Supplementary information for:

An integrated transcriptomic and functional genomic approach identifies a type I interferon signature as a host defense mechanism against *Candida albicans* in humans

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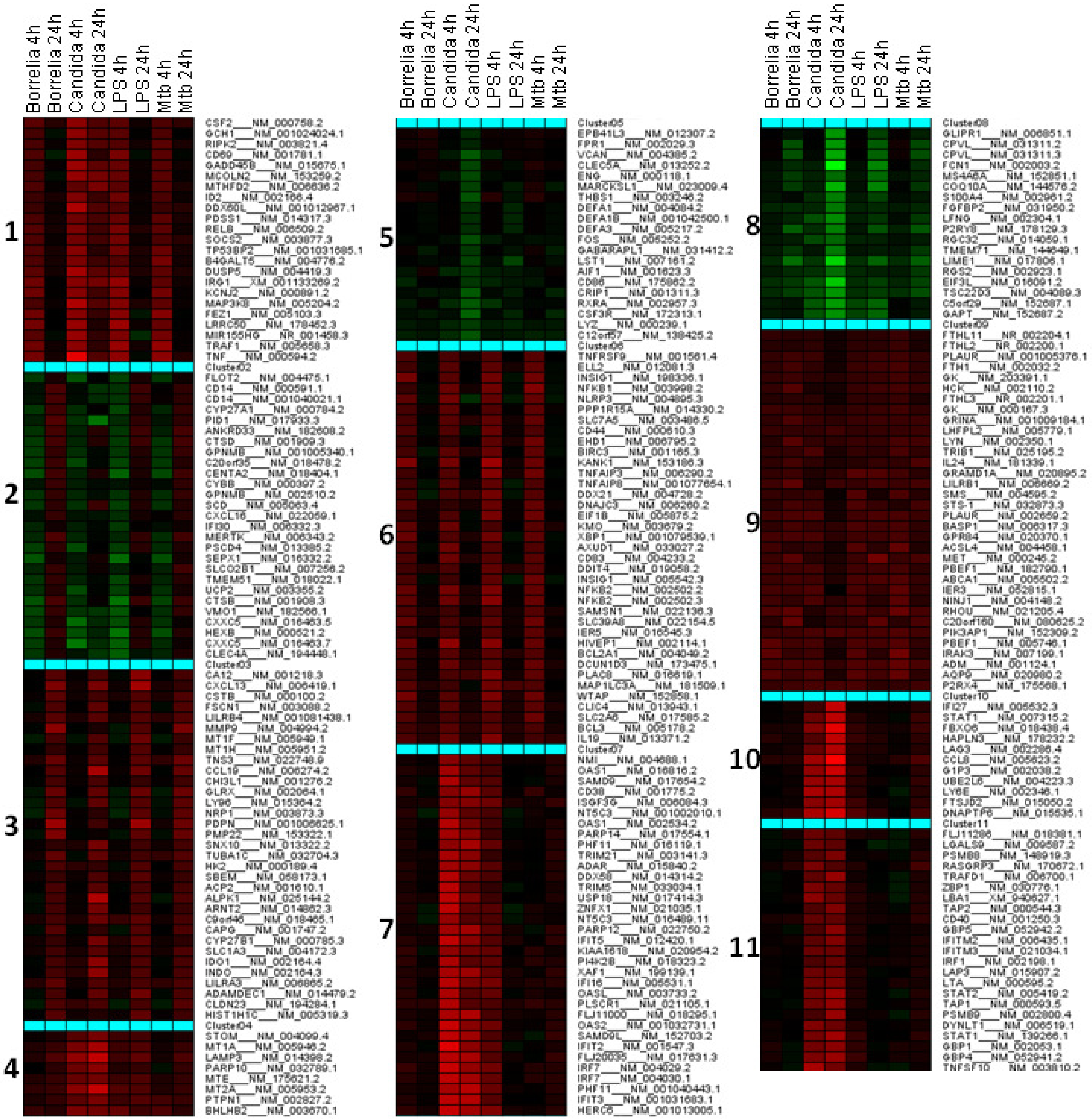
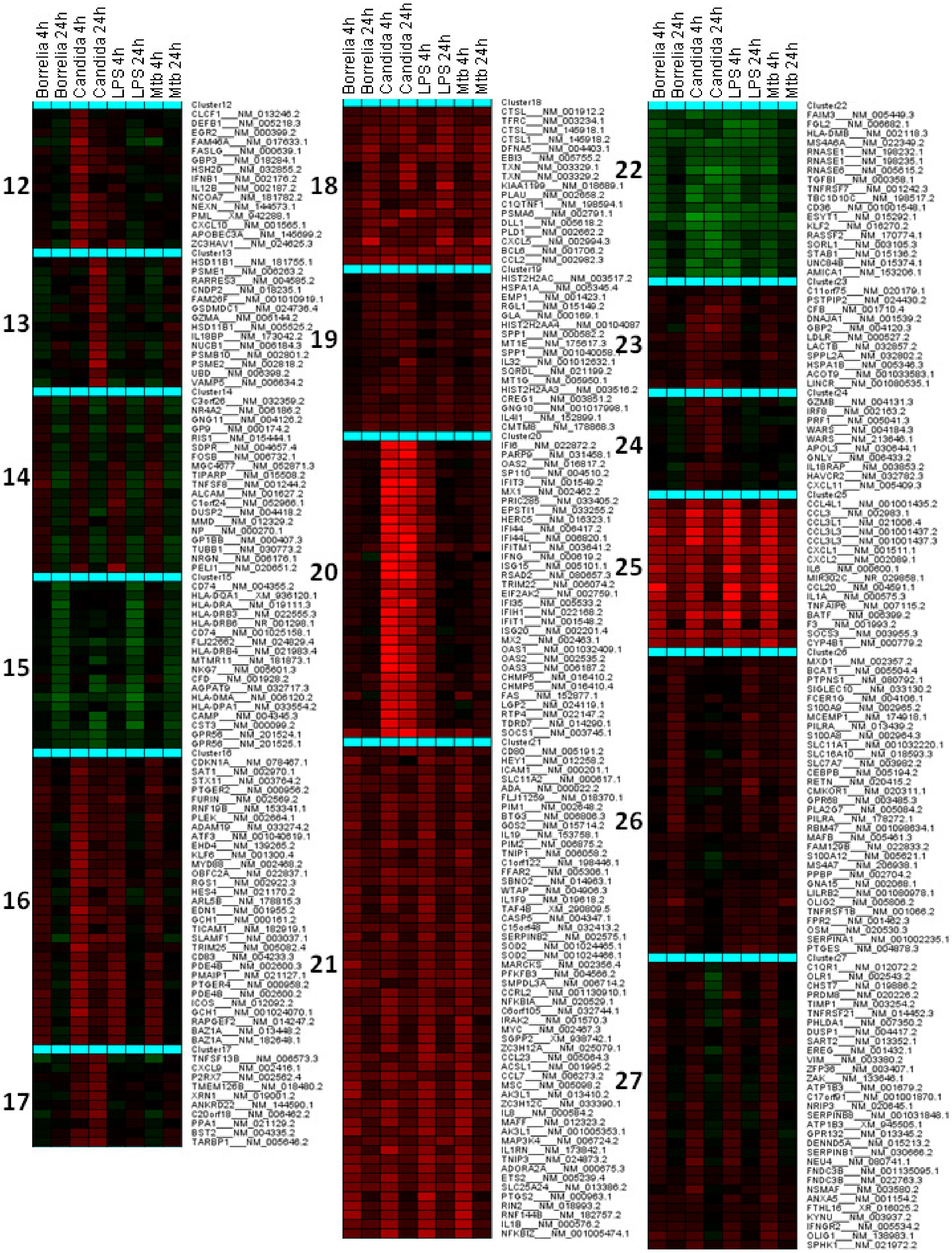
Supplementary Figure S1 K-means clustered analysis (1-11)



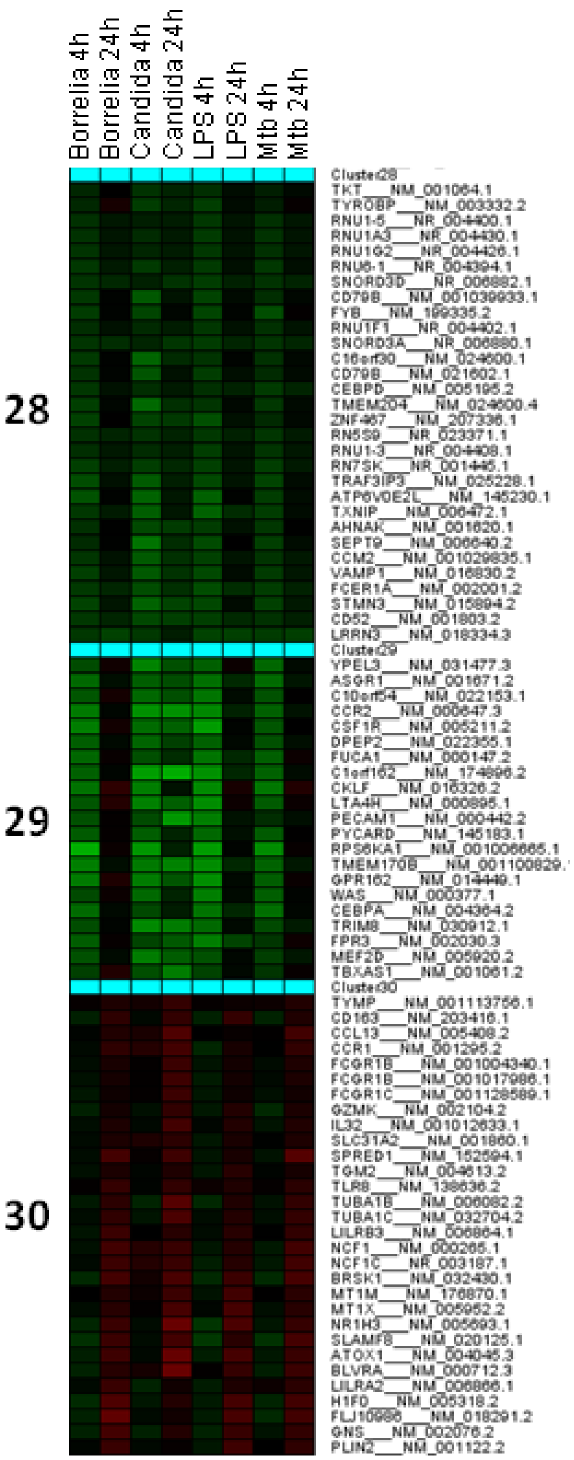
Supplementary Figure S1. K-means cluster analysis of transcriptional responses to Candida. An expanded view of expression profiles clusters 1-11 shown in Figure 1, describing responses to stimulation with *Borrelia burgdorferi*, *Candida albicans*, *E.coli*-derived LPS, and *Mycobacterium tuberculosis* (M.tb) is displayed.

Supplementary Figure S2 K-means clustered analysis (12-27)



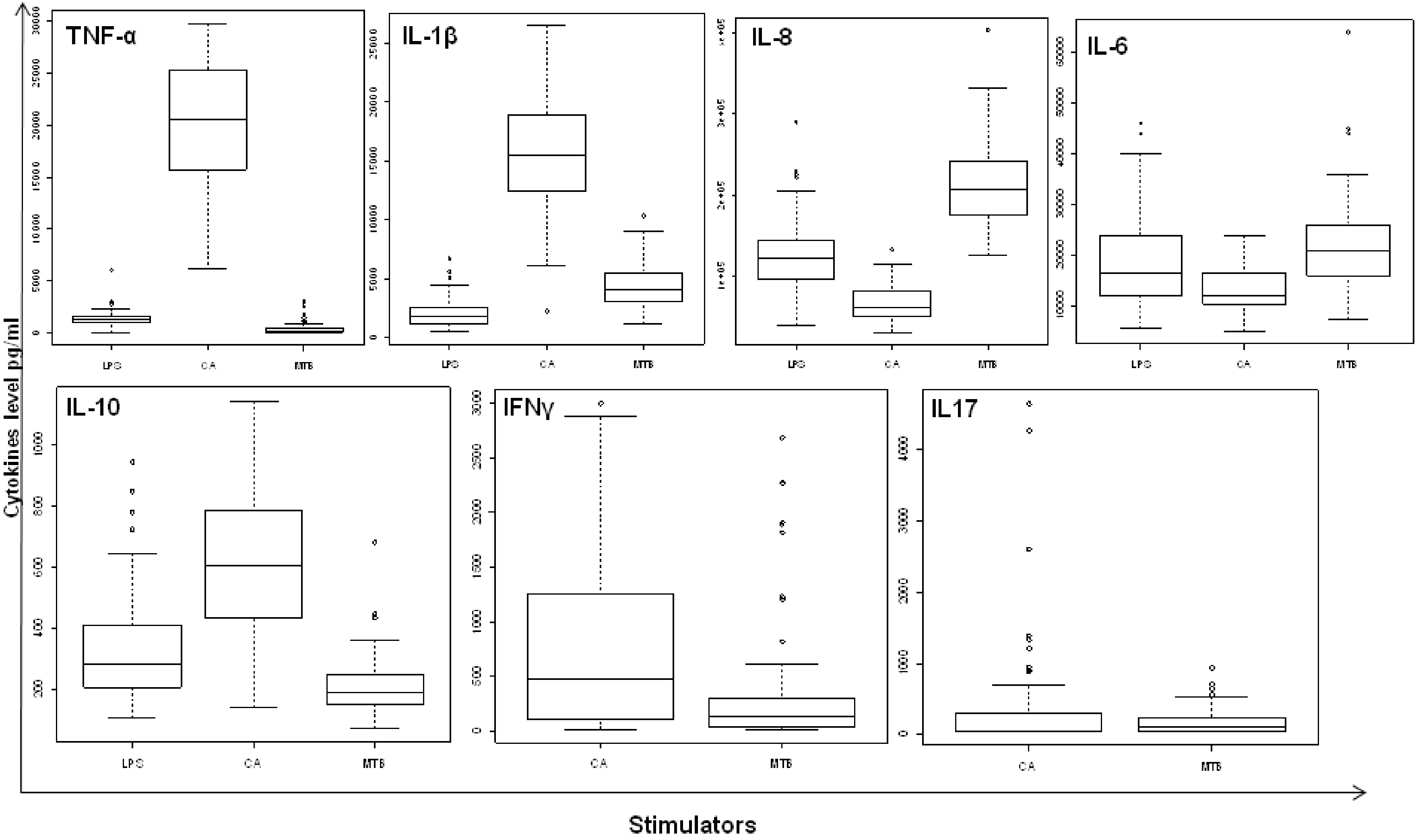
Supplementary Figure S2. K-means cluster analysis of transcriptional responses to Candida. An expanded view of expression profiles clusters 12-27 shown in Figure 1, describing responses to stimulation with *Borrelia burgdorferi*, *Candida albicans*, *E.coli*-derived LPS, and *Mycobacterium tuberculosis* (M.tb) is displayed.

Supplementary Figure S3 K-means clustered analysis (28-30)



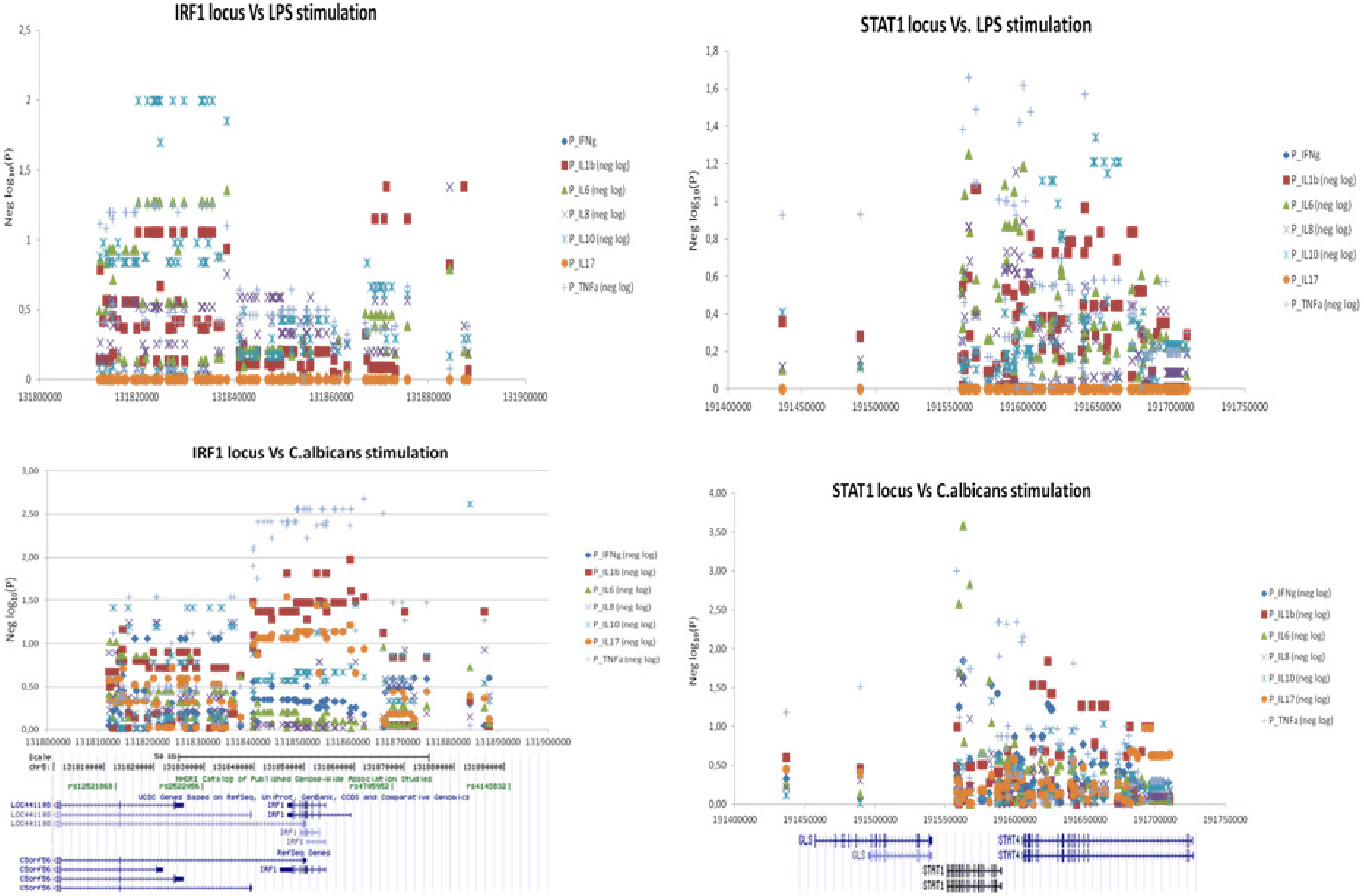
Supplementary Figure S3. K-means cluster analysis of transcriptional responses to Candida. An expanded view of expression profiles clusters 28-30 shown in Figure 1, describing responses to stimulation with *Borrelia burgdorferi*, *Candida albicans*, *E.coli*-derived LPS, and *Mycobacterium tuberculosis* (M.tb) is displayed.

Supplementary Figure S4 Correlation plots for cytokines versus corresponding stimuli.



Supplementary Figure S4. In contrast to other microbial stimuli such as LPS and MTB, *C. albicans* induced higher levels of TNF-α, IL-1β and IL-10 production, and lower levels of IL-8 and IL-6 in human PBMCs. Boxplots represent median ± interquartile range.

Supplementary Figure S5 Correlation plots for all cytokines and SNP polymorphisms


IRF1 locus Vs LPS stimulation

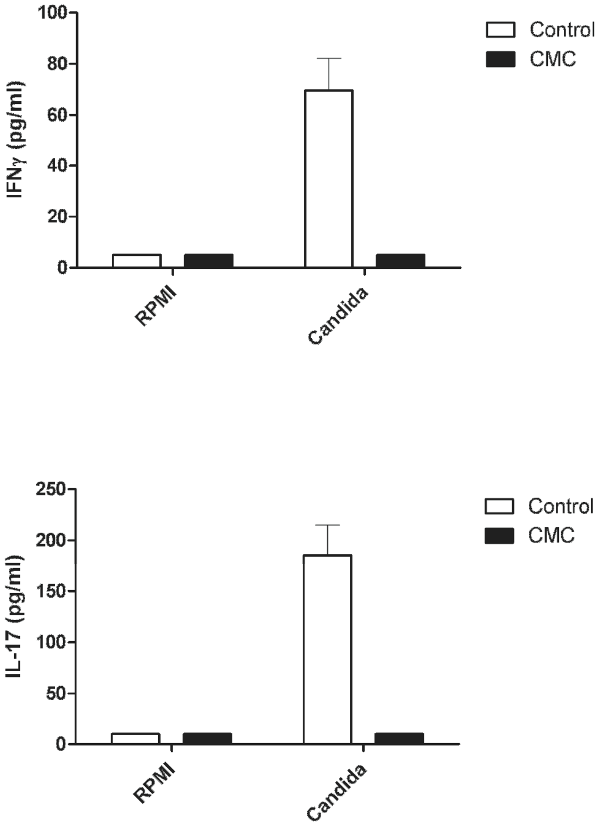
STAT1 locus Vs. LPS stimulation

IRF1 locus Vs C.albicans stimulation

STAT1 locus Vs C.albicans stimulation

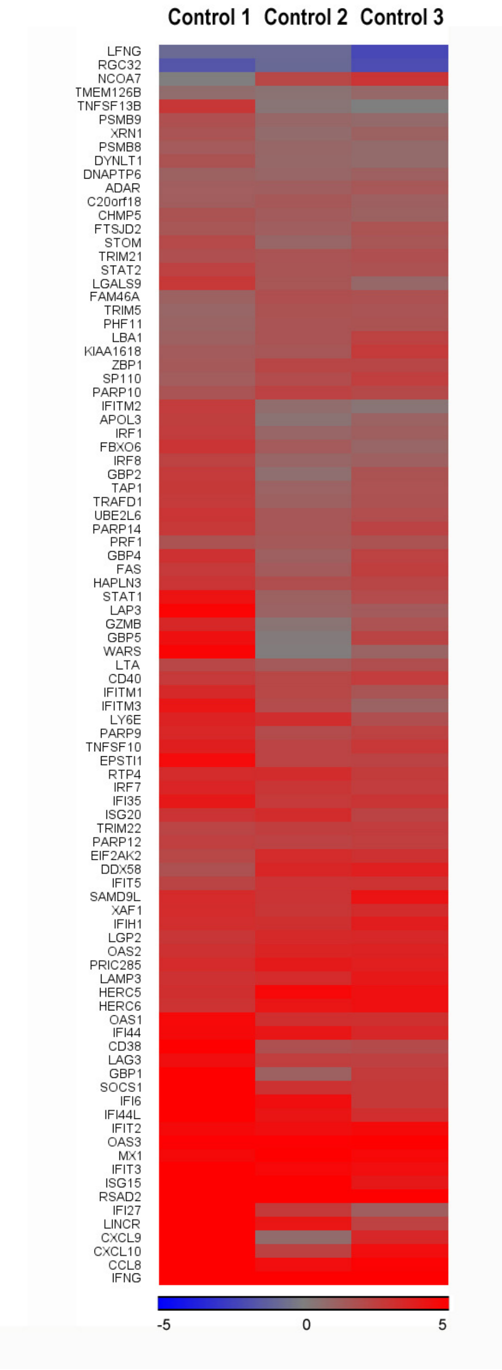
Supplementary Figure S5. Consistent with the specificity of the type I IFN pathway for *Candida* stimulation, the association was significant with cytokine levels induced by *Candida*, but not by LPS or MTB stimulation.

Supplementary Figure S6



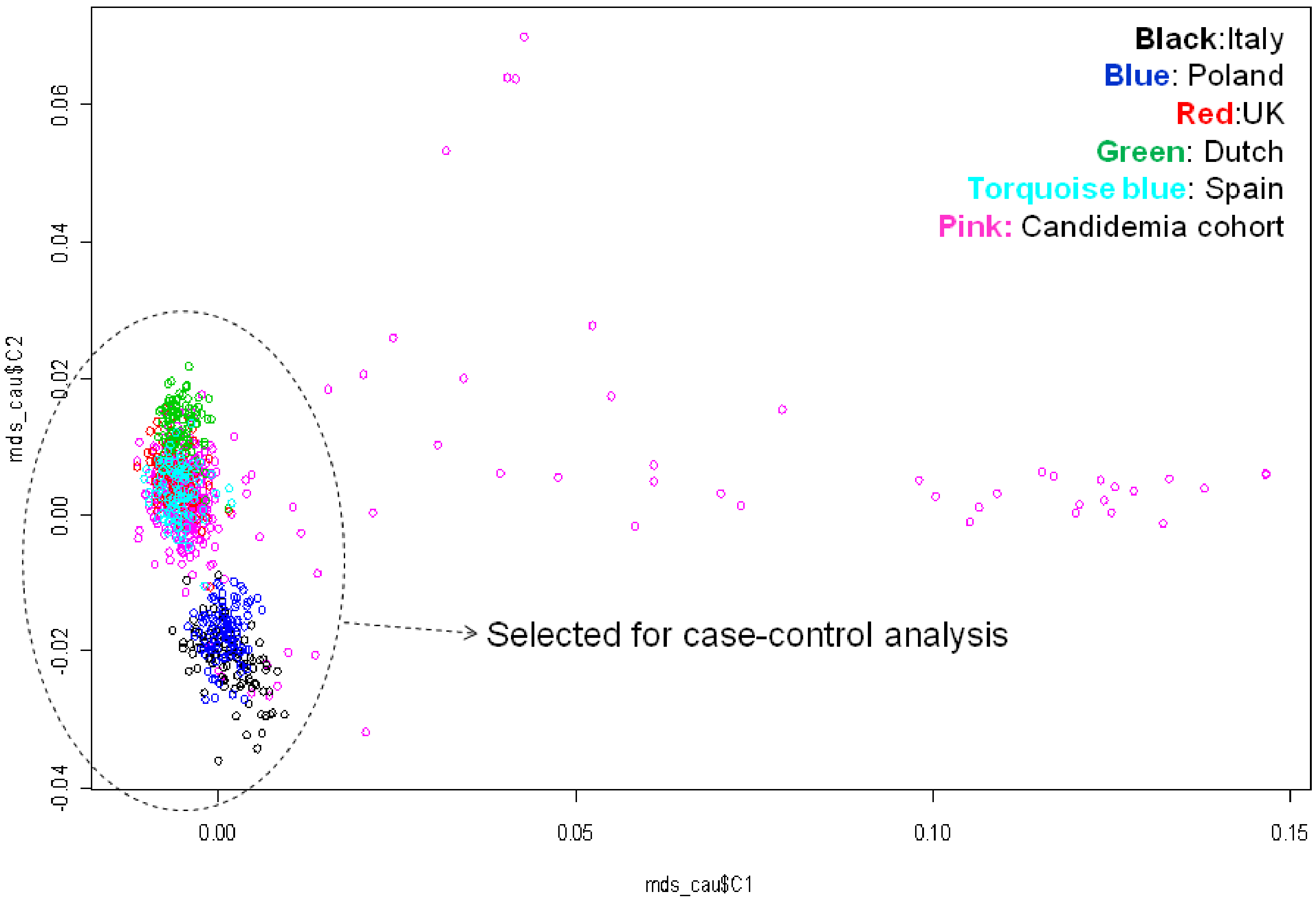
Supplementary Figure S6. Defective Th1 and Th17 development in DC/T-cell cocultures from CMC patients harboring a gain of function mutation in STAT1. Bars represent mean ± SEM.

Supplementary Figure S7 Multidimensional scaling (MDS) analysis: genetic background in Candidemia cohort



Supplementary Figure S7. Heatmap showing the differential expression for 91 genes as a response to c. albicans stimulation in cells from healthy controls. This compares the fold change genes expression levels of 91 genes in *in vitro* stimulated *vs.* unstimulated cells (*Candia Albicans*). The scale of this heatmap is given as log2 fold change with a range from -5 (blue) to +5 (red).

Supplementary Figure S8 Multidimensional scaling (MDS) analysis: genetic background in Candidemia cohort



Supplementary Figure S8. The multidimensional scaling (MDS) analysis (implemented in PLINK, MDS on the *N x N* matrix of genome-wide IBS pairwise distances) was performed on individuals from Candidemia cohort (pink colour) by including healthy control samples of known ethnicity as reference. Only samples which overlap with the known ethnic populations were included (shown within dashed lines) and outliers (n=40) were excluded from further case-control analysis.

Supplementary Table S1. Candida-response signature

ProfileSummary	UniqueID	Symbol	RefSeq
Down	LFNG___NM_002304.1	LFNG	NM_2304.1
Down	RGC32___NM_014059.1	RGC32	NM_14059.1
Up	STOM___NM_004099.4	STOM	NM_4099.4
Up	TNFSF13B___NM_006573.3	TNFSF13B	NM_6573.3
Up	FAM46A___NM_017633.1	FAM46A	NM_17633.1
Up	PRF1___NM_005041.3	PRF1	NM_5041.3
Up	GZMB___NM_004131.3	GZMB	NM_4131.3
Up	TMEM126B___NM_018480.2	TMEM126B	NM_18480.2
Up	CD40___NM_001250.3	CD40	NM_1250.3
Up	HAPLN3___NM_178232.2	HAPLN3	NM_178232.2
Up	LTA___NM_000595.2	LTA	NM_595.2
Up	IRF8___NM_002163.2	IRF8	NM_2163.2
Up	XRN1___NM_019001.2	XRN1	NM_19001.2
Up	KIAA1618___NM_020954.2	KIAA1618	NM_20954.2
Up	NCOA7___NM_181782.2	NCOA7	NM_181782.2
Up	PSMB9___NM_002800.4	PSMB9	NM_2800.4
Up	IFI27___NM_005532.3	IFI27	NM_5532.3
Up	SOCS1___NM_003745.1	SOCS1	NM_3745.1
Up	IRF1___NM_002198.1	IRF1	NM_2198.1
Up	DYNLT1___NM_006519.1	DYNLT1	NM_6519.1
Up	FAS___NM_152877.1	FAS	NM_152877.1
Up	CXCL9___NM_002416.1	CXCL9	NM_2416.1
Up	LINCR___NM_001080535.1	LINCR	NM_1080535.1
Up	IFNG___NM_000619.2	IFNG	NM_619.2
Up	CD38___NM_001775.2	CD38	NM_1775.2
Up	LGALS9___NM_009587.2	LGALS9	NM_9587.2
Up	APOL3___NM_030644.1	APOL3	NM_30644.1
Up	PSMB8___NM_148919.3	PSMB8	NM_148919.3
Up	LAMP3___NM_014398.2	LAMP3	NM_14398.2
Up	LBA1___XM_940627.1	LBA1	XM_940627.1
Up	LAG3___NM_002286.4	LAG3	NM_2286.4
Up	ZBP1___NM_030776.1	ZBP1	NM_30776.1
Up	TRIM5___NM_033034.1	TRIM5	NM_33034.1
Up	FLJ11286___NM_018381.1	FLJ11286	NM_18381.1
Up	PARP10___NM_032789.1	PARP10	NM_32789.1
Up	C20orf18___NM_006462.2	C20orf18	NM_6462.2
Up	IFITM2___NM_006435.1	IFITM2	NM_6435.1
Up	IFITM3___NM_021034.1	IFITM3	NM_21034.1
Up	CHMP5___NM_016410.2	CHMP5	NM_16410.2
Up	CHMP5___NM_016410.4	CHMP5	NM_16410.4
Up	TRAFD1___NM_006700.1	TRAFD1	NM_6700.1
Up	WARS___NM_004184.3	WARS	NM_4184.3
Up	FLJ11000___NM_018295.1	FLJ11000	NM_18295.1

Up	TRIM21___NM_003141.3	TRIM21	NM_3141.3
Up	DDX58___NM_014314.2	DDX58	NM_14314.2
Up	TNFSF10___NM_003810.2	TNFSF10	NM_3810.2
Up	CCL8___NM_005623.2	CCL8	NM_5623.2
Up	CXCL10___NM_001565.1	CXCL10	NM_1565.1
Up	PARP14___NM_017554.1	PARP14	NM_17554.1
Up	DNAPTP6___NM_015535.1	DNAPTP6	NM_15535.1
Up	LAP3___NM_015907.2	LAP3	NM_15907.2
Up	GBP2___NM_004120.3	GBP2	NM_4120.3
Up	FBXO6___NM_018438.4	FBXO6	NM_18438.4
Up	IFITM1___NM_003641.2	IFITM1	NM_3641.2
Up	STAT2___NM_005419.2	STAT2	NM_5419.2
Up	TAP1___NM_000593.5	TAP1	NM_593.5
Up	GBP4___NM_052941.2	GBP4	NM_52941.2
Up	GBP5___NM_052942.2	GBP5	NM_52942.2
Up	GBP1___NM_002053.1	GBP1	NM_2053.1
Up	UBE2L6___NM_004223.3	UBE2L6	NM_4223.3
Up	STAT1___NM_139266.1	STAT1	NM_139266.1
Up	STAT1___NM_007315.2	STAT1	NM_7315.2
Up	EPSTI1___NM_033255.2	EPSTI1	NM_33255.2
Up	ADAR___NM_015840.2	ADAR	NM_15840.2
Up	FTSJD2___NM_015050.2	FTSJD2	NM_15050.2
Up	LGP2___NM_024119.1	LGP2	NM_24119.1
Up	SP110___NM_004510.2	SP110	NM_4510.2
Up	PARP9___NM_031458.1	PARP9	NM_31458.1
Up	LY6E___NM_002346.1	LY6E	NM_2346.1
Up	IFI6___NM_022872.2	IFI6	NM_22872.2
Up	G1P3___NM_002038.2	G1P3	NM_2038.2
Up	IFIT5___NM_012420.1	IFIT5	NM_12420.1
Up	ISG20___NM_002201.4	ISG20	NM_2201.4
Up	RTP4___NM_022147.2	RTP4	NM_22147.2
Up	IFI35___NM_005533.2	IFI35	NM_5533.2
Up	TRIM22___NM_006074.2	TRIM22	NM_6074.2
Up	FLJ20035___NM_017631.3	FLJ20035	NM_17631.3
Up	PARP12___NM_022750.2	PARP12	NM_22750.2
Up	SAMD9L___NM_152703.2	SAMD9L	NM_152703.2
Up	XAF1___NM_199139.1	XAF1	NM_199139.1
Up	PHF11___NM_001040443.1	PHF11	NM_1040443.1
Up	PHF11___NM_016119.1	PHF11	NM_16119.1
Up	HERC6___NM_001013005.1	HERC6	NM_1013005.1
Up	IFI44L___NM_006820.1	IFI44L	NM_6820.1
Up	IFI44___NM_006417.2	IFI44	NM_6417.2
Up	EIF2AK2___NM_002759.1	EIF2AK2	NM_2759.1
Up	IFIT3___NM_001031683.1	IFIT3	NM_1031683.1
Up	IRF7___NM_004029.2	IRF7	NM_4029.2
Up	OAS3___NM_006187.2	OAS3	NM_6187.2

Up	IFIH1___NM_022168.2	IFIH1	NM_22168.2
Up	IRF7___NM_004030.1	IRF7	NM_4030.1
Up	PRIC285___NM_033405.2	PRIC285	NM_33405.2
Up	MX1___NM_002462.2	MX1	NM_2462.2
Up	RSAD2___NM_080657.3	RSAD2	NM_80657.3
Up	IFIT3___NM_001549.2	IFIT3	NM_1549.2
Up	OAS1___NM_001032409.1	OAS1	NM_1032409.1
Up	IFIT2___NM_001547.3	IFIT2	NM_1547.3
Up	ISG15___NM_005101.1	ISG15	NM_5101.1
Up	OAS2___NM_016817.2	OAS2	NM_16817.2
Up	HERC5___NM_016323.1	HERC5	NM_16323.1
Up	OAS2___NM_002535.2	OAS2	NM_2535.2

Supplementary Table S2 Enrichment analysis for the 101-transcript *Candida*-response signature

#	MetaGO_GeneGO_Process_Networks	Enrichment p-value
1	Interferon signaling	3.82E-35
2	Innate immune response to RNA viral infection	1.25E-12
3	Inflammasome	2.50E-06
4	Jak-STAT Pathway	1.52E-05
5	IFN-gamma signaling	2.39E-05
6	NK cell cytotoxicity	3.00E-04
7	Death Domain receptors & caspases in apoptosis	2.87E-03
8	Negative regulation of cell proliferation	3.21E-03
9	Chemotaxis	4.56E-03
10	Antigen presentation	4.62E-03
11	IL-10 anti-inflammatory response	4.98E-03
12	IL-12,15,18 signaling	1.15E-02
13	Leucocyte chemotaxis	2.33E-02
14	T helper cell differentiation	2.57E-02
15	Lymphocyte proliferation	2.60E-02
16	Apoptotic nucleus	3.76E-02
17	Glycoconjugates	4.22E-02
18	Proteolysis in cell cycle and apoptosis	7.76E-02

Supplementary Table S3 shows the number of tag-SNPs tested in each locus for case-control and cytokine correlation analyses

Case-control analysis

Number of cases	Number of controls	Locus	Tag-SNPs	Top SNP	P_logistic	Bonferroni threshold-P (0.05/number of SNPs)
217	12,068	CCL8-CCL13	40	1kg_17_29697448	0.00069*$	0.0012
217	12,068	STAT1	77	imm_2_191584314	0.0042$	0.00064
217	12,068	SP110-140	75	imm_2_230863948	0.012	0.00066
217	12,068	PSMB8-9	38	rs3198005	0.019	0.0013

Cytokine levels vs. SNP genotypes

Number of controls	Locus	Tag-SNPs	Top SNP	Wilcoxon-Rank sum test P	Bonferroni threshold-P (0.05/number of SNPs)
74	STAT1	77	rs2280234 vs TNF-alpha levels	0.001$	0.00064
74	STAT1	77	rs4511150 vs IL-6 levels	0.00026*$	0.00064
74	IRF1	35	rs2548997 vs TNF-alpha levels	0.0028$	0.0014
74	IRF1	35	rs1124211 vs IL-10 levels	0.0024$	0.0014

[*] Clear the Bonferroni correction for multiple testing if we correct for number of SNPs tested in each locus.

[$] Clear the Bonferroni correction for multiple testing if we correct for number of genes tested (0.05/11genes; P < 0.0045).

1kg_17_29697448 indicates the location of SNP on chromosome 17 at position 29697448 (hg18)

Supplementary Table S4 GO term enrichment of 27 differentially expressed genes for *Candida albicans* response in patients vs. controls.

GO Term	Genes	Gene Count	Frequency	PValue	Bonferroni
Antiviral defense	IFIH1, ISG15, IRF7, IFNG, RSAD2, MX1, EIF2AK2, TRIM22, STAT2	9	33.3	1.09E-14	7.62E-13
GO:0009615~response to virus	IFIH1, ISG15, IRF7, IFNG, RSAD2, IFI44, MX1, EIF2AK2, TRIM22, STAT2	10	37.0	1.59E-14	5.77E-12
GO:0006955~immune response	IFIH1, TNFSF10, IFNG, OAS3, RSAD2, OAS1, OAS2, TRIM22, DHX58	9	33.3	3.21E-06	0.00115691
GO:0003723~RNA binding	IFIH1, OAS3, OAS1, PRIC285, OAS2, EIF2AK2, DHX58, ZBP1, ADAR	9	33.3	5.85E-06	3.86E-04
IPR018952:2'-5'-oligoadenylate synthetase 1, domain 2/C-terminal	OAS3, OAS1, OAS2	3	11.1	1.19E-05	8.34E-04
IPR006117:2-5-oligoadenylate synthetase, conserved site	OAS3, OAS1, OAS2	3	11.1	1.19E-05	8.34E-04
IPR006116:2-5-oligoadenylate synthetase, ubiquitin-like region	OAS3, OAS1, OAS2	3	11.1	1.98E-05	0.00138778
host-virus interaction	IFIH1, ISG15, IRF7, EIF2AK2, TRIM22, STAT2	6	22.2	3.51E-05	0.002456665
rna-binding	IFIH1, OAS3, OAS1, OAS2, EIF2AK2, DHX58, ADAR	7	25.9	6.79E-05	0.004742343
hsa04622:RIG-I-like receptor signaling pathway	IFIH1, ISG15, IRF7, DHX58	4	14.8	1.39E-04	0.002221087
polymorphism	IFIH1, RTP4, OAS3, RSAD2, OAS1, FAM46A, SAMD9L, ISG15, IFNG, XAF1, MX1, DHX58, ZBP1, HERC6, HERC5, IFI44, TRIM22, STAT2, IFIT2, TNFSF10, PARP12, IRF7, PRIC285, EIF2AK2, ADAR	25	92.6	2.80E-04	0.019428562

Supplementary Table S4 GO term enrichment of 27 differentially expressed genes for *Candida albicans* response in patients vs. controls. Shown are significantly enriched GO terms ordered for p-value