	10327472	10334334	+	3.98	6.89E-05
RP5-1086K13.1	<i>AP000295.7</i>	ENSG00000223799	21	34636178	34638565	-	3.93	8.49E-05

Supplementary Table 5. Association of candidemia SNPs with severity of fungal disease

SNP rs number	Persistent fungemia (P-value)	Disseminated disease (P-value)
rs17035850 (CD58)	0.005	NS
rs12025416 (CD58)	NS	NS
rs3127214 (TAGAP)	NS	0.017
rs4845320 (LCE4A-C1orf68)	NS	NS
NS; not significant		

Supplementary Table 6. The names of the institutional review boards that approved the study

Name of Review Board	Study Population
Review board of the department of Medicine of the Radboud University Nijmegen Medical Centre	Candidemia cohort
Review board of Duke University Hospital	Candidemia cohort
Review board of Duke University Hospital	Candidemia control cohort
Review board of the department of Medicine of the Radboud University Nijmegen Medical Centre	In vitro macrophage experiment