**Table S1. Immune and/or Host Defense Functions of single nucleotide polymorphisms associated with depression based on meta-analyses of genome-wide association (GWAS) studies**

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| **Liu et al. Meta-analysis of genome-wide association data of bipolar disorder and major depressive disorder. *Mol Psychiatry* 2011; 16: 2-6 [(a)]** | | |
| **Gene ID** | **Gene Name** | **Immune Function of Gene** |
| *CACNA1C* | calcium channel, voltage-dependent, L type, alpha 1C subunit | See article text for a discussion of immune and host defense functions of CACNA1C |
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| **McMahon et al. Meta-analysis of genome-wide association data identifies a risk locus for major mood disorders on 3p21.1. *Nat Genetics* 2010; 4: 128-31 [(a)]** | | |
| **Gene ID** | **Gene Name** | **Immune Function of Gene** |
| *PBRM1* | polybromo 1 aka BRG1-associated factor 180 (BAF180) | PBRM1 codes for a protein component (BRG1-associated factor 180 [BAF 180]) of the SWI/SNF chromatin remodeling complex, which is crucial for activation and proliferation of T cells in response to antigen stimulation,[1] and which regulates induction and temporal sequencing of proinflammatory cytokines in response to an immune challenge,[2] as well as antigen receptor assembly (i.e. VDJ recombination) in B cell precursors;[3] following bacterial TLR stimulation, the BRG1/BRM subunits of the SWI/SNF complex are consistently required for the activation of secondary response genes and primary response genes induced with delayed kinetics within macrophages;[4] BRG1 and other BAF elements within the SWI/SNF complex has been identified as activators of transcription within the nuclear interactome for the HIV-1 virulence factor "Trans-Activator of Transcription" (Tat),[5-7] and the SWI/SNF complex more generally regulates retroviral gene integration into, and expression in, infected host cells,[8-11] and contributes to viral replication;[12] PBRM1 (BAF 180) is required for expression of the IFITM1 gene in response to interferon signaling,[13] and IFITM1 has been shown to restrict entry of a range of viruses, including HIV and SARS, into host cells,[14,15] |

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| | | consistent with fact that BAF complex within SWI/SNF is essential for IFN-target-gene dependent cellular antiviral activities;[16] BRG1 is essential for IFN-gamma induction of CIITA, the master regulator of major histocompatibility complex (MHC) class II expression,[17] and a switch from hBrm to BRG1 regulation of expression is an indicator of genes that are responsive to IFN-gamma signaling;[18] BRG1 contributes to MHC I immunity by upregulating enhancer A;[19] knock-down of BRG-1 activity blocks human papillomavirus E-2 driven transcriptional activation and DNA replication;[20] mice that constitutively express the SWI/SNF complex are highly susceptible to experimentally induced autoimmune encephalomyelitis;[1] |
| *GNL3* | guanine nucleotide binding protein-like 3 | GNL3 codes for a GTPase nucleostemin that is involved in stem cell proliferation and that upregulates the transcription factor CDX2,[21] which is a homeodomain transcription factor specific to the intestinal epithelium crucial for pathogenic *E. coli* to induce the di/tripeptide transporter PepT1 in gut and also to activate NFkB and MAPK leading to production of IL-8.[22] The chemokine CCL25 which plays an important role in recruiting lymphocytes to the intestinal epithelium is enhanced by CDX2, which regulates CDDL25 transcription.[23] CCL25, in turn, is believed to play a role in the development of T cells,[24] and is chemotactic for thymocytes, macrophages and dendritic cells.[25,26] |
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| **Shyn et al. Novel loci for major depression identified by genome-wide association study of Sequenced Treatment Alternatives to Relieve Depression and meta-analysis of three studies. *Mol Psychiatry* 2011; 16: 202-15 [(b)]** | | |
| **Gene ID** | **Gene Name** | **Immune Function of Gene** |
| *ATP6V1B2* | ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B2 | ATP6V1B2 is a component of vacuolar ATPase (V-ATPase) that is involved in cytoskeletal functioning necessary for T cell movement and ability to form functional immunological synapses with antigen presenting cells;[27] V-ATPase is important for host defense against *M. tuberculosis* by contributing to phagosomal maturation/acidification;[28] via secretion of SidK *L. pneumophila* (cause of Legionnaires' disease) inhibits V-ATPase allowing for vacuolar survival and enhanced virulence;[29] V-ATPase contributes to early intracellular survival strategy of *F. Tularensis*;[30] V-ATPase is a target for *P. aeruginosa* produced pyocyanin, which kills competing microbes and mammalian cells during pseudomonal infection;[31] by contributing to endosomal acidification V-ATPases promote influenza A virus infection,[32] conversely V-ATPase inhibition has been shown to be protective against highly virulent |

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| | | influenza strains;[33] V-ATPase inhibition inhibits rhinovirus infection of airway epithelial cells via blocking viral RNA entry into endosomes and by reducing ICAM-1 expression in epithelial cells.[34] during pregnancy and in tumorgenesis, a2NTD, which is cleaved from the a2 isoform of V-ATPase upregulates pro- and anti-inflammatory mediators including IL-1b and IL-10;[35-38] V-ATPase promotes fetal implantation and survival by modulating cytokine network at implantation site and attenuating maternal immune response against fetal trophoblast cells;[38] |
| *SP4* | Specificity protein 4 transcription factor | SP4 activates the HIV-1 LTR promoter,[39] possibly enhancing HIV-1 Tat-mediated transactivation of the viral promoter. Consistent with these effects an intergenic SNP in *SP4* (rs6951646) may confer vulnerability for mother-to-child transmission of HIV;[40] Curcumin shown to inhibit NFκB signaling in part via downregulation of SP4;[41] COX-2 inhibitors inhibit VEGF gene expression via activation of proteasome-dependent degradation of SP4;[42] |
| *GRM7* | glutamate receptor, metabotropic 7 | Mice with targeted deletion of mGluR7 show enhanced sensitivity to glucocorticoid inhibitory feedback on the HPA axis,[43] which would be expected to reduce inflammatory signaling. This raises the possibility that mGluR7 signaling may support proinflammatory activity |
| *AK294384* | similar to Muskelin 1 (MKLN1) | Muskelin gene expression is reduced in neutrophils from patients with generalized aggressive peridontitis, a proinflammatory condition characterized by increased neutrophil IL-1b gene expression;[44] muskelin appears to be an isoform-specific anchoring protein for the prostaglandin EP3 receptor[45] |
| *LY86* | lymphocyte antigen 86 aka MD-1 | LY86 codes for myeloid differentiation protein MD-1, which has been recently shown to bind LPS;[46] MD-1-null mice show impairment in LPS-induced B-cell proliferation, antibody production, and B7.2/CD86 up-regulation;[47] inhibition of MD-1 increases expression of IL-4, IL-10 and TGF-beta and decreases IL-2, IFN-gamma and TNF-alpha expression with resultant improvement in allograft and fetal graft survival;[48-50] dorsal root ganglion neurons express the unusual combination of CD-14, TLR4, and MD-1. Blocking antibodies against TLR4 and MD-1 prevents induction of nociceptin/orphanin FQ (N/OFQ), an opioid-related peptide that is markedly up-regulated in sensory neurons in vivo following peripheral inflammation that plays a key role in pain physiology;[51] blockade of MD1 functional activity in dendritic results in elevated Treg induction in response to allogeneic stimulation (in vivo or in vitro) in the presence of LPS;[52] via linkage to CD14, MD-1 comprises a "danger receptor complex," and activation of this complex regulates dendritic cell surface expression of CD80/CD86, which signal T cells.[53] |

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| *KSP37* aka *FGFBP2* | killer-specific secretory protein of 37 kDa aka fibroblast growth factor binding protein 2 | Within leukocytes, Ksp37 expression is limited to Th1-type CD4(+) T cells, effector CD8(+) T cells, gamma-delta T cells, and CD16(+) NK cells. Most of these Ksp37-expressing cells coexpress perforin, suggesting that Ksp37 is selectively and commonly expressed in the lymphocytes that have cytotoxic potential.[54] |
| *IGSF9B* | immunoglobulin superfamily, member 9B | No functional data available for IGSF9B, however likely immune and/or host defense relevance is suggested by the fact that members of the immunoglobulin superfamily include cell surface antigen receptors, co-receptors and co-stimulatory molecules of the immune system, molecules involved in antigen presentation to lymphocytes, cell adhesion molecules, certain cytokine receptors and intracellular muscle proteins |
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| **Muglia et al. Genome-wide association study of recurrent major depressive disorder in two European case-control cohorts. *Mol Psychiatry* 2010; 15: 589-601 [(b)]** | | |
| **Gene ID** | **Gene Name** | **Immune Function of Gene** |
| *SMG7* | smg-7 homolog, nonsense mediated mRNA decay factor | No specific immune and/or host defense functions reported for SMG7; however SMG7, UPF1, SMG5 and SMG6 comprise the nonsense-mediated mRNA decay (NMD) pathway, a surveillance mechanism for eliminating mRNAs containing premature termination codons that is important in degrading retroviral DNA in eukaryotic cells;[55] Depletion of UPF1 by siRNA dramatically reduces steady-state HIV-1 RNA and pr55(Gag), and, conversely, overexpression of UPF1 leads to significant up-regulation of HIV-1 expression at the RNA and protein synthesis levels;[56] |
| *NFKB1* aka *NFκBp50* | nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 | A database too extensive for full inclusion in this table demonstrates that the transcription factor NF-κB has multiple immune effects relevant to innate and adaptive immunity, host defense and the development of inflammatory/autoimmune diseases (including cancer); with p50 central to innate immunity via the classical NF-κB pathway;[57-66] Examples of p50 effects relevant to host defense include (but are not limited to):<br>• Many bacterial pathogens (e.g. enteropathic *E. coli*) utilize a type III secretion system (T3SS) to inject effector proteins into host cells during infection that enhance virulence by degrading the p50, p65 and cRel subunits of NF-κB;[67] |

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| | | • *M. tuberculosis* promotes its own intracellular survival by inhibiting Th1 type immune responses via the ability of the bacterial protein PPE18 to block nuclear translocation of the p50 and p65 subunits of NF-κB as a result of PPE18 inducing SOCS3 masking the phosphorylation site of IκBα;[68]<br>• Varicella-zoster virus enhances its replication in melanocytic skin cells by inhibiting I-CAM producing in the center of skin lesions, in part by inhibiting TNF-alpha induced translocation of p50 to the nucleus;[69]<br>• Upon rhinovirus exposure, beta-2 adrenergic receptor agonists reduces rhinovirus titers and RNA, cytokine concentrations, and susceptibility to rhinovirus infection inhibited the activation of nuclear factor kappa-B (NF-κB) proteins, including p50 and p65, in the nucleus while increasing cytosolic concentrations of the inhibitory kappa B-alpha;[70]<br>• Apoptosis is significantly reduced in the CNS of p50-null mice following reovirus infection, but massively increased in concert with uncontrolled reovirus replication in the heart, an effect associated with marked reductions in reovirus-induced IFN-beta mRNA in the heart and partially reversed by IFN-beta administration;[71]<br>• Downregulation of NFKB1 expression during Dengue infection in children is likely protective given that increased NFKB1 expression correlates with increased incidence of hemorrhagic events and with a trend toward increases in multiple other life-threatening complications;[72]<br>• Increased NF-κB production in response to *Y. Pestis* reduces infectious severity and mortality in animal models;[73]<br>• In the context of a number of infection by a number of viruses (e.g. HSV-1, HCMV), p50 appears to have conflicting effects on viral replication and spread, reducing these phenomena by stimulating apoptosis of infected cells while at the same time encouraging viral spread via herpes manipulation of the transcription factor for its own replicative purposes;[74,75]<br>• NF-κB protects against Toxoplasma gondii encephalitis via stimulation of CD8+ T cells and IFN-gamma production;[76]<br>• Polymorphisms in *NFKB1* have been associated with acute respiratory distress syndrome,[77,78] autoimmune and inflammatory diseases in Asian populations by meta- |

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| | | analysis,[79] and with both incidence and severity of inflammatory bowel disease in other populations in individual studies,[80,81] and persistent viremia in HCV infection;[82]<br>• NF-kappaB p50 subunit is protective during intestinal Entamoeba histolytica infection of the gut in animal models;[83] |
| *LOC654346* | aka LGALS9C lectin, galactoside-binding, soluble, 9C | LOC654346 codes for a protein identical, or highly similar, to galectin 9, which has widespread, highly complex, and partially paradoxical immune effects that in general appear to be anti-inflammatory via suppression of T1 and Th17 T cell immunity and enhancement of Treg;[84-86] However, galectin-9 y binding to T cell Ig mucin-3 (Tim3) expressed on different cells, galectin-9 activates innate immune dendritic cells via a specific carbohydrate recognition domain (CRD), suggesting that it may enhance antigen presentation;[87,88] via interaction with Tim3 expressed on T(H)1 cells, galectin-9, which is expressed by *M. tuberculosis*-infected macrophages, restricts intracellular bacterial growth. Tim3-galectin-9 interaction accomplishes this by leading to macrophage activation with resultant bactericidal activity induced by caspase-1-dependent IL-1β secretion;[89] galectin-9 has been shown to be an immunomodulator in the context of *L. major* infection. Galectin 9 recognizes *L. major* by binding to the L. major-specific polygalactosyl epitope and promotes interaction between L. major and macrophages;[90] galectin-9 attenuates CD8(+) T cell immunity to herpes simplex virus infection via direct inhibition of TIM3(+) CD8(+) T cells and indirectly by enhancing Foxp3(+) Treg activity;[91] galectin-9 is an eosinophil chemoattractant produced by activated T cells,[92] but also demonstrates anti-allergic effects by blocking IgE-antigen complex formation,[93] as well as an ability to inhibit contact hypersensitivity and psoriatic reactions;[94] by attenuating Th1 responses galectin-9 inhibits autoimmune diabetes in NOD mice,[95] and ameliorates arthritis in animal models via regulation of Fc gamma receptor expression on macrophages,[96] as well as by suppressing the generation of Th17 cells and inducing Treg;[85] galectin-9 promotes NK cell-mediated anti-tumor activity by expanding macrophages with a unique plasmacytoid cell-like phenotype (PDCA-1 and B220);[97] |
| *NMNAT2* | nicotinamide nucleotide adenylyltransferase 2 | No specific immune and/or host defense functions reported. |
| *LAMC2* | laminin, gamma 2 | Gamma 2 laminin chain production is stimulated by TNF-alpha;[98] In response to wounding, laminin gamma2 chains are processed to smaller sizes and function to promote epithelial sheet migration over the wound bed;[99,100] Pathogens that avidly bind laminin as a means of |

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| | | entering host cells thereby initiating infection include *Aspergillus fumigates, Heliobacter pylori, Histoplasma capsulatum, Mycobacterium leprae, Paracoccidioides brasilienses*, rotavirus, *Streptococcus pyogenes, Treponema pallidum, Trypanosoma cruzi*;[101] During inflammatory processes the enzyme neutrophil elastase digests the gamma 2 laminin chain into fragments that are chemotactic for neutrophils.[102] |
| *UGT2A2* | uridine 5'-diphospho glucuronosyltransferase (UDP) 2 family, polypeptide A2 | Expressed primarily in nasal epithelium where it glucuronidates an array of inhaled substances.[103] No known immune/host defense effects. |
| *UGT2A1* | UDP glucuronosyltransferase 2 family, polypeptide A1, complex locus | No specific immune and/or host defense functions reported for *UGT1A1*; however, because UGT2A1 enhances bilirubin elimination by catalyzing its conjugation glucuronic acid,[104] an anti-inflammatory effect might be expected, given that increased levels of bilirubin are associated with increased levels of proinflammatory cytokines;[105] in animal models, increased bilirubin associated with impaired PMN phagocytosis of S. Aureus, suggesting that UGT21 activity may enhance host defense against bacterial pathogens, as a result of reducing bilirubin levels;[106] |
| *ATG7* | autophagy related 7 homolog | The autophagy degradation pathway is essential for eliminating intracellular pathogens, presenting endogenous antigens to immune cells and regulating T and B lymphocyte survival, proliferation and function[107];[108] knocking down ATG7 inhibits hepatitis C virus (HCV) growth via increased activity in interferon (IFN)-alpha and IFN-alpha-inducible protein 27 signaling pathways, as well as by increased caspase activation, polymerase cleavage and apoptosis of infected cells;[109] ATG7 is essential for production of myeloid and lymphoid progenitor cells;[110] |
| *CUGBP1* | CUG triplet repeat, RNA binding protein 1 | CUGBP1 is a downstream effector of IFN-beta signaling in primary macrophages that is thought to play a pivotal role in innate immune responses that control acute HIV/SIV replication in the brain;[111] CUGBP1 participates in acute phase response in liver following LPS exposure by inducing the low molecular weight CCAAT/Enhancer binding protein (C/EBP) beta isoform, liver-enriched transcriptional inhibitory protein (LIP);[112] CUGBP1 impairs stabilization of TNF-alpha mRNA transcripts;[113] |
| *NFE2L3* | nuclear factor (erythroid-derived 2)-like 3 | NFE2L3 modulates T cell development, based on finding that knockdown of the gene significantly increases development of T cell lymphoblastic lymphoma;[114] NFE2L3 one of 20 genes upregulated in human uterine microvascular endothelial cells following administration |

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| | | of IFN-gamma, other IFN-gamma induced genes include chemokines and antiviral factors;[115] NFE2L3 involved in the control of gene expression and inflammation during cutaneous wound repair;[116] |
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| **Lewis et al. Genome-wide association study of major recurrent depression in the U.K. population. *Am J Psychiatry* 2010; 167: 949-57 [(b)]** | | |
| **Gene ID** | **Gene Name** | **Immune Function of Gene** |
| *LOC647167* | encodes a protein similar to eukaryotic translation elongation factor 1 alpha 2 (*EF1-alpha*) | EF1-alpha binds and interacts with the HIV-1 Gag polyprotein, which play key functions at almost all stages of the viral life cycle. This interaction impairs *in vitro* viral RNA, a result consistent with a previously proposed model in which inhibition of translation by the accumulation of Gag serves to enhance viral spread by releasing viral RNA from polysomes, permitting the RNA to be packaged into nascent virions;[117] severe acute respiratory syndrome coronavirus (SARS-CoV) pathogenicity arises in part from the interaction off the viral C terminus (amino acids 251 to 422) of the N protein with human EF1-alpha which induces aggregation of EF1alpha, inhibiting protein translation and cytokinesis by blocking F-actin bundling;[118] EF1-alpha contributes to apoptosis during viral infection, and in response to LPS and IL-1-beta, via interaction with interferon-induced protein with tetratricopeptide repeats-1(IFIT1), which is rapidly synthesized in response to viral infection, functions as an inhibitor of translation by binding to the eukaryotic initiation factor-3, and consequently enhances resistance activity against viral invasion to cells;[119] TNF-alpha down-regulates gene expression of EF1-alpha in endothelial cells;[120] |
| *VCAN* | versican | In context of cervical cancer, versican reduces number of infiltrating CD8+ T cells;[121] versican important for hyaluronan-dependent binding of moncytes to the extracellular matrix of lunch fibroblasts stimulated by the viral mimetic agent, polyinosine-polycytidylic acid. These findings implicate versican in ability of viral infections to exacerbate asthma and other lung disorders;[122] Stimulation of mononuclear cells with GM-CSF increases the expression of versican mRNA as well as cytokine induction in these cells;[123] |
| *NLGN1* | neuroligin 1 | NLGN1 reported to modulate immune functioning in CNS following trauma via interactions with ERK1/2 and neurexin-1-beta;[124] |

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| *LOC728275* | | Functionality of gene not established |
| *BBOX1* | butyrobetaine (gamma), 2-oxoglutarate dioxygenase (gamma-butyrobetaine hydroxylase) 1 | BBOX is one of less than 1% of genes in cultured macrophages which demonstrates a change in gene expression in response to diesel exhaust particles (BBOX1 is downregulated);[125] because gamma butyrobetaine hydroxylase catalyzes the formation of L-carnitine from gamma-butyrobetaine, the last step in the L-carnitine biosynthetic pathway, one might predict host defense relevance given evidence that L-carnitine has stimulatory effects on a number of immune functions including neutrophil activity, delayed-type hypersensitivit and the conycentrations of immunoglobulins A and G (but not IgM);[126] deficiency in L-carnitine activity/availability has been repeatedly associated with increased risk of encephalopathy in response to viral infection;[127-129] L-carnitine shown to have anti-inflammatory properties in obese diabetic patients;[130] |
| *ATF3* | activating transcription factor 3 | ATF3 functions as a "hub" of the cellular adaptive-response network that modulates inflammatory responses, cellular division and apoptosis;[131,132] NF-kappaB, C/EBPdelta and ATF3 have been shown to form a regulatory circuit that discriminates between transient and persistent Toll-like receptor 4-induced signals, which is hypothesized to be a mechanism that enables the innate immune system to detect the duration of infection and to respond appropriately;[133] ATF3 overexpression stimulates apoptotic cell death following Coxsackie virus B3 (CVB3) infection and augments CVB3 infection-induced eIF2alpha phosphorylation. However, ATF3 overexpression does not affect viral protein production, but rather promotes virus progeny release;[134] via interaction with a cis-regulatory site on the IFN-gamma gene, ATF3 reduces NK cell activity against murine cytomegalovirus (MCMV), with a resultant increase in viral pathology. Correspondingly, ATF3null mice show exhibit decreased hepatic viral load and reduced liver histopathology upon challenge with MCMV;[135] ATF3 is one of a small set of genes upregulated by adenovirus infection prior to commencement of viral gene expression;[136,137] ATF3 is required for the interferon-induced serine/threonine protein kinase (PKR) to induce apoptosis of virally infected cells;[138] ATF3 is also functionally important in mediating the pro-apoptotic effects of the proinflammatory p38 MAPK signaling pathway;[139] ATF3 production is stimulated by IL-12, IL-18 and IFN-alpha. Conflicting data suggest ATF3 may enhance or repress the development of a Th1 cytokine profile in CD+ T cells;[140,141] Blocking ATF3 reduces IL-6 production in response to TLR stimulation;[142].ATF3 is induced by, and induces TGF-beta and is essential for activation of TGF-beta target genes;[143] ATF3 induces STAT1;[144] ATF3 enhances inflammatory responses to grafted islet cells promoting rejection;[145] ATF3 is required for mast cell maturation and function;[132] with heat shock transcription factor-1, ATF3 is necessary for ability of febrile temperatures to suppress IL-6 |

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| | | production;[146] ATF3acts as a transcriptional repressor of TLR4 signaling,[147] leading to transcriptional repression of TNF-alpha production in macrophages;[148] LPS-induced expression of matrix metalloproteinases in human monocytes is suppressed by IFN-gamma via superinduction of ATF-3;[149] in a mouse model of human asthma, ATF3-deficiency significantly increases airway hyperresponsiveness, pulmonary eosinophilia, and enhances chemokine and Th2 cytokine responses in lung tissue and in lung-derived CD4(+) lymphocytes;[150] ATF is increased by COX-2 activity;[151] |
| *C14orf49* | aka NET53 and nesprin-3 | No specific immune and/or host defense functions reported |
| *LOC440742* | hypothetical LOC440742 | Functionality of gene not established |
| *LOC338805* | LOC338805 | Functionality of gene not established |
| *ACYP2* | acylphosphatase 2, muscle type | No specific immune and/or host defense functions reported |
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| **Terracciono et al. Genome-wide association scan of trait depression. *Biol Psychiatry* 2010; 68: 811-17 [(b)]** | | |
| **Gene ID** | **Gene Name** | **Immune Function of Gene** |
| *RORA* | retinoic acid receptor-related orphan receptor alpha | RORA, in combination with ROR-gamma, is essential for differentiation of naïve T cells in to Th17 phenotype, and RORA blockade prevents Th17 differentiation;[152-154] knocking down RORA receptor activity in mice is associated with increased T cell IFN-gamma production following T-cell receptor stimulation, with increased TNF-alpha and IL-6 production upon activation of macrophages or mast cells, with increased IgG antibodies following immunization with a T-Cell dependent antigen and with increased CD8+ T cell cytotoxic activity against *L. monocytogenes* infected cells;[155] RORA one of 22 genes upregulated by hepatitis B virus (HBV) infection and downregulated by treatment of HBV-infected cells with lamivudine;[156] RORA has anti-inflammatory effect in experimental autoimmune uveoretinitis;[157,158] allelic differences in RORA are associated with circulating levels of CRP in a meta-analysis of 15 GWAS studies;[159] RORA gene expression profoundly inhibited by LPS |

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| | | in humans in vivo;[160] in resting astrocytes RORA essential to maintain basal IL-6 levels, however following inflammatory stimulation, RORA suppresses astrocytic IL-6 production;[161] stable transfection experiments have demonstrated that overexpression of RORA specifically increases endogenous fibrinogen-beta mRNA levels, with immunoprecipitation studies showing that the human fibrinogen-beta gene is a direct target for RORA;[162] acting via inhibition of NFκB, RORA suppresses TNF-alpha-induced expression of vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1) in human umbilical vein endothelial cells;[163] |
| *SLFN12L* | Schlafen family member 12-like | No immune and/or host defense functions reported specifically for *SLFN12*; however, mice with a functional impairment in a related Schlafen family member gene (*SLFN2*) show enhanced susceptibility to bacterial and viral infection and diminished numbers of T cells and inflammatory monocytes that fail to proliferate after infection;[164] Genes from the Schlafen family are differentially expressed during, and profoundly influence, thymocyte development;[165] Schlafen family genes also show a strong association with circulating NK cell levels;[166] |
| *CDH18* | Cadherin 18, type 2 | No immune and/or host defense functions reported specifically for *CHD18;* however extensive data link other cadherins (especially E-cadherin [CDH1]) to host defense. For example, multiple pathogens (e.g. *L monocytogenes, C. botulinum H. pylori, anthrax, Enterotoxigenic Bacteroides, C. rodentium*) secrete factors that enhance virulence by interacting with E-cahedrin to disrupt cellular junctions thus promoting entry of pathogen or toxins into host tissues;[167-173] cleavage of E-cadherin by calpains generated in response to TLR2 mediated Ca(2+) fluxes promote the transepithelial migration of PMNs within the lung during P aeruginosa infection;[174] mechanisms that regulate the retention of tissue-resident memory T cells include transforming growth factor-β (TGF-β)-mediated induction of the E-cadherin receptor CD103 and downregulation of the chemokine receptor CCR7. These pathways enhance protection in internal organs, such as the nervous system, and in the barrier tissues--the mucosa and skin. Memory T cells that reside at these surfaces provide a first line of defense against subsequent infection, and defining the factors that regulate their development is critical to understanding organ-based immunity.[175] |
| *EIF3F* | eukaryotic translation initiation factor 3, subunit F | EIF3F is a protein synthesis initiation factor that potently inhibits HIV-1 replication;[176,177] EIF3F is a component of the nuclear interactome of the HIV-1 encoded regulatory protein Tat, which is essential for HIV-1 replication and primarily orchestrates HIV-1 provirus transcriptional regulation;[5] EIF3F is required for initiation of HCV RNA translation in host cells and its |

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| | | induction is essential for the ability of iron to increase HCV expression;[178-181] In cells infected with poliovirus, cellular mRNA fails to bind to ribosomes, and synthesis of the majority of cellular proteins ceases, a pathological process dependent upon viral 2Apro cleavage of EIF3F;[182,183] EIF3F-induced deubiquitination essential for activation of Notch signaling pathway.[184] The Notch pathway has numerous effects relevant to inflammation/host-pathogen defense,[185-187] including 1) activation of IFN-gamma production in CD4+ T cells and IFN-alpha production in dendritic cells in response to HSV-2 infection;[188]; 2) promotion of Kaposi's sarcoma-associated herpesvirus latency (with increased cancer risk) via induction of RBP-Jκ, the master regulator of the Notch signaling pathway;[189]; 3) promotion of herpes virus transition from latency to activation status;[190] 3) promotion of Th17 activity and protective granuloma formation in response to *M. tuberculosis* infection via TLR9 signaling;[191] 4) modulation of either a pathogen promoting Th2 or disease-controlling Th1 CD4+ T cell response *L. major* infection;[192] 5) promotion of more competent, less pathogenic antiviral response to RSV infection;[193] 6) cooptation by gamma herpesviruses to establish lifelong infection;[194] 7) efficient induction of cytotoxic CD+ T cells and increased ability of dendritic cells to induce cytotoxic CD8 cells;[195] 8) regulation of IL-10 IFN-gamma-secreting CD4(+) T cells that suppress cytotoxic CD8+ cells;[196] 9) induction of Th2 type T cell responses at the expense of Th1 responses, in part by regulating the transcription factors T-bet and GATA-3;[197] 10) activation of microglia to produce proinflammatory cytokines in response to cerebral ischemia,[198] 11) induction of inflammatory mediators and apoptosis in context of renal ischemia/reperfusion injury;[199] 12) retention and survival of T cells in areas of arterial vessel wall inflammation;[200] |
| *FAM155A* | FAM155A family with sequence similarity 155, member A | Functionality of gene not established |
| *CDH13* | Cadherin 13 (heart) | SNP variants within CDH13 have been shown to interact with PTPN22 1858T to increase risk of developing autoimmunity (rheumatoid arthritis);[201] for information on cadherins more generally see discussion under *CDH18* above |
| *ITGB1* | integrin, beta 1 | Integrin beta-1 is a primary pathway whereby several viruses (e.g. Hantaan virus, cytomegalovirus) gain access to host cells, [202,203] and blockade of ITGB1 enhances host survival following infection with viruses that utilize ITGB1 as a means of cellular entry;[202] integrin beta 1 plays an important role in the ability of a number of bacterial species (e.g. *Y. pseudotuberculosis*, *Y. enterocolitica, S. pyogenes, B. burgdorferi)* to gain entry into host |

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| | | epithelial/endothelial cells and thereby commence infection;[204-207] ITGB1 contributes to host defense against *S. pneumonia* by allowing leukocytes direct access to lung bronchioles early in the infectious process;[208] blockade of integrin beta-1 significantly reduces TNF-alpha production by monocytes, peritoneal and alveolar macrophages in response to heat-killed *S. aureus*;[209] integrin beta-1contributes to development of non-T cell-dependent extrafollicular antigen-specific splenic plasmablasts important for protection against intracellular bacteria such as l pathogens such as *Ehrlichia muris*;[210] human CMV infection may increase risk of cardiovascular disease by increasing endothelial cell proliferation, motility, and capillary tube formation in dependence upon binding to and signaling through the beta(1) and beta(3) integrins and the epidermal growth factor receptor, via their ability to activate the phosphatidylinositol 3-kinase and the mitogen-activated protein kinase signaling pathways;[211] human CMV ability to activate IFN-alpha signaling is partially dependent on viral interactions with integrin beta-1, whereas HCMV induced proinflammatory cytokine production is TLR2, but not ITGB1-dependent;[211] binding interactions of bacteria intimin with epithelial integrin beta-1 are essential for infection of human colonic epithelium by Shiga toxin-producing Enterohemorrhagic *E. coli*;[212] anopheline antiplatelet protein (AAPP) isolated from the saliva of Anopheles stephensi, a human malaria vector mosquito, exhibites a strong and specific inhibitory activity toward collagen-induced platelet aggregation (allowing blood feeding to proceed effectively) that depends in part upon integrin beta-1;[213] integrin beta-1 required for long-term retention of memory CD4+ T cells in bone marrow following L. monocytogenes infection, although integrin beta-1 is not required for maintenance of long-term pathogen-specific memory CD+ T cells;[214] stimulation of the TLR4 by LPS activates PI3K/AKT signaling and promotes downstream beta-1 integrin function, which has been implicated in increased cancer cell adhesiveness and metastatic potential;[215] |
| *GRM8* | glutamate receptor, metabotropic 8 | GRM8 (a type III mGlu) has been identified as a vulnerability gene for inflammatory bowel disease (Crohn's) in more than one population sample,[216] suggesting a link between GRM8 and inflammatory functioning; GRM8 activation reduces hyperalgesia in response to inflammatory stimulation in animal models;[217] in response to inflammatory signaling, polymorphonuclear leukocytes release glutamate that decreases human brain endothelial barrier function via reductions in phosphorylated vasodilator-stimulated phosphoprotein,[218] suggesting that type III mGlu signaling is involved in PMN migration in response to infection; type III mGlu stimulation mediates the excitotoxic effects of the proinflammatory mediators homocysteine and homocysteic acid;[219] type III mGlu stimulation blocks TLR4-activated microglia inhibition of oligodendrocyte progenitor cells (which is driven by microglia TNF-alpha/IL-6 production);[220] |

**(a) = a study that finds genome-wide level significance for associations between allelic variants and depression; (b) = a study that failed to find genome-wide level significance for associations between allelic variants and depression**

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