PANTHER: A Library of Protein Families and Subfamilies Indexed by Function



Genome Res. 2003 13: 2129-2141

Diemer, Anushya Muruganujan and Apurva Narechania Paul D. Thomas ,et al

.

Group C

Members:郭書麟、曾致遠、柯懿婷、陳珮欣

Speaker: 吳行展

Date: 95/12/21

PANTHER version 6: protein sequence and function evolution data with expanded representation of biological pathways



Nucleic Acids Research, 2006, Vol. 00, Database issue D1–D6

Huaiyu Mi, Nan Guo, Anish Kejariwal and Paul D. Thomas*

Outline

- Introduction
- Method
- Manipulation
- Conclusion

Introduction

 In the genomic era, one of the fundamental goals is to characterize the function of proteins on a large scale.

Introduction



 PANTHER (Protein ANalysis THrough Evolutionary Relationships)

• A freely available, comprehensive software system for relating protein sequence evolution to the evolution of specific protein functions and biological roles.

Genes, transcripts and proteins

Classifies genes by their functions

- Database of genes, transcripts and proteins in the following species:
 - o Human (NCBI, Celera)
 - o Mouse (NCBI, Celera)
 - o Rat (NCBI, Celera)
 - Drosophila melanogaster (FlyBase)

Genes, transcripts and proteins

 Classifications for these genes are based on Hidden Markov Models (HMMs), statistical models that describe families and subfamilies of protein sequences.

Genes, transcripts and proteins

- Proteins are classified by expert biologists into families and subfamilies of shared function
- Categorized by molecular function and biological process ontology terms.

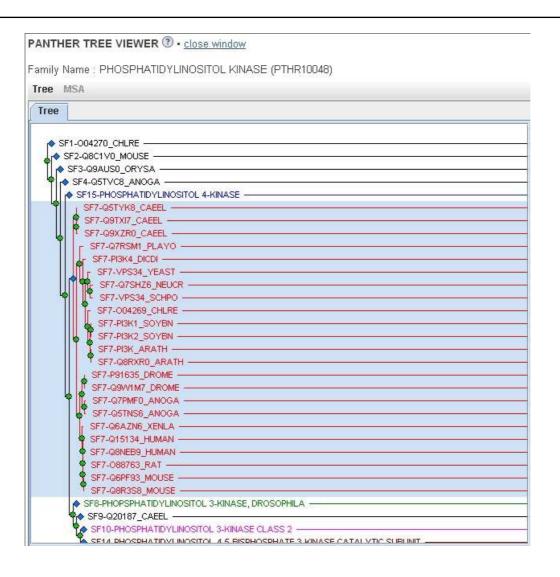
Families and HMMs

- A library (PANTHER/LIB) of protein families and subfamilies and associated data such as
 - Phylogenetic trees
 - Multiple sequence alignments(MSA)
 - HMMs.

Families and HMMs

- O PANTHER version 6.1 contains 5547 protein families, divided into 24,582 functionally
- Distinct protein subfamilies by expert biologist curators.
- Each protein family is represented by a phylogenetic tree defining its subfamilies.
- Families and subfamilies are also represented by HMMs and associated with functional ontology terms.

Families and HMMs



Pathways

 PANTHER Pathway consists of over 130, primarily signaling pathways, each with subfamilies and protein sequences mapped to individual pathway components.

•

 A component is usually a single protein in a given organism, but multiple proteins can sometimes play the same role.

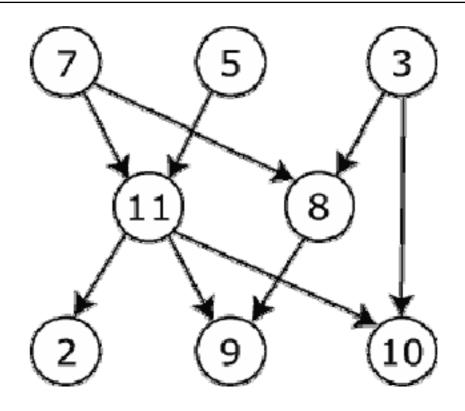
Pathways

- Pathways are drawn using CellDesigner software, capturing molecular level events in both signaling and metabolic pathways, and can be exported in SBML format.
- Pathway diagrams are interactive and include tools for visualizing gene expression data in the context of the diagrams

Ontologies

- A collection of terms (PANTHER/X) describing protein molecular functions and biological processes.
- o The PANTHER/X ontology is a controlled vocabulary of molecular function and biological process terms, arranged as directed acyclic graphs (DAGs) similar to the Gene Ontology™ (GO), but greatly abbreviated and simplified to facilitate high-throughput analyses.

Ontologies

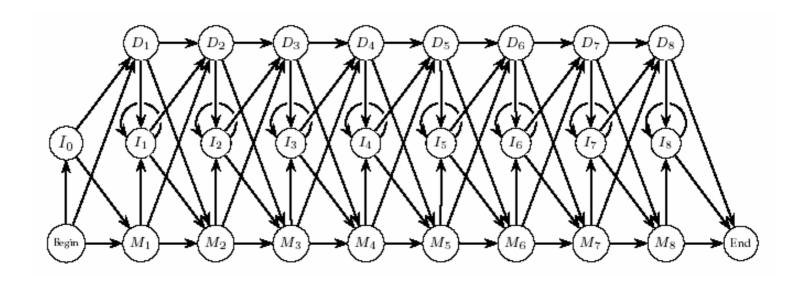


A simple directed acyclic graph (DAG)

Methods

- Making a Collection of HMM for Protein Families
 - Use BLAST to separate a protein database into families of related proteins
 - Construct a multiple alignment for each protein family.
 - Construct a profile HMM model and optimize the parameters of the model (transition and emission probabilities).
 - Align the target sequence against each HMM to find the best fit between a target sequence and an HMM

Methods



A profile HMM

Methods

- 1. Family clustering.
- 2. Multiple sequence alignment (MSA), family HMM, and family tree building.
- 3. Family/subfamily definition and naming.
- 4. Subfamily HMM building.
- 5. Molecular function and biological process association.





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The PANTHER (Protein ANalysis Through Evolutionary Relationships) Classification System is a unique resource that classifies genes by their functions, using published scientific experimental evidence and evolutionary relationships to predict function even in the absence of direct experimental evidence. Proteins are classified by expert biologists into families and subfamilies of shared function, which are then categorized by molecular function and biological process ontology terms. For an increasing number of proteins, detailed biochemical interactions in canonical pathways are captured and can be viewed interactively.

To get started, try either a <u>text search</u>, <u>browsing by function</u>, or take a look at interactive pie charts that summarize the functions of whole genomes for <u>Human</u>, <u>Mouse</u>, <u>Rat</u> and <u>Drosophila melanogaster</u>.

Genes

Our database of genes, transcripts and proteins in the following species: Human, Mouse, Rat, and Drosophila melanogaster.

- Search by keyword
- > Search by location
- Browse by function
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Families and HMMs

A library (PANTHER/LIB) of protein families and subfamilies and associated data such as phylogenetic trees, multiple sequence alignments and HMMs.

- Search PANTHER Families
- Score a sequence against PANTHER HMMs
- More...

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(December 8, 2006)

PANTHER 6.1 released

PANTHER Pathways version 1.31 released

Additional PANTHER HMMs have been integrated into InterPro

additional info...

Publications

How to cite PANTHER

"Applications for protein sequence-function evolution data: mRNA/protein expression analysis and coding SNP scoring tools."
Thomas, et al.

"The PANTHER database of protein families, subfamilies, functions and pathways." Mi,

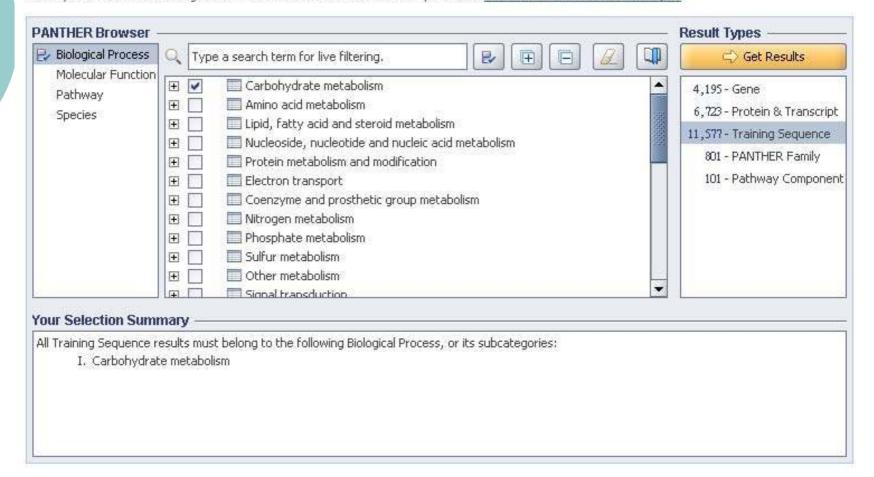




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Prowler ?

Browse the PANTHER system using the Prowler, and retrieve results for different data associated with the ontology and pathway terms, such as individual genes or families and subfamilies of proteins. About the PANTHER Ontologies







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Genes

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How to cite PANTHER

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> p53 pathway->p53

PANTHER GENE INFORMATION ③

Gene ID: GeneID:7157

Gene Name: tumor protein p53 (Li-Fraumeni syndrome)

Gene Symbol(s): TP53

TRP53 p53

LFS₁

Public Gene Location: Chr. 17

7512464 - 7531642 Map Viewer

Organism: Homo sapiens

Related sequences: M13121 M22881 U94788 X02469

ABI Assays: TagMan® Gene Expression Assays
TagMan® SNP Genotyping Assays

PANTHER CLASSIFICATION

PANTHER Molecular Function: Transcription factor → Other transcription factor. PANTHER Biological Process: Nucleoside, nucleotide and nucleic acid metabolism → DNA metabolism → DNA repair MRNA transcription ► mRNA transcription regulation <u>Apoptosis</u> ☐ Induction of apoptosis Cell cycle Gell cycle control Cell proliferation and differentiation Oncogenesis ↓ Tumor suppressor. Pathway Categories: p53 pathway feedback loops 1 4 P53 Huntington disease P53 tumor suppressor phosphoprotein Apoptosis signaling pathway ► Tumor protein p53 p53 pathway **4** p53 p53 pathway **4** p53 p53 pathway feedback loops 2

4 p53

TRANSCRIPT / PROTEIN PAIRS

Transcript Protein	PANTHER Score	PANTHER Links	PANTHER Best Hit
NM 000546 NP 000537	<u>0E+00</u> •●●	Tree MSA Additional scores	CELLULAR TUMOR ANTIGEN P53 (PTHR11447:SF6)

PANTHER GENE INFORMATION ③

Gene ID: GeneID:7157

Gene Name: tumor protein p53 (Li-Fraumeni syndrome)

Gene Symbol(s): TP53

TRP53 p53 LFS1

Public Gene Location: Chr. 17

7512464 - 7531642 Map Viewer

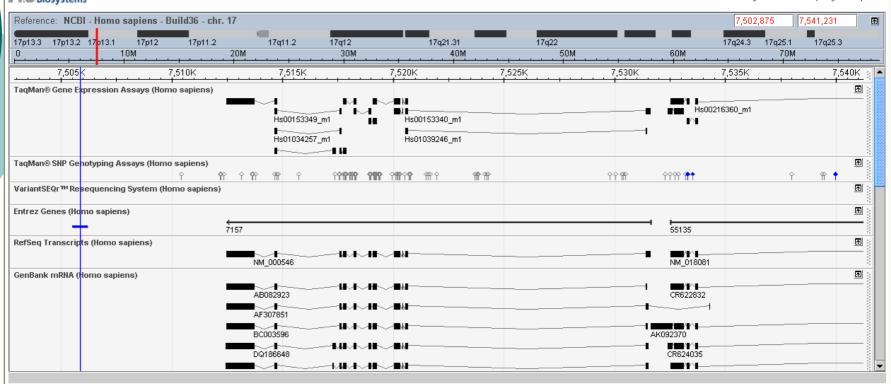
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PANTHER SUBFAMILY INFORMATION ③

Subfamily: CELLULAR TUMOR ANTIGEN P53 (PTHR11447:SF6)

Family: CELLULAR TUMOR ANTIGEN P53-RELATED

PANTHER Links:





Tree MSA

PANTHER Molecular Function: Transcription factor

Other transcription factor

PANTHER Biological Process:

Nucleoside, nucleotide and nucleic acid metabolism

DNA metabolism

4 DNA repair

mRNA transcription

MRNA transcription regulation

<u>Apoptosis</u>

Induction of apoptosis

Cell cycle

Gell cycle control

Cell proliferation and differentiation

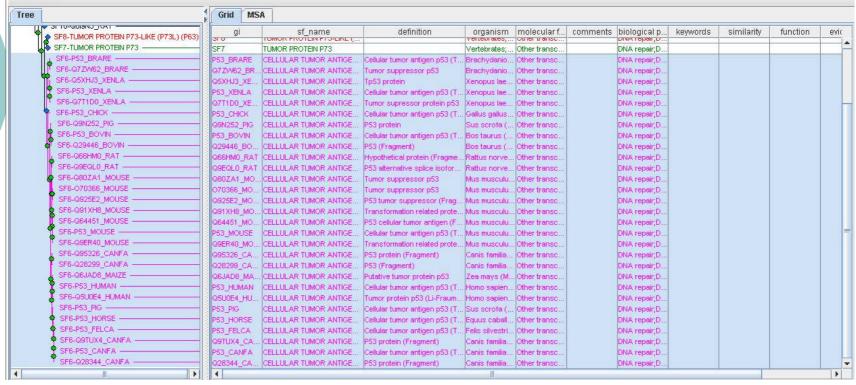
Oncogenesis

Tumor suppressor

PANTHER TREE VIEWER 3 - close window

Family Name: CELLULAR TUMOR ANTIGEN P53-RELATED (PTHR11447)

Tree MSA

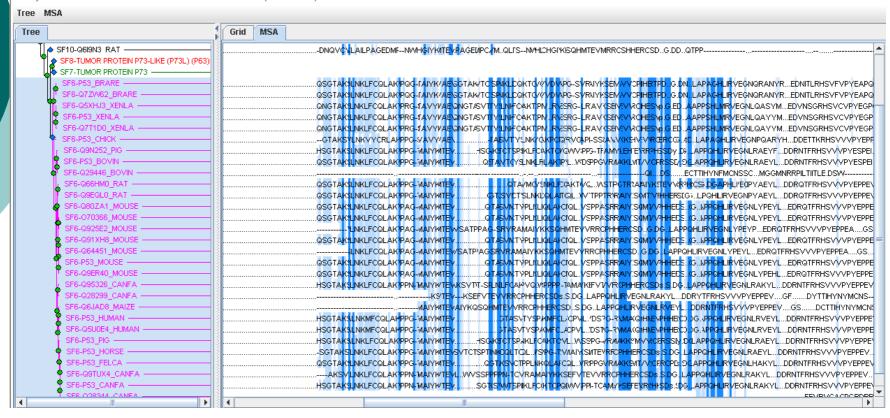




PANTHER TREE VIEWER ? - close window

Family Name: CELLULAR TUMOR ANTIGEN P53-RELATED (PTHR11447)







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TRANSCRIPT / PROTEIN INFORMATION ②

Transcript ID: NM 000546

Protein ID: NP 000537

Gene ID: GeneID:7157

Gene Name: tumor protein p53 (Li-Fraumeni syndrome)

Gene Symbol: TP53

Organism: Homo sapiens

Public Gene Location: Chr.17

7512464 - 7531642 Map Viewer

ABI Assays: TagMan® Gene Expression Assays

TagMan® SNP Genotyping Assays

Related sequences: <u>U94788</u> X02469 <u>M22881</u> <u>M13121</u>

SEQUENCE DETAILS

Transcribed Sequence - all exons

>NM 000546

ACTTGTCATGGCGACTGTCCAGCTTTGTGCCAGGAGCCTCGCAGGGGTTGATGGGATTGGGGTTTTCC
CCTCCCATGTGCTCAAGACTGGCGCTAAAAGTTTTGAGCTTCTCAAAAGTCTAGAGCCACCGTCCAGG
GAGCAGGTAGCTGCTGGGCTCCGGGGACACTTTGCGTTCGGGCTGGGAGCGTGCTTTCCACGACGGTG
ACACGCTTCCCTGGATTGGCAGCCAGACTGCCTTCCGGGTCACTGCCATGGAGAGCCGCAGTCAGAT
CCTAGCGTCGAGCCCCCTCTGAGTCAGGAAACATTTTCAGACCTATGGAAACTACTTCCTGAAAACAA
CGTTCTGTCCCCCTTGCCGTCCCAAGCAATGGATGATTTGATGCTGTCCCCGGACGATATTGAACAAT
GGTTCACTGAAGACCCAGGTCCAGATGAAGCTCCCAGAATGCCAGAGGCTGCTCCCCGCGTGGCCCCT
GCACCAGCAGCTCCTACACCGGCGGCCCCTGCACCAGCCCCTCCTGGCCCCTGTCATCTTCTGTCCC
TTCCCAGAAAACCTACCAGGGCAGCTACGGTTTCCGTCTGGGCTTCTTGCATCTTCTGTCCC
CTGTGACTTGCACGTACTCCCCTGCCCTCAACAAGATGTTTTTGCCAACTGGCCAAGACCTGCCCTTGTG
CAGCTGTGGGTTGATTCCACACCCCCGCCCGCGCCCCTCCTGCCCCTTGCACTACAAGCAGTC
ACAGCACATGACGGAGGTTGTGAGGCGCTGCCCCCACCATGAGCGCTTTTTGGATGACAGAAACACT
TTTCGACATAGTGTGGTGGTGCCCCTATGAGCCCCTTGAGTTTTGGATGACCACCATCACTA

Protein Sequence

>NP 000537

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAMDDLMLSPDDIEQWFTEDPGPDEAPRMPE
AAPRVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAKSVTCTYSPALNKMFCQ
LAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHERCSDSDGLAPPQHLIRVEGNLRVE
YLDDRNTFRHSVVVPYEPPEVGSDCTTIHYNYMCNSSCMGGMNRRPILTIITLEDSSGNLLGRNSFEV
RVCACPGRDRRTEEENLRKKGEPHHELPPGSTKRALPNNTSSSPQPKKKPLDGEYFTLQIRGRERFEM
FRELNEALELKDAQACKEPGGSRAHSSHLKSKKGQSTSRHKKLMFKTEGPDSD

PANTHER CLASSIFICATION

PANTHER Best Hit: CELLULAR TUMOR ANTIGEN P53(PTHR11447:SF6) Score: 0.00E00 ••• Links Tree MSA Additional scores PANTHER Molecular Function: Transcription factor → Other transcription factor PANTHER Biological Process: <u>Nucleoside</u>, <u>nucleotide</u> and <u>nucleic acid metabolism</u> DNA metabolism DNA repair Apoptosis ➡ Induction of apoptosis Cell cycle ► Cell cycle control Cell proliferation and differentiation Oncogenesis ➡ Tumor suppressor



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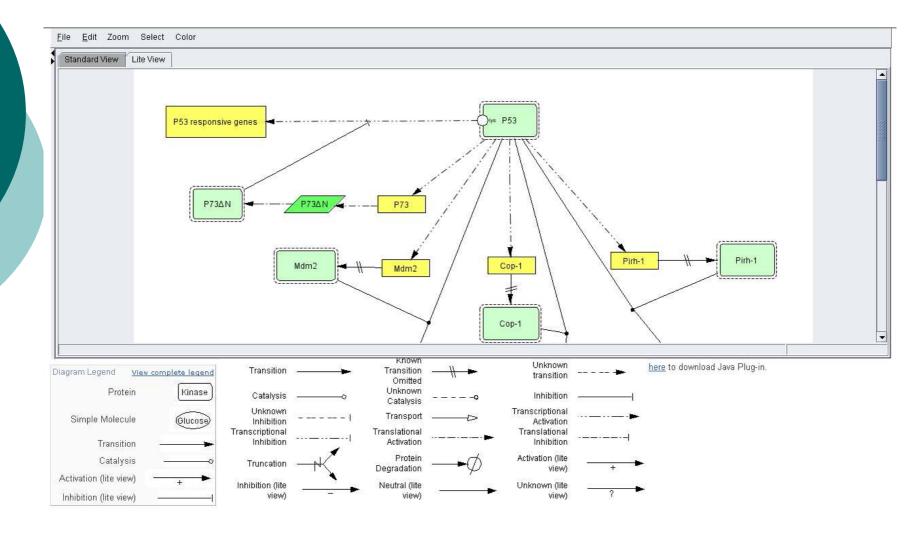
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] 4.	P0005	<u>59</u>	р53	pathway		7	0	88	548
5.	P0439	2	<u>P53</u>	pathway fee	dback loops 1	1	1	8	73
6.	P0439	<u> 18</u>	<u>p53</u>	pathway fee	dback loops 2	3	2	<u>51</u>	393

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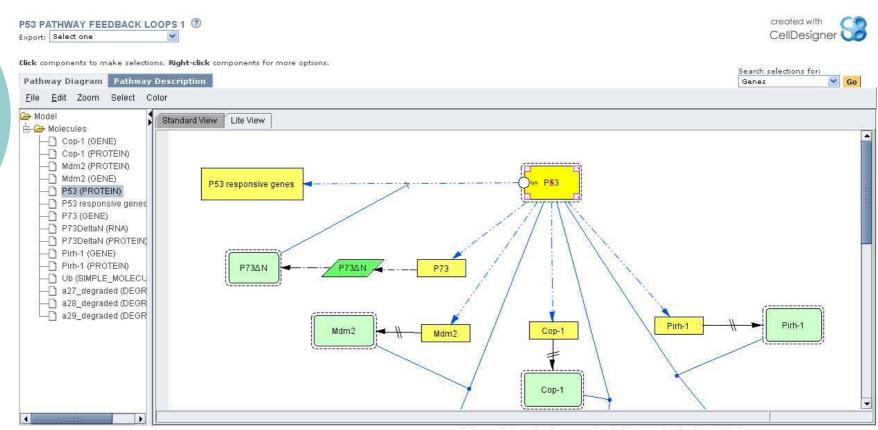
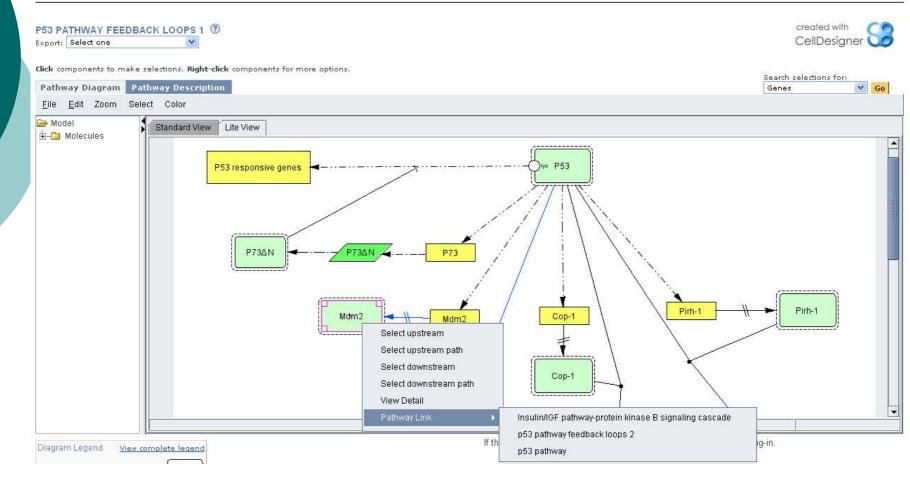


Diagram Legend View complete legend

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P53 PATHWAY FEEDBACK LOOPS 1 ②



Pathway Diagram Pathway Description

Definition: The p53 pathway responds to stresses that can disrupt the fidelity of DNA replication and cell division. A stress signal is transmitted to the p53 protein by post-translational

modifications. This results in the activation of the p53 protein as a transcription factor that initiates a program of cell cycle arrest, cellular senescence or apoptosis. The transcriptional network of p53-responsive genes produces proteins that interact with a large number of other signal transduction pathways in the cell and a number of positive and negative

autoregulatory feedback loops act upon the p53 response. This diagram illustrates 3 such negative feedback loops.

Pathway Accession: P04392

Components: 11

Families/Subfamilies: 8

Training Sequences: 73

References: PubMed: 15838523

Author: Huaiyu Mi, Arnie Levine

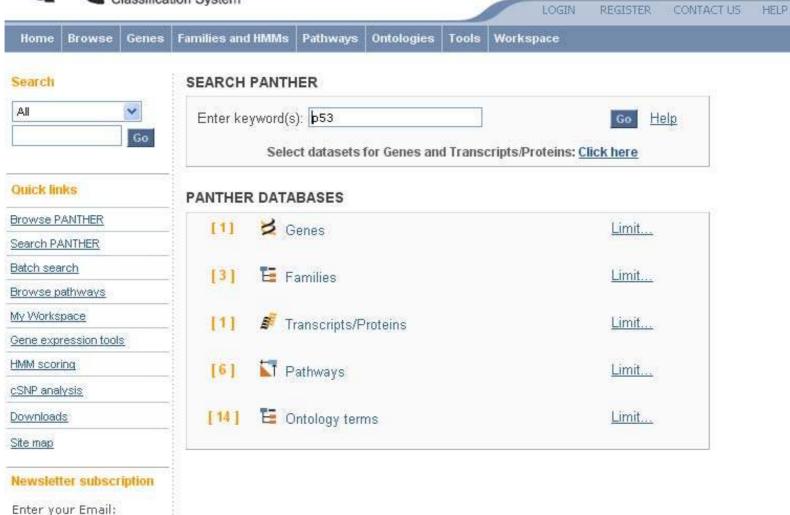
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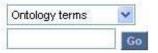




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Biological process > Nucleoside, nucleotide and nucleic acid metabolism

PANTHER CATEGORY INFORMATION ②

Name: Nucleoside, nucleotide and nucleic acid metabolism

Definition: Metabolic processes of nucleotides and nucleic acids, including the

breakdown and biosynthesis of nucleosides, nucleotides and nucleic

acids.

Category ID: BP00031

Child: Chromatin packaging and remodeling

DNA metabolism

Metabolism of cyclic nucleotides

Nucleoside, nucleotide and nucleic acid transport

Other nucleoside, nucleotide and nucleic acid metabolism

Pre-mRNA processing Purine metabolism Pyrimidine metabolism RNA catabolism

RNA catabolism RNA localization

Regulation of nucleoside, nucleotide metabolism

Reverse transcription mRNA transcription rRNA metabolism tRNA metabolism

Number Subfamilies/Families: 3773

GENE ONTOLOGY™ MAPPING

Co Name CO ID Manning





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Research Tools

Score proteins against the PANTHER HMM library, use PANTHER to do gene expression analyses, and download PANTHER tools and data.

Gene Expression Data Analysis

Analyze gene lists, and expression data files with PANTHER. Map lists to PANTHER molecular function and biological process categories, as well as biological pathways. Overlay your results on pathway diagrams to visualize the relationships between genes/proteins in known pathways.

PANTHER scoring

Score proteins against the entire PANTHER library of over 38,000 HMMs to obtain PANTHER classifications and alignments.

Evolutionary analysis of coding SNPs

Estimates the likelihood that a particular nonsynonymous coding SNP will cause a functional impact on the protein, as described in <u>Thomas et al., 2003</u> and <u>Thomas & Kejariwal, 2004</u>.

Downloads

Download the entire PANTHER HMM library, tools to run PANTHER scoring on your own system, Cell Designer to visualize pathways, and more.

Conclusion

- To characterize the function of proteins is important.
- For this, PANTHER is a strong and powerful hunter.

Thanks for your attention

Nelson