R4 regulators of G protein signaling (RGS) identify a conserved genomic region that contains MHC–related markers

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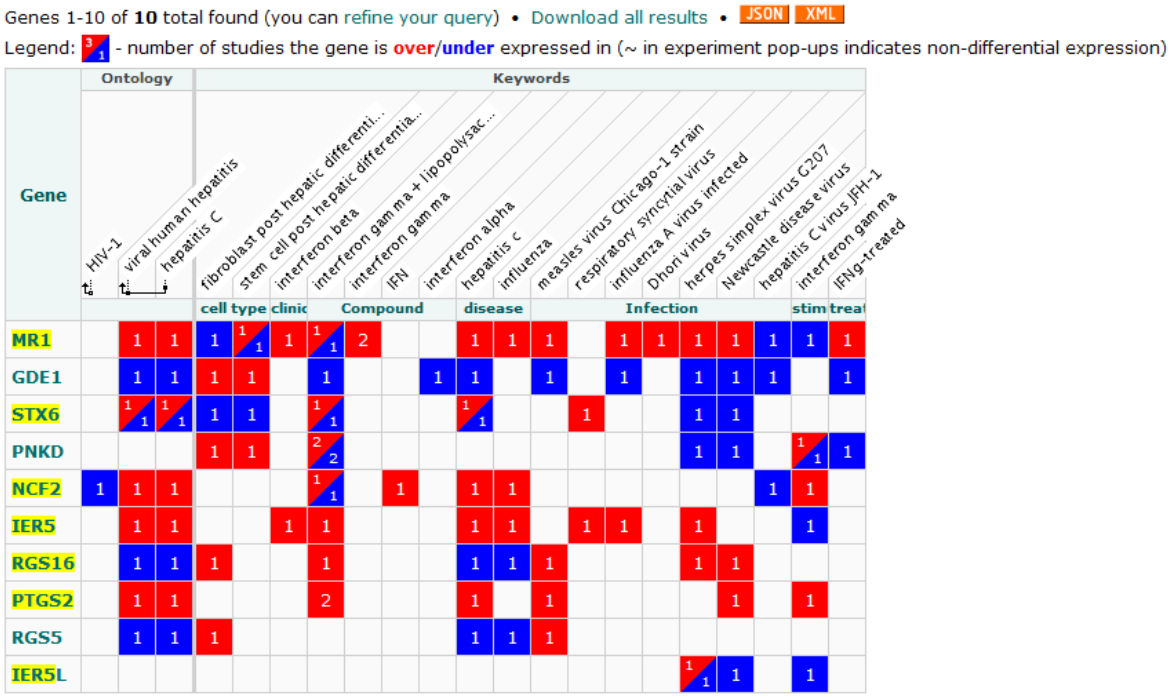
Online Resource 4.

This file contains expression data about some human *RGS1/RGS16* region genes.

Online Resource 4A – Representation of the publicly available microarray data from ArrayExpress for human RGS1/RGS16 region genes DHX9, IER5, MR1, NCF2, PTGS2 and RGS16. It can be seen that the expression of several of these genes is affected in the same direction in different experimental conditions and tissues, all involving viral/interferon challenge.

Online Resource 4B – Literature suggests that many genes in RGS1/RGS16 surrounding are involved in immune/antiviral responses, at least in human and mouse.

Online Resource 4A. Gene Atlas expression data for selected genes of the *RGS1/RGS16* region. Genes marked with yellow on the figure are those present in the *RGS1/RGS16* region.



Online Resource 4B. Genes of the *RGS1/RGS16* region are involved in immune mechanisms.

CFH	The complement factor gene *CFH* is differentially modulated by IFNg (Brooimans et al. 1990; Kim et al. 2009, Luo et al. 2012). *CFHR4,* one of the CFH paralogues located next to it, has been shown to be significantly upregulated by a viral infection (Miyazaki et al. 2011).
NCF2 and GLRX2	Interferon-inducible gene *NCF2* (Eklund and Kakar 1999) encodes p67phox, a subunit of NADPH oxidase, which produces superoxide and leads to oxidative burst during bacterial and viral infections. One of the enzymes protecting cells against the harmful effects of oxidative stress is mitochondrial glutaredoxin 2, encoded by the gene *GLRX2* which is also located in the *RGS1/RGS16* region (Wu et al. 2011).
PLA2G4A and *PTGS2*	*PLA2G4A* and *PTGS2* are enzymes directly responsible for prostaglandin production. Prostaglandins are involved in immune activation and inhibit interferon production in response to viral infections, as can be seen by the ability of acetylsalicylic acid (Aspirin) and other COX2 inhibitors to increase the production of interferon (Cesario et al. 1989).
TPR	TPR mediates the translocation of the product of interferon-inducible mouse gene *Ifi204* from cytoplasmic to the nuclear compartment following IFN treatment (De Andrea et al. 2002).
EDEM3	The knockdown of EDEM3 results in increased virus production as it participates in the ER-associated degradation pathway and has been shown to be required for the ubiquitinylation and subsequent degradation of the glycoproteins of many viruses (Saeed et al. 2011).
APOBEC4	APOBEC4 is a member of the AID/APOBEC family of polynucleotide (deoxy)cytidine deaminases. Members of this family have been shown to inhibit viral replication (Mangeat

	et al. 2003; Noguchi et al. 2007; Rosler et al. 2005; Yu et al. 2004), and are thus inducible by both type I and II interferon, and by viruses themselves (Miyazaki et al. 2011; Noguchi et al. 2007).
DHX9	*DHX9* encodes RNA helicase A, which is a sensor for viral dsRNA in myeloid dendritic cells when bound to IPS-1 (Zhang et al. 2011), and can recognize DNA viruses in plasmacytoid dendritic cells (Kim et al. 2010). Knockdown of this gene significantly reduces the ability of dendritic cells to produce type I interferon and proinflammatory cytokines in response to RNA viruses (Zhang et al. 2011). In fact, RNA helicase A implication in virus/host intereactions is complex since it is required for efficient replication of different viruses such as influenza, HIV and HCV (Fujii et al. 2001; He et al. 2008; Lin et al. 2012).
RNAseL	RNase L is one of the best-studied interferon-induced antiviral effectors and has the ability to cleave single-stranded RNA. Also, small RNAs produced by Rnase L activity may modulate IFNβ signaling, and RNase L may be also implicated in protecting the central nervous system against virus-induced demyelination (reviewed by Chakrabarti et al. 2011).
IER5	IER5 (immediate early response 5) mediates cellular responses to mitogenic signals (Williams et al. 1999).
MR1	The gene *MR1* encodes a non-classical conserved MHC molecule which mediates cell activation through antigen presentation (Huang et al. 2005).
STX6	STX6 (syntaxin 6) is a SNARE (Soluble NSF Attachment protein REceptor) that regulates several key processes often involved in antiviral responses such as chemotactic cell migration, integrin trafficking, exocytosis, proliferation and survival (Murray et al. 2005; Riggs et al. 2012; Zhang et al. 2008).
AL359853.2	The product of AL359853.2 is also known as interferon responsive gene 15 and thus responds to interferon.

References

Brooimans RA, van der Ark AA, Buurman WA, van Es LA, Daha MR (1990) Differential regulation of complement factor H and C3 production in human umbilical vein endothelial cells by IFN-gamma and IL-1. J Immunol 144:3835-40

Cesario TC, Yousefi S, Carandang G (1989) The regulation of interferon production by aspirin, other inhibitors of the cyclooxygenase pathway and agents influencing calcium channel flux. Bull N Y Acad Med 65:26-35

Chakrabarti A, Jha BK, Silverman RH (2011) New insights into the role of RNase L in innate immunity. J Interferon Cytokine Res 31:49-57

De Andrea M, Zannetti C, Noris E, Gariglio M, Azzimonti B, Landolfo S (2002) The mouse interferon-inducible gene Ifi204 product interacts with the Tpr protein, a component of the nuclear pore complex. J Interferon Cytokine Res 22:1113-21

Eklund EA, Kakar R (1999) Recruitment of CREB-binding protein by PU.1, IFN-regulatory factor-1, and the IFN consensus sequence-binding protein is necessary for IFN-gamma-induced p67phox and gp91phox expression. J Immunol 163:6095-105

Fujii R, Okamoto M, Aratani S, Oishi T, Ohshima T, Taira K, Baba M, Fukamizu A, Nakajima T (2001) A Role of RNA Helicase A in cis-Acting Transactivation Response Element-mediated Transcriptional Regulation of Human Immunodeficiency Virus Type 1. J Biol Chem 276:5445-51

He QS, Tang H, Zhang J, Truong K, Wong-Staal F, Zhou D (2008) Comparisons of RNAi approaches for validation of human RNA helicase A as an essential factor in hepatitis C virus replication. J Virol Methods 154:216-9

Huang S, Gilfillan S, Cella M, Miley MJ, Lantz O, Lybarger L, Fremont DH, Hansen TH (2005) Evidence for MR1 antigen presentation to mucosal-associated invariant T cells. J Biol Chem 280:21183-93

Kim T, Pazhoor S, Bao M, Zhang Z, Hanabuchi S, Facchinetti V, Bover L, Plumas J, Chaperot L, Qin J, Liu YJ (2010) Aspartate-glutamate-alanine-histidine box motif (DEAH)/RNA helicase A helicases sense microbial DNA in human plasmacytoid dendritic cells. Proc Natl Acad Sci U S A 107:15181-6

Kim YH, He S, Kase S, Kitamura M, Ryan SJ, Hinton DR (2009) Regulated secretion of complement factor H by RPE and its role in RPE migration. Graefes Arch Clin Exp Ophthalmol 247:651-9

Lin L, Li Y, Pyo HM, Lu X, Raman SN, Liu Q, Brown EG, Zhou Y (2012) Identification of RNA helicase A as a cellular factor that interacts with influenza A virus NS1 protein and its role in the virus life cycle. J Virol 86:1942-54

Luo C, Chen M, Madden A, Xu H (2012) Expression of Complement Components and Regulators by Different Subtypes of Bone Marrow-Derived Macrophages. Inflammation 35:1448-61

Mangeat B, Turelli P, Caron G, Friedli M, Perrin L, Trono D (2003) Broad antiretroviral defence by human APOBEC3G through lethal editing of nascent reverse transcripts. Nature 424:99-103

Miyazaki D, Haruki T, Takeda S, Sasaki S, Yakura K, Terasaka Y, Komatsu N, Yamagami S, Touge H, Touge C, Inoue Y (2011) Herpes simplex virus type 1-induced transcriptional networks of corneal endothelial cells indicate antigen presentation function. Invest Ophthalmol Vis Sci 52:4282-93

Murray RZ, Wylie FG, Khromykh T, Hume DA, Stow JL (2005) Syntaxin 6 and Vti1b form a novel SNARE complex, which is up-regulated in activated macrophages to facilitate exocytosis of tumor necrosis Factor-alpha. J Biol Chem 280:10478-83

Noguchi C, Hiraga N, Mori N, Tsuge M, Imamura M, Takahashi S, Fujimoto Y, Ochi H, Abe H, Maekawa T, Yatsuji H, Shirakawa K, Takaori-Kondo A, Chayama K (2007) Dual effect of APOBEC3G on Hepatitis B virus. J Gen Virol 88:432-40

Riggs KA, Hasan N, Humphrey D, Raleigh C, Nevitt C, Corbin D, Hu C (2012) Regulation of Integrin Endocytic Recycling and Chemotactic Cell Migration by Syntaxin 6 and VAMP3 Interaction. J Cell Sci [Epub ahead of print]

Rosler C, Kock J, Kann M, Malim MH, Blum HE, Baumert TF, von Weizsacker F (2005) APOBEC-mediated interference with hepadnavirus production. Hepatology 42:301-9

Saeed M, Suzuki R, Watanabe N, Masaki T, Tomonaga M, Muhammad A, Kato T, Matsuura Y, Watanabe H, Wakita T, Suzuki T (2011) Role of the endoplasmic reticulum-associated degradation (ERAD) pathway in degradation of hepatitis C virus envelope proteins and production of virus particles. J Biol Chem 286:37264-73

Williams M, Lyu MS, Yang YL, Lin EP, Dunbrack R, Birren B, Cunningham J, Hunter K (1999) Ier5, a novel member of the slow-kinetics immediate-early genes. Genomics 55:327-34

Wu H, Lin L, Giblin F, Ho YS, Lou MF (2011) Glutaredoxin 2 knockout increases sensitivity to oxidative stress in mouse lens epithelial cells. Free Radic Biol Med 51:2108-17

Yu Q, Chen D, Konig R, Mariani R, Unutmaz D, Landau NR (2004) APOBEC3B and APOBEC3C are potent inhibitors of simian immunodeficiency virus replication. J Biol Chem 279:53379-86

Zhang Z, Yuan B, Lu N, Facchinetti V, Liu YJ (2011) DHX9 pairs with IPS-1 to sense double-stranded RNA in myeloid dendritic cells. J Immunol 187:4501-8

Zhang Y, Shu L, Chen X (2008) Syntaxin 6, a regulator of the protein trafficking machinery and a target of the p53 family, is required for cell adhesion and survival. J Biol Chem 283:30689-98