

# Human Protein Reference Database—2009 update

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## ABSTRACT

Human Protein Reference Database (HPRD—<http://www.hprd.org/>), initially described in 2003, is a database of curated proteomic information pertaining to human proteins. We have recently added a number of new features in HPRD. These include PhosphoMotif Finder, which allows users to find the presence of over 320 experimentally verified phosphorylation motifs in proteins of interest. Another new feature is a protein distributed annotation system—Human Proteinpedia (<http://www.humanproteinpedia.org/>)—through which laboratories can submit their data, which is mapped onto protein entries in HPRD. Over 75 laboratories involved in proteomics research have already participated in this effort by submitting data for over 15 000 human proteins. The submitted data includes mass spectrometry and protein microarray-derived data, among other data types. Finally, HPRD is also linked to a compendium of human signaling pathways developed by our group, NetPath (<http://www.netpath.org/>), which currently contains annotations for several cancer and immune signaling pathways. Since the last update, more than 5500 new protein sequences have been added,

making HPRD a comprehensive resource for studying the human proteome.

## INTRODUCTION

Human Protein Reference Database (HPRD; <http://www.hprd.org/>) is a resource for experimentally derived information about the human proteome including protein–protein interactions, post-translational modifications (PTMs) and tissue expression (1–4). The contents of several proteomic databases, including HPRD, pertaining to human proteins have recently been evaluated in terms of the number of nonredundant protein–protein interactions, number of direct interactions per protein, number of proteins with disease annotation and the number of linked citations (5). The curation and annotation process in HPRD involves entry of protein data through BioBuilder, a tool developed by our group for editing and managing data through a web browser (6). We have incorporated new features, such as PhosphoMotif Finder, links to a signaling pathway resource called NetPath, Human Proteinpedia for enhanced community participation and the use of BLAST for querying mRNA/protein data. Since the last update, we have added approximately 5500 new protein sequences and corresponding information in HPRD, which now contains information on most of the human proteins including their isoforms.

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**Human Protein Reference Database**  
 You are at HPRD >> Query >> Janus kinase 2  
**Janus kinase 2**

Molecular Class: Tyrosine kinase  
 Molecular Function: Protein-tyrosine kinase activity  
 Biological Process: Cell communication; Signal transduction

Gene Symbol: JAK2 Molecular Weight (Da): 130673 Gene Map Locus: 9p24

JAK2 is involved in the following pathway(s)  
 IL-2 IL-3 IL-4 IL-5 IL-6 Notch EGFR1 Kit Receptor

Physical Interaction	
Interacting molecule	Pathway
PPP2CA	IL-3
GSE2RB	IL-3
IL3RA	IL-3
TEC	IL-3
IL4R	IL-4
DNM2	IL-5
IL5RA	IL-5
SQCS1	IL-5
GSE2RB	IL-5
SHC1	IL-6
TEC	IL-6
PTPN12	EGFR1
HES1	Notch
HES5	Notch
STAT3	Notch
KIT	Kit Receptor
TNFRSF1A	TNF-alpha

Substrate	Upstream enzyme	PTM type	Pathway
JAK2		Dephosphorylation	IL
JAK2	PTPN12	Dephosphorylation	EGFR1
JAK2		Phosphorylation	IL
JAK2		Phosphorylation	IL
JAK2	JAK2	Phosphorylation	IL
JAK2	JAK2	Phosphorylation	IL
JAK2	JAK2	Phosphorylation	IL
JAK2	JAK2	Phosphorylation	IL
JAK2	JAK2	Phosphorylation	IL
STAM	JAK2	Phosphorylation	Kit Receptor
PPP2CA	JAK2	Phosphorylation	IL
JAK2	JAK2	Phosphorylation	IL
JAK2	JAK2	Phosphorylation	IL

**NetPath**  
 Home Browse FAQs  
 Immune Signaling Pathways Cancer Signaling Pathways

Interleukin-5 belongs to the family of cytokines, which includes IL-3 and GM-CSF. It signals through a receptor complex comprising of an IL-5 receptor alpha subunit (IL5RA), and a common beta chain which is shared between all members of this cytokine family. Binding of IL-5 to IL5RA recruits the beta chain to the complex, this then activates the JAK2/STAT3 and Raf/MAPK signaling modules.

Pathway Statistics	Value
Molecules Involved	57
Physical Interactions	27
Enzyme Catalysis	40
Transport	6
Genes Transcriptionally Regulated	140

Molecules Involved in IL-5 signaling pathway (Total = 57)

AKT1	ALOX5	APB	ATE2	BAX	BLK	CBL	CRKL	GSE2RB	GIMNB1	DNM2	ELK1	FOXO3A	GRB2	GRK3A
GRK3B	HCK	HCL1	IL2RB	IL3	IL5RA	JAK1	JAK2	JUN	KRAS	LYN	MAP2K2	MAPK1	MAPK14	MAPK3
MEK3	MEK3B	ERK2G	ERK3	ERK3B	FLA2G1A	FRS3B1	FRS3G	FRS3C	PTPN11	PTPN6	RAC1	RARGF1	RFBP4A1	SICR2
SHC1	SHC2	SQCS1	SOX4	STAT1	STAT3	STAT3A	STAT5B	SYK	UNC119	XAV1	Y90A2			

Reactions in IL-5 pathway (Total = 79)  
 Physical Interactions  
 Enzyme Catalysis  
 Transport

Genes Transcriptionally Regulated by IL-5 pathway (Total = 140)  
 Upregulated genes  
 Downregulated genes

Download Pathway Download Transcriptionally Regulated Genes

BiopAX level 2.0  
 PSI-MI Version 2.5  
 SBML Version 2.1

Excel Sheet  
 Tab Delimited

**Figure 2.** Linking to human signaling pathways from HPRD. 'Pathways' button in the HPRD page of JAK2 is hyperlinked to its NetPath page. It shows the list of signaling pathways in which the protein is involved along with the description of its interactors in each pathway. Each interaction or catalysis event is linked to the PubMed abstract of the original article. The pathway name is linked to the specific signaling pathway annotated in NetPath.

form of Excel sheet and tab delimited text documents. Integration of NetPath data in HPRD will assist users in visualizing the probable role of proteins in diverse signaling networks. For example, Janus Kinase 2 (JAK2) is involved in diverse pathways including EGFR1, Kit receptor, Notch, IL-2, IL-3, IL-4, IL-5 and IL-6 signaling pathways. NetPath provides the list of physical interactions and catalysis events of JAK2 with various proteins under different signaling pathways. Each interaction or catalysis event is linked to the PubMed abstract of the original article (Figure 2).

### Annotation of proteomic information

**Protein isoforms.** We have included most of human protein isoforms present in the RefSeq Database (8). Currently, 25661 protein sequences encoded by 19433 genes have been annotated in HPRD. Phosphodiesterase 9A, cAMP response element modulator, collagen type XIII alpha1 and dystrophin are examples of proteins with the highest number of isoforms with 20, 20, 19 and

18 isoforms, respectively. However, only data pertaining to the sequence, subcellular localization, mRNA/protein expression, biological motifs and domains are currently being annotated as isoform specific whereas protein-protein interactions and enzyme-substrate relationships are annotated as common to all isoforms. This is mainly due to the general lack of experimental data for the latter.

**Protein-protein interactions.** Protein-protein interactions are one of the most requested components of HPRD among those who downloaded this dataset. We have added more than 5000 protein-protein interactions in HPRD since the previous update in 2006. Among the 38167 protein-protein interactions documented in HPRD, 8958 interactions were based on yeast two-hybrid analysis alone, whereas 8827 interactions were based on *in vitro* and 7163 on *in vivo* methods. Detection of 2410 protein-protein interactions was confirmed by all three methods. Overall, in HPRD, 8710 proteins are annotated with at least one protein-protein interaction, whereas 2015 and 774 proteins have more than



**Table 1.** Statistics of proteomic data annotated by HPRD team and submitted to Human Proteinpedia

Dataset	Dataset annotated by HPRD team	Data submitted through Human Proteinpedia
Protein–protein interactions	38 167	15 231
PTMs	16 972	17 410
Subcellular localization	19 670	2906
mRNA/protein expression	65 536	150 368

**Table 2.** Statistics of PTM data annotated among various PTM types

PTM type	Count
Phosphorylation	10 858
Dephosphorylation	3118
Glycosylation	1860
Sumoylation	305
Acetylation	259
Methylation	274
Palmitoylation	149
Myristoylation	43
Glutathionylation	11
ADP-ribosylation	7
Others	88
Total	16 972

5 or 10 protein–protein interactions, respectively. The 14-3-3 gamma protein has a maximum of 173 protein–protein interactions. 15 231 protein–protein interactions (Table 1) have been submitted to HPRD by the scientific community using Human Proteinpedia (9,10). Enzyme–substrate relationships determined through peptide/protein arrays is a new data type included in HPRD, as represented by the phosphorylation of Tyr 16 of RNA binding motif protein 10 by c-Src.

**PTMs and subcellular localization.** HPRD currently contains information for 16 972 PTMs (Table 2) which belong to various categories with phosphorylation (10 858), dephosphorylation (3118) and glycosylation (1860) forming the majority of the annotated PTMs (Table 2). At least one enzyme responsible for PTMs has been annotated for 8960 PTMs, which resulted in the documentation of 7253 enzyme–substrate relationships. Of these, 1277 PTMs have more than one enzyme annotated. Human Proteinpedia has contributed over 17 400 PTMs, which are mainly derived from mass spectrometry studies. One or more site of subcellular localization has been annotated for 8620 proteins in HPRD with 586 of them being isoform specific. In addition to these, scientific investigators have contributed 2906 entries pertaining to subcellular localization through Human Proteinpedia.

### Community participation through ‘Human Proteinpedia’

We have developed a distributed annotation system called Human Proteinpedia and incorporated in HPRD (9,10). Proteomic investigators can directly contribute protein

data derived from diverse platforms including the yeast two-hybrid, mass spectrometry, peptide/protein array, immunohistochemistry, Western blot, coimmunoprecipitation and fluorescence microscopy to HPRD using Human Proteinpedia. The protein features that can be mapped to corresponding entries in HPRD include PTMs, mRNA/protein expression in tissues or cell lines, subcellular localization, enzyme–substrate relationships and protein–protein interactions. These annotations are made available for viewing in a separate box beneath the HPRD annotation (Figure 3). Each entry is also linked to experimental evidence, such as mass spectra, images of Western blots and fluorescence micrographs. Figure 3 shows five serine phosphorylation sites for Adducin 1 protein in HPRD, submitted through Human Proteinpedia. PTM sites are linked to the meta-annotation of mass spectrometry data in Human Proteinpedia database as submitted by the investigator. The corresponding MS/MS spectrum can also be viewed by following a link in the meta-annotation page.

Investigators worldwide have already submitted 15 231 protein–protein interactions, 17 410 PTMs and 150 368 mRNA/protein expression to HPRD through Human Proteinpedia. Human Proteinpedia has increased quantity of the HPRD data by 2-fold in a relatively short span of time (Table 1). By involving investigators and experimentalists in the annotation of proteomic data, Human Proteinpedia has transformed HPRD into a true community database.

### Usage of HPRD data by the community

Over the years, the biomedical community has provided valuable suggestions by interacting with HPRD team through ‘Comments’ and ‘Help’ buttons provided in HPRD page. More than 8000 gene comments, expert suggestions and help requests have been received and nearly 100 scientists have been designated as ‘Molecule Authorities’ based on their expertise. We hope to further increase participation by the community by implementing a microattribution system, which provides a citable credit to the investigators. Web resources that display or have made use of HPRD data include Entrez-Gene, VisANT (11) Genes2Networks (12), Cerebral (13), BioNetBuilder (14), COXPRESdb (15), STRING 7 (16) and UniHI (17). Molecular Signature Database (MSigDB) (18) used for Gene Set Enrichment Analysis of gene expression data incorporates pathway gene sets curated from HPRD. Sequence analysis tools which use HPRD data include CompariMotif (19) and SLiMfinder (20). CutDB, a database of proteolytic events (21), PepBank, a database of peptides (22) and T1Dbase, a database for type 1 diabetes research (23) are other resources that also incorporate curated proteomic data from HPRD.

### CONCLUSIONS

With the inclusion of most of human protein sequences, HPRD has grown into an integrated knowledgebase for genomic and proteomic investigators. Incorporation of PhosphoMotif Finder and signaling pathways will help





**Figure 3.** Display of PTM data in HPRD submitted through Human Proteinpedia. Adducin1 molecule page in HPRD shows five novel phosphorylation sites submitted through Human Proteinpedia. Phosphorylation sites are hyperlinked to Human Proteinpedia page with information on the investigator, laboratory and meta-annotation of mass spectrometry experiment. Corresponding MS/MS spectrum for a peptide is also displayed using spectrum viewer developed by PRIDE.

users to generate novel hypotheses or to point out likely molecules involved in a biological process of their interest. Further, the implementation of Human Proteinpedia has transformed HPRD into a community driven database and we hope that this trend will continue so that each and every entry is directly or indirectly verified by the individual experimentalists.

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