



**A REPORT ON GENETIC DATA ANALYSIS ON
ACRAL LENTIGINOUS MELANOMA
GUNDLAPALLI SANDEEP KUMAR**

**DEPARTMENT OF BIO INFORMATICS
SCHOOL OF BIO AND CHEMICAL ENGINEERING
SATHYABAMA UNIVERSITY
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CHENNAI - 600119 . TAMIL NADU
DECEMBER TO APRIL 2021**

A REPORT ON GENETIC DATA ANALYSIS ON ACRAL LENTIGINOUS MELANOMA

Submitted in partial fulfilment of the requirements for the
award of

Bachelor of Technology Degree in
BIO INFORMATICS

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ACKNOWLEDGEMENT

First and foremost, I would like to thank my supervisor Dr. Daniel Alex Anand for his invaluable guidance and support throughout the course of my project . Without his valuable encouragement and motivation, this internship would not have been such a success. I thank him for letting me explore, experience and learn through mistakes in the lab without any kind of hesitation.

Special thanks to my Guide Dr Jemmy Jacob for his constant support from my first year of college until now. I thank him for the trust and the hope he gave me to attain my goals and also for entrusting this research internship to me. The experience and knowledge that I have gathered through this internship and my project works till now would have not been possible, if it was not for his motivation and guidance.

“WORKING ON MY SELF , BY MYSELF , FOR MYSELF ”

I thank Ms. Swetha Sunkar , Ms. Jayanthi for being a pillar of support and for navigating us from day one until now.

I thank our late Colonel Dr. Jeppiar, Chancellor Tmt Dr. Remibai Jeppiar, Pro-Chancellor Dr. Mariazeena Johnson, President Dr. Marie Johnson, Pro Vice Chancellor Dr. T Sasi Prabha, Dr. Preethi Seshadri, Dr. A. Chitra Devi, Dean Dr. Anima Nanda, Head of the Department Dr. jemmy Jacob and Swetha Sunkar and Dr Alex Anand Counsellor and year co- ordinator Dr. Jayanthi and all the faculty members for helping me throughout the course and for supporting my every step.

ABSTRACT

The report in genetic analysis contains briefly explained chapters which explains my Project .

The content of all chapters explain the practical works and the Through data analysis tools through laboratory work .

This project focused mainly on the Genetic Data Analysis on the Acral Lentiginous Melanoma . A large gain of knowledge on the Analysis related assays was achieved during the period of Project . The principle, working and interpretation of the data for various sophisticated equipments were learnt.

The report gives a brief on the how gene data is retrieved , handling, extracting the data regarding the genes Structural analysis . Which is followed by a deep explanation on the why only these gene are mainly affecting for this disease and , ratios Network statistics , Pathways , Different process ,GDA summary results . Also, the experience gained by visualising 2D and 3D Structures has also been explained briefly.

APPROVAL

It is to hereby certify that I have read this report entitled “**GENETIC DATA ANALYSIS ON ACRAL LENTIGNIOUS MELANOMA**” and in my opinion it is satisfactory in terms of scope, quality and presentation.

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Date:

DECLARATION

I hereby declare that the dissertation titles “**GENETIC DATA ANALYSIS ON ACRAL LENTIGNIOUS MELANOMA** ” submitted by me is of my original report work based on my experience in the hosting organisation. It does not form part of my any previous dissertations, report submitted to this university or any other universities.

Place:

Date:

Gundlapalli Sandeep Kumar

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CHAPTER 1

INTRODUCTION

1.1 OVERVIEW OF THE REPORT

In the recent years due to acral lentiginous melanoma the death rate is increased to 21 % to 24%. Well it is caused only to 2- 4% of the entire melanoma patients but the death rate is high when compared to other melanoma. which is getting increased day to day well the ALM is known as Acral lentiginous melanoma (is a type of malignant melanoma. Malignant melanoma is a form of skin cancer that happens when the skin cells called melanocytes become cancerous. Melanocytes contain your skin color. In this type of melanoma, the word “acral” refers to the occurrence of the melanoma on the palms or soles. The word “lentiginous” means that the spot of melanoma is much darker than the surrounding skin. It also has a sharp border between the dark skin and the lighter skin around it. This contrast in colour is one of the most noticeable symptoms of this type of melanoma. ALM is the most common type of melanoma in people with darker skin and those of Asian descent.

A tumour will continue to grow and spread until its removed. Unlike other forms of melanoma, acral lentiginous melanoma is not associated with excess sun exposure. It's believed that genetic mutations contribute to the development of acral lentiginous melanoma.

The easiest ways to describe the acral lentiginous melanoma is based on these five

ABCDEs OF MALIGNANT MELANOMA

ASYMMETRY



BORDERS



COLOR



DIAMETER



ELEVATION



CHAPTER 2

LITERATURE REVIEW

2.1 ACRAL LENTIGNIOUS MELANOMA

Acral lentiginous melanoma (ALM) may be a distinct variant of melanoma with a predilection for the soles, palms, and nail beds. This melanoma has characteristic histologic features, and its biologic behavior is analogous thereto of nodular melanoma. It occurs predominantly within the sixth, seventh, and eighth decades of life, with a peak incidence within the seventh decade for males and within the sixth decade for females. Diagnosis of ALM during the radial growth phase is usually difficult, and it's going to not be recognized initially, but treatment during this phase offers a superb prognosis. there's a high incidence of regressive changes and desmoplasia in ALM, these changes, along side the anatomic peculiarities of nail beds, palms, and soles as compared with other skin areas, make it difficult to work out the Clark's level and to live the depth of invasion. Wide local excision with lymph gland dissection is suggested for subungual melanomas measuring quite 1.00 mm and for lesions showing severe regression. Volar melanomas but 1.00 mm deep and people within the radial growth phaswitminmainvasion require only wide local excision.

TERT GENE

In Acral melanoma, the telomerase polymerase (TERT) promoter mutations, that have emerged because the prominent somatic alterations, accompany the markers of poor patient outcome . together with BRAF/NRAS mutations, the noncoding TERT promoter mutations in primary tumors were shown to end in poor disease-free and melanoma-specific survival . The extension of the study to live the effect of individual TERT promoter mutations, unexpectedly, resulted within the discovery that the less frequent -138/-139CC > TT tandem mutation related to the worst disease-free and melanoma-specific survival in stage I and stage II patients. Of the three main TERT promoter alterations, the presence of the -146C > T mutation in tumors had the smallest amount effect on patient survival. The effect of the -138/-139CC > TT tandem mutation was particularly enhanced together with the BRAF/NRAS mutations

WRN GENE

The elevated risk of melanoma in WS provides a striking example of bizarre histology. The melanoma seen in WS patients is exclusively acral lentiginous melanoma (ALM), a relatively rare melanoma subtype that arises on the palms and soles, or in mucosa of the cavity or esophagus. the danger of ALM is most clearly elevated in Japanese WS patients. this means the existence of patient- and population-specific modifiers for ALM within the absence of WRN function. A final expression of elevated cancer risk and predisposition in WS is that the occurrence of multiple tumors: there are numerous reports of multiple, concurrent, or sequential neoplasms of various histology; for instance , thyroid carcinoma and osteosarcoma, with up to 5 neoplasms having been reported in individual patients. Estimates of the increased risk of neoplasia in WS patients range from ~30-fold elevated overall lifetime risk across all tumor types to ~ 1000-fold elevated risk for acral lentiginous melanoma

BRAF GENE

BRAF variants play a smaller role in acral melanoma (10%-35% of cases). Both typical V600E and other mutations (eg, V600L) are reported. Alternative BRAF mutations to V600E occurred in 5% of cases during a recent study. A molecular sub classification of acral melanoma supported BRAF mutation was proposed: acral melanoma with typical BRAF mutations observed in cutaneous melanoma, potentially aware of BRAF inhibitors; and acral melanoma with non-BRAF mutations with other potentially actionable targets. This study also found that acral melanomas with BRAF mutations were less likely to be of the acral lentiginous melanoma subtype.

KIT GENE

The presence of various clones within an equivalent tumor seems to influence the aggressiveness of tumors. Patients with mutations within the KIT gene have shown an honest response to tyrosine kinase inhibitor therapy. We tested the hypothesis of intra tumor heterogeneity through analysis of KIT gene mutations in ALM and determined the correlation between KIT mutations and demographic, clinical, and histopathological variables. Twenty-five ALM samples were examined. We selected up to four different regions per tumor for sequencing by the Sanger method for analysis of KIT gene exon 11 and exon 13 mutations. Advanced lesions were predominant, and therefore the main histopathological characteristics of lesions were Breslow index >4.0 mm. No significant correlations between histopathological variables and either KIT mutations or intra tumor heterogeneity were observed. The hypothesis of intra tumor heterogeneity of KIT gene mutations in acral lentiginous melanoma was supported.

KRAS GENE

Recent approaches awaken the hope to use KRAS inhibition (KRASi) as a clinical tool. during this study, we identified wild-type KRAS as a completely unique therapeutic target in melanoma. KRASi functions synergistically with BRAF inhibition to scale back melanoma proliferation and to induce apoptosis independently of BRAF mutational status. Moreover, acquired resistance to BRAF inhibitors in melanoma depends on dynamic regulation of KRAS expression with subsequent AKT and extracellular-signal regulated kinase activation and may be overcome by KRASi. this means KRASi as novel approach in melanoma-alone or together with other therapeutic regimes.

CDKN2A GENE

Deletions within the 9p21 region where the CDKN2A gene is found are widely detected . However, other genes from this region might be implicated in melanoma since retention of the CDKN2A locus has been found in tumours with deletions at one or each side of CDKN2A . Other reported aberrations include large amplifications of 12q , 7q or 20q and gains localized at 5p15, 11q13, 11q14 and 22q11-13

9p21 alterations were detected in 69% of tumours, one sample did not yield a result . Whilst five tumours carried focal deletions of CDKN2A, CDKN2B and/or MTAP, 6 showed loss of the 9p21 region. No mutations were detected in CDKN2A.

H3P10 GENE

Malignant transformation and metastatic spread are known to be mediated by both genetic abnormalities[1] and epigenetic alterations.[2] Epigenetic's, defined as heritable change in organic phenomenon occurring independent of changes in primary DNA sequence, is strongly implicated within the underlying mechanisms of cancer progression.[3] Microenvironment-mediated epigenetic regulation of cancer-related organic phenomenon through DNA methylation, histone modification, and chromatin compartments is now believed to require part during a broad spectrum of cancer behaviors starting from initiation to phenotypic alteration.[4] Histone modifications, including methylation, phosphorylation, and acetylation are covalent post-translational modifications to histone proteins. These modifications allow histones to change the structure of chromatin, leading to transcriptional activation or repression, that affect changes in cell behavior. for instance , histone H3 lysine 4 di tri- methylation (H3K4me2/3) and histone H3 acetylation (H3ac) are generally related to gene activation,[5] whereas H3K27me, which marks active cis-regulatory elements, is related to gene inactivation

SLN GENE

Microarray experiments were performed to screen SLN genes in recurrence (N = 39) versus non-recurrence (N = 58) groups within the training dataset. Quantitative reverse-transcriptase polymerase chain reaction (RT-PCR) assay was applied to verify the expression of selected SLN genes, which were further verified using an independent validation cohort (N = 30). Area under the receiver operating characteristic function (AUC) was calculated to guage prognostic accuracy of the chosen SLN gene panel, and therefore the prognostic value of our SLN gene signature was also compared with the present American Joint Committee on Cancer (AJCC) staging system.

We identified two SLN genes (PIGR and TFAP2A) that provided high prognostic accuracy in SLN-positive melanoma patients (AUC = 0.864). These two SLN

genes, along side clinicopathological features, can differentiate the high- and low-risk groups in node-positive melanoma patients during this cohort.

PTEN GENE

Phosphatase and tensin homologue (PTEN) may be a tumor suppressor located on chromosome 10q23.3 that encodes the protein PTEN, which dephosphorylates lipids and proteins, therefore inhibiting the PI3K pathway. PTEN regulates cell growth and survival through Akt-dependent and -independent pathways; formation of tumor cells is related to alterations of PTEN acting within the Akt-independent pathway, although Akt could also be involved indirectly as well³. Akt may be a protein kinase B that functions as a signaling molecule and receives a phosphate group from PIP₃; it phosphorylates proteins like Bad, caspase-9, and mdm2, and also accelerates degradation of p53, a tumor suppressor⁴. PTEN/PI3K/Akt also promotes p53 translation and protein stability, suggesting that additional mechanisms could also be involved within the Akt-mediated regulation of p53 in tumors⁵.

We have analyzed the degree of expression of PTEN, Akt, and p53 in several sorts of acral melanocytic lesions including benign acral nevi, acral dysplastic nevi, acral melanoma within the radial growth phase and acral melanoma with a vertical growth component, and our results suggest a possible role of the above mentioned proteins within the formation of acral melanoma.

PD1 GENE

PD-L1 expression within the tumor immune microenvironment is recognized as both a prognostic and predictive biomarker in patients with cutaneous melanoma, a finding closely associated with its adaptive (IFN- γ -mediated) mechanism of expression. Approximately 35% of cutaneous melanomas express PD-L1, however, the expression patterns, levels, and prevalence in rarer melanoma subtypes aren't well described. We performed immunohistochemistry for PD-L1 and CD8 on 200 formalin-fixed paraffin-embedded specimens from patients with acral melanoma. Most studies in Acral melanoma patients that have examined the connection between PD-L1 expression within the pretreatment TME and response to anti-PD-1/PD-L1 have focused on conventional cutaneous melanoma, ie, melanoma arising on hair-bearing, non-chronically sun-damaged skin. Approximately two-thirds of those melanomas harbor BRAF mutations, and are most frequently classified histologically as superficial spreading and nodular melanomas. The chi-square test was used to assess differences within the proportion of PD-L1(+) tumors among all melanoma subtypes. The Kruskal-Wallis test was used to compare the amount of PD-L1 expression across all subtypes. The Fisher's exact test was used to compare the proportion of samples with CD8+ T-cell infiltration in PD-L1(+) and PD-L1(-) samples.

.

PDGFRA GENE

The incidence of melanoma is increasing worldwide. almost like KIT, PDGFRA may be a type III receptor tyrosine kinase (RTK) and a possible target for tyrosine kinase inhibitors (TKIs), like imatinib and crenolanib, in cancer treatments. Genetic mutations of PDGFRA are reported in many cancers, but its mutations in melanomas haven't been well studied. Moreover, sensitivity of PDGFRA mutants to TKIs has not been fully evaluated. Defined sensitivity of mutant PDGFRA to TKIs might provide stratification criteria for patients with melanoma, who would enjoy TKI-based targeted therapy. Our study demonstrates that PDGFRA

mutations are detected during a small population of melanoma patients, primarily in acral and mucosal melanomas. Our study suggests that a subgroup of patients with melanoma harboring PDGFRA mutations may enjoy TKIs, casting new light within the selection of melanoma patients sensitive to TKIs, like imatinib and crenolanib.

FASL GENE

melanoma cells expressing Fas ligand (FasL) could kill Fas-positive lymphocytes, suggesting that FasL expression was an important factor for melanoma cell survival in vivo . These findings led us to research apoptosis, and to histochemically analyze involvement of Fas and FasL within the induction of apoptosis, in human melanoma tissues. the odds of terminal deoxynucleotidyl transferase-mediated biotin-dUTP nick end-labeling -positive melanoma cells and of proliferating cell nuclear antigen-positive melanoma cells in melanoma tissues were greater than those in melanocytes in uninvolved skin and nevus cells in nevi tissues. The infiltrating lymphocytes around melanomas were also TUNEL positive. Immune histochemistry revealed expression of Fas and FasL in melanoma cells and lymphocytes, whereas no Fas or FasL expression was detected in normal skin melanocytes and nevus cells. There was significant correlation between Fas-positive indices and TUNEL indices in melanoma tissues. Moreover, TUNEL-, Fas-, and FasL-positive indices of melanoma cells

HLA-DQA1 GENE

The association of melanoma with HLA class II loci is under extensive debate. Different investigators have found discrepant results thanks to , a minimum of partially , sample size, patient series heterogeneity, choice of control population and differences within the techniques employed for the detection of HLA antigens and alleles.

This study was designed to analyse the possible association of melanoma with HLA class II loci with reference to different clinic pathological factors and to research other risk factors for melanoma susceptibility, like HLA homozygosity. Patients and methods: HLA-DRB1, -DQA1 and -DQB1 genotyping was performed for 117 eastern Spanish patients presenting with primary melanoma.

Although there have been no significant alterations within the phenotypic frequencies of HLA-DQA1, -DQB1 or -DRB1 alleles in any subgroup of patients in comparison with controls, patients exhibited a statistically significant increase in HLA-DQA1 homozygosity rate. This DQA1 homozygosity-specific association was particularly hooked in to some features in melanoma patients like light hair colour, skin type I or II, early age at diagnosis, absence of atypical naevi, or absence of atypical naevus syndrome phenotype (aetiological fractions about 10-20%). Analysis of homozygosity for single DQA1 alleles showed an increased homozygosity rate for DQA1*0505 and DQA1*0301 as compared with controls. These DQA1 alleles are in strong linkage disequilibrium with DQB1*0301 in white populations, and DQB1*0301 homozygous individuals were significantly increased in red in or fair-haired patients

HFM GENE

Subungual melanoma (SUM) may be a subgroup of HFM that arises from structures within the nail apparatus. SUM is exceedingly rare, representing 0.7–3.5% of all MMs in Caucasian populations, with an annual incidence of roughly 0.1 per 100 000 . These tumors develop totally on big toe and thumb. SUM seems to be not associated with sun exposure, however, in Australian Melanoma Genome

Project UVR signatures on acral melanomas occurred most often in subungual parts . Both HFM and SUM seem to possess poorer survival outcomes comparing to MMs of the opposite sites, with 5-year overall survival (OS) within the range 20–60%, although ‘Lieberherr’s in meta-analysis reports 77%. Poor survival rates are partially as a results of delayed diagnosis since frequent misdiagnosis .

SNIP1 GENE

This gene encodes a protein that contains a coiled-coil motif and C-terminal forehead-associated (FHA) domain. The encoded protein functions as a transcriptional coactivator that increases c-Myc activity and inhibits transforming protein beta (TGF-beta) and nuclear factor kappa-B (NF-kB) signaling. The encoded protein also regulates the steadiness of cyclin D1 mRNA, and should play a task in cell proliferation and cancer progression. Mutations during this gene are a explanation for psychomotor retardation, epilepsy, and craniofacial dysmorphism (PMRED).SNIP1 (Smad Nuclear Interacting Protein 1) may be a Protein Coding gene. Diseases related to SNIP1 include Psychomotor Retardation, Epilepsy, And Craniofacial Dysmorphism and Benign Epilepsy With Centrotemporal Spikes. Among its related pathways are TGF-beta Signaling Pathway (WikiPathways) and Regulation of nuclear SMAD2/3 signaling. a crucial paralog of this gene is SLC4A1APRequired for pre-mRNA splicing as component of the spliceosome (PubMed:29360106). Down-regulates NF-kappa-B signaling by competing with RELA for CREBBP/EP300 binding. Involved within the microRNA (miRNA) biogenesis. could also be involved in cyclin-D1/CCND1 mRNA stability through the SNARP complex which associates with both the 3'end of the CCND1 gene and its mRNA

1.2 OBJECTIVES OF STUDY

1.2.1 GENERAL OBJECTIVE

To study the different types of genes which are associated for causing the Acral lentiginous melanoma cancer . Analysing different data and structural analysis for which it is causing the main disease factor in homo sapiens .

1.2.2 SPECIFIC OBJECTIVE

- 1) Genetic data extraction from DisGenet for acral lentiginous melanoma
- 2) Statistical data analysis from Panther DB for the specific genes which are retrieved from the DisGenet
- 3) Gene expression analysis from Network Analyst for the genes which produces 3d and 2d visualisation for the connected Genes
- 4) Protein - Protein interactions from STRING DB were used for construction of biological network for the given Genes
- 5) With the help of all associated data by concluding the specific genes which are mainly causing the disease

1.3 HYPOTHESIS

Learning all the network analysis and statistical analysis from the data base and concluding the genes mainly which are affecting for the production of disease

CHAPTER 3

METHODOLOGY

DisGeNET :

The comprehensive repositories of human gene-disease associations

DisGeNET contains a compilation of genes associated to diseases, that comes from different publicly available databases: the Comparative Toxicogenomics DatabaseTM (CTDTM), UniProt/SwissProt, the Cancer Genome Interpreter, Orphanet, the Mouse Genome Database (MGD), PsyGeNET, Genomics England, ClinGen, and therefore the Rat Genome Database (RGD). The variant-disease associations in DisGeNET are annotated from ClinVar, the NHGRI-EBI GWAS Catalog, and therefore the GWAS db. It also contains gene-disease, and variant-disease associations retrieved using text mining approaches .

DisGeNET covers information on all disease areas (Mendelian, complex and environmental diseases). With quite 400 000 genotype-phenotype relationships from different origins integrated and annotated with explicit provenance and evidence information, DisGeNET may be a valuable knowledge and evidence-based discovery resource for Translational Research. DisGeNET is an open access resource that creates available a comprehensive knowledge domain on disease genes and different tools for his or her exploitation and analysis.

DisGeNET is out there through an internet interface, a Cytoscape plugin,[2] as linked data for the Semantic Web, and supports programmatic access to its data. These valuable set of tools allows investigating the molecular mechanisms underlying diseases of genetic origin,[3] and are designed to support the info exploitation from different perspectives and to satisfy the requirements of various sorts of users, including the bioinformaticians, biologists and healthcare practitioners. integration is performed by means of gene and disease vocabulary mapping and by using the DisGeNET gene-disease association ontology as described below (2.4).In DisGeNET, the info is grouped consistent with their type and level of curation: CURATED (containing gene-disease associations from human expert curated data sources), PREDICTED (containing gene-disease

associations from animal model repositories), INFERRED (GDAs inferred from HPO and from VDAs), and every one (containing CURATED, PREDICTED, INFERRED, and data derived from text mining the biomedical literature). For the up-to-date list and outline of knowledge sources available in DisGeNET, please visit the DisGeNET Discovery Platform Website DisGeNET database integrates over 400 000 associations between > 17 000 genes and > 14 000 diseases from human to animal model expert curated databases with text mined GDAs from MEDLINE employing a NLP-based approach.[4] The highlights of DisGeNET are the info integration, standardisation and a fine-grained tracking of the provenance information. the mixing is performed by means of gene and disease vocabulary mapping and by using the DisGeNET association type ontology

The screenshot displays the DisGeNET Discovery Platform interface. At the top, there are three tabs: 'diseases' (selected), 'genes', and 'variants'. Below the tabs is a search bar with the placeholder text 'enter diseases separated by double colon (;)'. To the right of the search bar is a magnifying glass icon and a close button (X). Below the search bar, there are examples: 'Examples: C0001080, Alzheimer's Disease, D009765, 213200' and a note 'Hold "ctrl" key for selecting multiple diseases'. Below the search bar, there is a text input field containing 'Acral Lentiginous Malignant Melanoma'. Below the input field, there is a section titled 'Name: Acral Lentiginous Malignant Melanoma' with various identifiers: 'UMLS CUI: C0346037', 'Type: disease', 'MeSH Class: Neoplasms; Skin and Connective Tissue Diseases', 'MeSH: None', 'OMIM: None', 'Semantic Type: Neoplastic Process', 'Phenotypic abnormality: Abnormality of the integument; Neoplasm', and 'Disease Ontology: disease of anatomical entity; disease of cellular proliferation'. Below this section, there is a button labeled 'Similar diseases'. Below the button, there is a list of links: 'Summary of Gene-Disease Associations', 'Evidences for Gene-Disease Associations', 'Summary of Variant-Disease Associations', 'Evidences for Variant-Disease Associations', 'Summary of Disease-Disease Associations', and 'Disease Mappings'. At the bottom, there is a section titled 'General links' with a list of links: 'Summary of All Gene-Disease Associations.', 'All Evidences supporting the Gene-Disease Associations.', 'Summary of All Variant-Disease Associations.', and 'All Evidences supporting the Variant-Disease Associations.'

PANTHER DB

The PANTHER (protein analysis through evolutionary relationships) arrangement may be a large curated biological database of gene/protein families and their

functionally related subfamilies which will be used to classify and identify the function of gene products.[1] PANTHER is a component of the Gene Ontology Reference Genome Project[2] designed to classify proteins and their genes for high-throughput analysis.

Proteins are classified consistent with family, molecular function, organic process and pathway. It's one among the databases feeding into the EMBL Bioinformatics Institute's InterPro database.[4]—Application of PANTHER the foremost important application of PANTHER is to accurately infer the function of uncharacterized genes from any organism supported their evolutionary relationships to genes with known functions. By combining gene function, ontology, pathways and statistical analysis tools, PANTHER enables biologists to research large-scale, genome-wide data obtained from the present advance technology including: sequencing, proteomics or organic phenomenon experiments. Shortly, using the info and tools on the PANTHER, users are going to be ready to Obtain information a few particular gene of interest.

Discover protein families and subfamilies, pathways, biological processes, molecular functions and cellular components.

Create lists of genes associated with a specific protein family/subfamily, molecular function, organic process or pathway.

Analyze lists of genes, proteins or transcripts

The process for data generation is split into three steps:

Family Clustering

Phylogenetic Tree Building

Annotation of Tree Nodes

GENE LIST ANALYSIS

This tab is chosen by default because this the foremost frequently used option. you'll enter valid IDs within the box or upload a file, then select list type, choose organism of interest and choose the sort of study .

SEQUENCE SEARCH

By putting the protein sequence within the Sequence Search box, PANTHER will search against a library of family and subfamily HMMs, and return the subfamily that best matches the sequence. If you click on the subfamily name, it'll give some details .

Keyword search

Entering an enquiry term within the keyword search box, PANTHER will offer you the amount of records matching your keyword for genes, families, pathways and ontology terms. you'll filter them by determining the species of interest or by refining the search using other criteria. to look at the small print of the gene, you want to click on the gene identifier.

BROWSE

Using this folder tab and by selecting the ontology you're curious about , you'll browse different classification. it's also possible to pick quite one ontology; during this case, the results will meet the standards from all the selections. you're ready to see the association between ontology terms and PANTHER families, subfamilies and training sequences.

a comprehensive network visual analytics platform for organic phenomenon analysis

The data files you upload for analysis also as any analysis results, aren't downloaded or examined in any way by the administrators .

List(s) of genes or proteins: one or more lists of gene or protein IDs with optional expression profiles. Each gene should be during a row. Please ask our example data for more details.

Single organic phenomenon data table: a knowledge table containing expression values gene/probe intensities from microarray, counts from RNA-seq saved as a tab delimited document (.txt) with rows for features (genes/probes) and columns for samples. The tab delimited file are often generated from any spreadsheet program. More details are provided within the following sections.

Multiple organic phenomenon tables: organic phenomenon data from multiple studies collected under similar conditions are often integrated during a meta-analysis.

Network file: users can upload network files generated with a special software to perform network visualisation in NetworkAnalyst. More details on network file formats are provided within the corresponding questions below.

Short-read RNA-Seq fastq files: users can upload single or paired-ends RNA-Seq fastq files and perform quality checking, trimming, mapping using well-established Galaxy pipeline

NETWORK ANALYST

DIFFERENTIAL ANALYSIS

Limma may be a popular method for differential analysis that was first developed for microarray differential analysis. It addresses the matter of low sample sizes typical to whole-transcriptome studies by using the entire expression profile to form more stable estimates of organic phenomenon variance. EdgeR and DESeq2 were both developed to research RNA-seq data. All three methods are well-established and will give similar results. Please note:

EdgeR and DESeq2 are only designed for RNA-seq data and can be disabled for microarray data.

Due to high computational resources required, DESeq2 are going to be disabled when your dataset contain over 50 samples.

NetworkAnalyst currently offers three different approaches for module detection - the WalkTrap, InfoMap, and Label Propagation algorithms. the overall idea behind the Walktrap Algorithm is that if you perform random walks on a graph, a better number of walks are more likely to remain within a gaggle of nodes that are highly connected to every other because there are only a couple of edges that lead outside of them. The Walktrap algorithm runs many short random walks and uses the results to detect small modules, then merge separate smaller modules during a bottom-up manner. The InfoMap Algorithm is additionally supported random walks, which it uses to attenuate the hierarchical map equation for various partitions of the network into modules. The Label Propagation Algorithm works by randomly assigning a singular label to each node. On each iteration, node labels are updated to match the one that the utmost of its neighbours has. The algorithm converges when each node has an equivalent label because the majority of its neighbours.

The networks are generated by first mapping the many genes/proteins to the chosen underlying database. an enquiry algorithm is then performed to spot proteins that directly interact with the uploaded genes/proteins.

The seeds and their interaction partners are returned to create the subnetworks. This approach will typically return one giant subnetwork with multiple

smaller ones. Most subsequent analysis is performed on the continent. Note, networks with but 3 nodes are going to be excluded.

GSEA may be a statistical procedure that determines whether a predefined gene set (GO, KEGG, etc) demonstrates statistically significant difference between two groups. Taking as input an inventory of ranked genes and a gene set, it's at whether the genes from the gene set are randomly distributed within the ranked list or significantly enriched within the top and bottom extremes of the ranked list. within the following schema, the gene set A is significantly enriched, while gene set B represents a case where the genes are more randomly distributed. In contrast to ORA, GSEA can detect weakly coordinated changes of organic phenomenon in sets of functionally related genes because it's not limited by the difficulty of losing information when setting a threshold.



NetworkAnalyst -- a comprehensive network visual analytics platform for gene expression analysis

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Genes/protein list(s) upload

Please upload one or multiple lists of genes/proteins for network-based analysis and other data visualization, with built-in support for various functional enrichment analysis. For first time users, you are advised to explore the features using one of our example data sets.

Specify organism

---Not specified---

Set ID type

--- Not Specified ---

Copy-and-paste one or more gene lists (Insert a "/" line to indicate the start of a new gene list, or [click here](#) to upload multiple gene list files)

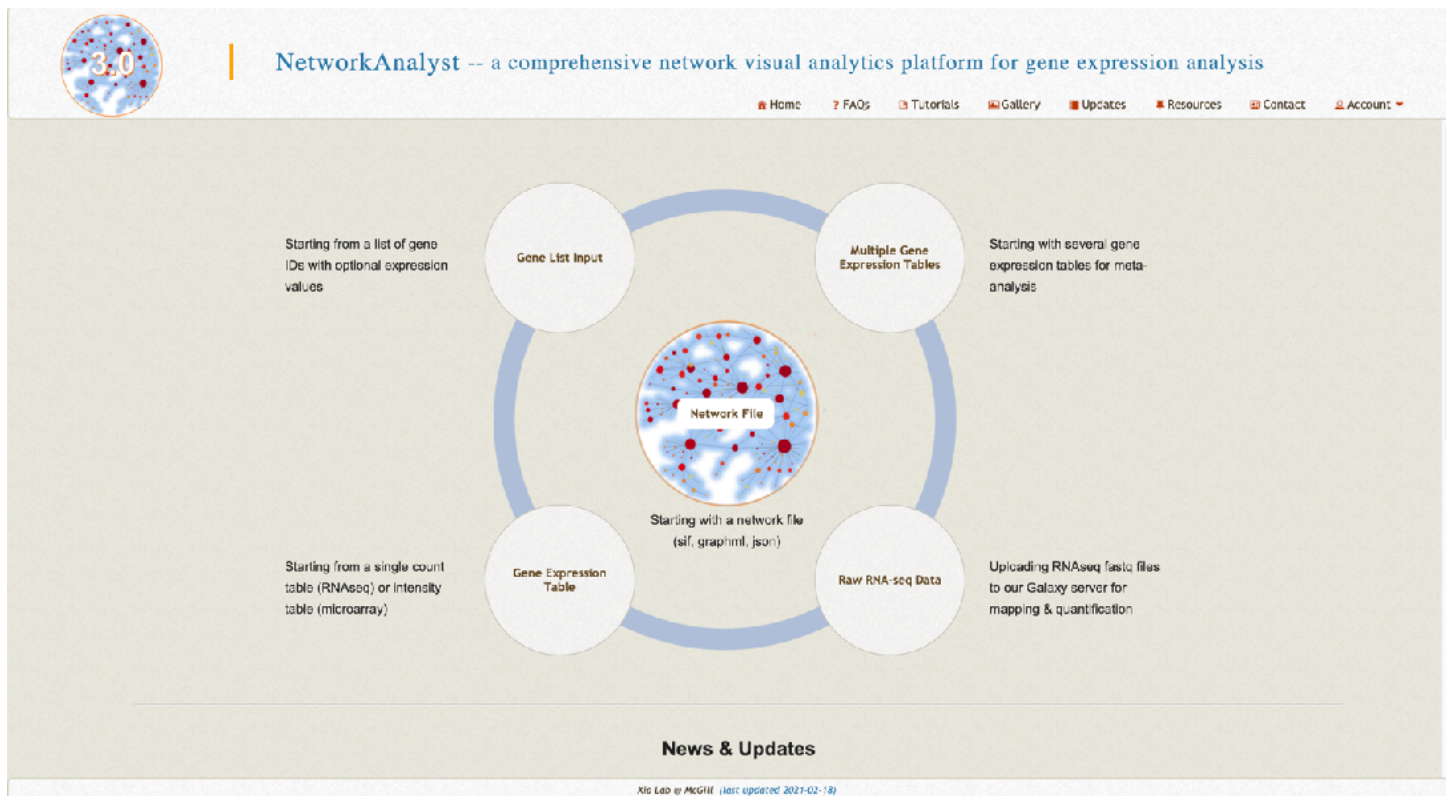
Try Example

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Xie Lab @ MCGH | Last updated 2021-02-16



STRING DB

STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) may be a biological database and web resource of known and predicted protein–protein interactions.

The STRING database contains information from numerous sources, including experimental data, computational prediction methods and public text collections. it's freely accessible and it's regularly updated. The resource also serves to spotlight functional enrichments in user-provided lists of proteins, employing a number of functional classification systems like GO, Pfam and KEGG. the newest version 11b contains information on about 24,5 million proteins from quite 5000 organisms. STRING has been developed by a consortium of educational institutions including CPR, EMBL, KU, SIB, TUD and UZH. Contents

Usage

Protein–protein interaction networks are a crucial ingredient for the system-level understanding of cellular processes. Such networks are often used for filtering and assessing genomics data and for providing an intuitive platform for annotating structural, functional and evolutionary properties of proteins. Exploring the anticipated interaction networks can suggest new directions for future experimental research and supply cross-species predictions for efficient interaction mapping .

Protein–protein interaction network visualised by STRING. during this view, the color saturation of the sides represents the arrogance score of a functional association

Features

The data is weighted and integrated and a confidence score is calculated for all protein interactions. Results of the varied computational predictions are often inspected from different designated views. There are two modes of STRING: Protein-mode and COG-mode. Predicted interactions are propagated to proteins in other organisms that interaction has been described by inference of orthology. an internet interface is out there to access the info and to offer a quick overview of the proteins and their interactions. Another possibility to access data STRING is to use the appliance programming interface by constructing a URL that contain the request.

Furthermore, STRING also store computationally predicted interactions from: (i) text mining of scientific texts, (ii) interactions computed from genomic features, and (iii) interactions transferred from model organisms supported orthology. All predicted or imported interactions are benchmarked against a standard reference of functional partnership as annotated by KEGG (Kyoto Encyclopedia of Genes and Genomes).

Imported data

STRING imports protein association knowledge from databases of physical interaction and databases of curated biological pathway knowledge (MINT, HPRD, BIND, DIP, BioGRID, KEGG, Reactome, IntAct, EcoCyc, NCI-Nature Pathway Interaction Database, GO). Links are supplied to the originating data of the respective experimental repositories and database resources.

Text mining

A large body of scientific texts (SGD, OMIM, FlyBase, PubMed) are parsed to look for statistically relevant co-occurrences of gene names.

Predicted data

Neighbourhood: Similar genomic context in several species suggest an identical function of the proteins.

Fusion-fission events: Proteins that are fused in some genomes are very likely to be functionally linked (as in other genomes where the genes aren't fused).

Occurrence: Proteins that have an identical function or an event within the same metabolic pathway, must be expressed together and have similar phylogenetic profile.

Coexpression: Predicted association between genes supported observed patterns of simultaneous expression of genes.

STRING may be a database of known and predicted protein-protein interactions.

The interactions include direct (physical) and indirect (functional) associations; they stem from computational prediction, from knowledge transfer between organisms, and from interactions aggregated from other (primary) databases.

Data Sources

Interactions in STRING are derived from five main sources:



SearchDownloadHelpMy Data

Protein by name>

Protein by sequence>

Multiple proteins>

Multiple sequences>

Proteins with Values/Ranks ^{New}>

Organisms>

Protein families ("COGs")>

Examples>

Random entry>

SEARCH

Multiple Proteins by Names / Identifiers

List Of Names: (one per line, examples: #1 #2 #3)

... or, upload a file:

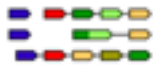
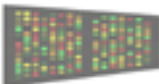
Browse ...

Organism:

auto-detected

[Advanced Settings](#)

SEARCH

 Genomic Context Predictions	 High-throughput Lab Experiments	 (Conserved) Co- Expression	 Automated Textmining	 Previous Knowledge in Databases
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CHAPTER 4

RESULTS AND DISCUSSION

DisGeNET

In The dash board by selecting diseases and giving the name Name: Acral
Lentiginous Malignant Melanoma; CUI: C0346037 :: and giving search giving the
results in different data

Name:

UMLS CUI:

Type:

Disease

MeSH Class:

MeSH:

OMIM:

Semantic Type:

Phenotypic abnormality:

Disease Ontology:

The different types of associations where produced namely

SUMMARY OF GENE - DISEASE ASSOCIATIONS

EVIDENCES FOR GENE - DISEASES ASSOCIATIONS

SUMMARY OF VARIANT - DISEASE ASSOCIATIONS

EVIDENCES FOR VARIANT - DISEASE ASSOCIATIONS

DISEASE MAPPINGS

SUMMARY OF GENE - DISEASE ASSOCIATIONS

Disease	Disease_id	Gene	Gene_id	UniProt	ie_Full_Na	rotein_Cla	diseases	DSI_g	DPI_g	pLI	Score_gda	EL_gda	EI_gda	N_PMIDs	_SNPs_gd	First_Ref	Last_Ref
Acral Lent C0346037	TERT		7015	Q14746	telomeras	Enzyme	703	0.374	0.846	0.99046	0.32		1	2	0	2016	2017
Acral Lent C0346037	WRN		7486	Q14191	WRN RecQ	Enzyme	172	0.524	0.808	0.0000000	0.1			0	0		
Acral Lent C0346037	BRAF		673	P15056	B-Raf prot	Kinase	1228	0.319	0.846	0.99995	0.08		1	8	2	2006	2019
Acral Lent C0346037	KIT		3815	P10721	KIT proto-	Kinase	715	0.366	0.808	0.98087	0.04		1	4	0	2016	2020
Acral Lent C0346037	NRAS		4893	P01111	NRAS prot	Enzyme m	611	0.39	0.808	0.49009	0.02		1	2	0	2016	2019
Acral Lent C0346037	CDKN2A		1029	P42771	Q8 cyclin dependent kin		1314	0.3	0.885	0.39474	0.02		1	2	0	2018	2019
Acral Lent C0346037	H3P10		11548271		H3 histone pseudoge		769	0.35	0.846		0.02		1	2	0	2018	2019
Acral Lent C0346037	LOC11080		11080626		TERT 5' regulatory re		245	0.464	0.731		0.02		1	2	0	2014	2016
Acral Lent C0346037	SLN		6588	O00631	sarcolipin		69	0.612	0.5	0.28701	0.01		1	1	0	2019	2019
Acral Lent C0346037	PTEN		5728	P60484	phosphata	Enzyme	1349	0.305	0.923	0.25651	0.01		1	1	0	2013	2013
Acral Lent C0346037	PLD1		5337	Q13393	phospholipase D1		104	0.576	0.731	0.0000000	0.01		1	1	0	2003	2003
Acral Lent C0346037	PDGFRA		5156	P16234	platelet di	Kinase	452	0.415	0.808	1	0.01		1	1	0	2016	2016
Acral Lent C0346037	FASLG		356	P48023	Fas ligand	Signaling	398	0.43	0.885	0.18345	0.01		1	1	0	2001	2001
Acral Lent C0346037	HLA-DQA1		3117	P01909	major hist	Immune re	427	0.416	0.846	0.023947	0.01		1	1	0	1997	1997
Acral Lent C0346037	HFM		170474		Hemifacial	microsom	22	0.722	0.385		0.01		0	1	0	2012	2012
Acral Lent C0346037	SNIP1		79753	Q8TAD8	Smad nuclear interac		45	0.682	0.462	0.42167	0.01		1	1	0	2010	2010

EVIDENCE FOR GENE - DATA ASSOCIATION

Disease	Disease_id	Gene	Gene_id	Score_gd	Association_T	Type	Original_Di	Sentence	PMID	PMID_Year
Acral Lent	C0346037	PLD1	5337	0.01	AlteredExpression	BEFREE	To elucidate	12839565	2003	
Acral Lent	C0346037	CDKN2A	1029	0.02	Biomarker	BEFREE	Loss of ex	30778854	2019	
Acral Lent	C0346037	LOC110801	110806263	0.02	Biomarker	BEFREE	In this stu	24588324	2014	
Acral Lent	C0346037	KIT	3815	0.04	GeneticVariation	BEFREE	We tested	31393283	2020	
Acral Lent	C0346037	FASLG	356	0.01	Biomarker	BEFREE	We address	11603392	2001	
Acral Lent	C0346037	TERT	7015	0.32	GeneticVariation	BEFREE	<span clas	26709572	2016	
Acral Lent	C0346037	NRAS	4893	0.02	Biomarker	BEFREE	Novel stud	29512974	2019	
Acral Lent	C0346037	H3P10	115482713	0.02	AlteredExpression	BEFREE	Acral Spitz	29537991	2018	
Acral Lent	C0346037	BRAF	673	0.08	GeneticVariation	BEFREE	BRAF muta	26138035	2015	
Acral Lent	C0346037	H3P10	115482713	0.02	Biomarker	BEFREE	Loss of ex	30778854	2019	
Acral Lent	C0346037	LOC110801	110806263	0.02	GeneticVariation	BEFREE	<span clas	26709572	2016	
Acral Lent	C0346037	PDGFRA	5156	0.01	Biomarker	BEFREE	TERT prom	26709572	2016	
Acral Lent	C0346037	BRAF	673	0.08	GeneticVariation	BEFREE	The KIT, N	23993026	2013	
Acral Lent	C0346037	KIT	3815	0.04	GeneticVariation	BEFREE	TERT prom	26709572	2016	
Acral Lent	C0346037	BRAF	673	0.08	Biomarker	BEFREE	TERT prom	26709572	2016	
Acral Lent	C0346037	HFM	170474	0.01	Biomarker	BEFREE	Compared	22175696	2012	
Acral Lent	C0346037	BRAF	673	0.08	GeneticVariation	BEFREE	In particul	16899595	2006	
Acral Lent	C0346037	KIT	3815	0.04	GeneticVariation	BEFREE	However, :	29951919	2018	
Acral Lent	C0346037	BRAF	673	0.08	GeneticVariation	BEFREE	<span clas	31021835	2019	
Acral Lent	C0346037	PTEN	5728	0.01	GeneticVariation	BEFREE	Only one c	23993026	2013	
Acral Lent	C0346037	BRAF	673	0.08	GeneticVariation	BEFREE	The mutat	25766129	2015	
Acral Lent	C0346037	HLA-DQA1	3117	0.01	Biomarker	BEFREE	Moreover,	9174138	1997	
Acral Lent	C0346037	KIT	3815	0.04	Biomarker	BEFREE	Novel stud	29512974	2019	
Acral Lent	C0346037	TERT	7015	0.32	GenomicAlterations	CGI				
Acral Lent	C0346037	BRAF	673	0.08	Biomarker	BEFREE	Novel stud	29512974	2019	
Acral Lent	C0346037	SLN	6588	0.01	GeneticVariation	BEFREE	<span clas	30883783	2019	
Acral Lent	C0346037	BRAF	673	0.08	GeneticVariation	BEFREE	In addition	29951919	2018	
Acral Lent	C0346037	SNIP1	79753	0.01	Biomarker	BEFREE	We obtain	19759547	2010	
Acral Lent	C0346037	TERT	7015	0.32	Biomarker	BEFREE	These find	28373299	2017	
Acral Lent	C0346037	CDKN2A	1029	0.02	AlteredExpression	BEFREE	Acral Spitz	29537991	2018	
Acral Lent	C0346037	NRAS	4893	0.02	GeneticVariation	BEFREE	TERT prom	26709572	2016	
Acral Lent	C0346037	WRN	7486	0.1	Biomarker	HPO				

EVIDENCE FOR VARIANT GENE ASSOCIATION

Disease	Disease_id	Variant	Gene	Gene_id	Risk_allele	Score_vd	abciation_T	Original_D	Sentence	PMID	PMID_Year
Acral Lent	C0346037	rs1134880	BRAF	673		0.02	GeneticVa	BEFREE	The mutat	25766129	2015
Acral Lent	C0346037	rs1134880	BRAF	673		0.02	GeneticVa	BEFREE	BRAF muta	26138035	2015
Acral Lent	C0346037	rs1219133	BRAF	673		0.02	GeneticVa	BEFREE	The mutat	25766129	2015
Acral Lent	C0346037	rs1219133	BRAF	673		0.02	GeneticVa	BEFREE	BRAF muta	26138035	2015

SUMMARY OF VARIANT GENE ASSOCIATION

Disease	Disease_id	Variant	Gene	Gene_id	_diseases_	DSI_v	DPI_v	Chr
Acral Lent	C0346037	rs1134880	BRAF	673	490	0.351	0.84	7
Acral Lent	C0346037	rs1219133	BRAF	673	480	0.354	0.84	7

DISEASE MAPPINGS

CUI	Disease	Vocabulary	Name in Vocabulary	Code
C0346037	Acral Lentiginous Malignant Melanoma	DO	acral lentiginous melanoma	6367
C0346037	Acral Lentiginous Malignant Melanoma	HPO	Acral lentiginous melanoma	HP:0012060
C0346037	Acral Lentiginous Malignant Melanoma	MONDO	acral lentiginous melanoma (disease)	0003865
C0346037	Acral Lentiginous Malignant Melanoma	NCI	Acral Lentiginous Melanoma	C4022
C0346037	Acral Lentiginous Malignant Melanoma	NCI	Acral Lentiginous Malignant Melanoma	C4022
C0346037	Acral Lentiginous Malignant Melanoma	NCI	Adenocarcinoma	TCGA

< 1 - 25 of 318 results >

Gene
TERT
WRN
BRAF
KIT
NRAS
CDKN2A
H3P10
LOC110806263
SLN
PTEN
PLD1
PDGFRA
FASLG
HLA-DQA1
HFM
SNIP1

SUMMARY OF DISEASE DATA ASSOCIATION

Index_disease	Index_disease_id	genes_in	variants_in	Associated_disease	ated_dise	genes_assoc	variants_assoc	shared_genes	Jlg	value_generated	shared_vari	Jlv	value_vari	diseaseid1
Acral Lentiginous M C0346037		16	0	Abdomen distended	CC000731	103	0	1	0.0084745		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Abdominal Pain	CC000737	302	0	4	0.0127388		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Congenital Abnormality	CC000768	1098	0	7	0.0063233		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Multiple congenital anomalies	CC000772	251	0	2	0.0075471		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Spontaneous abortion	CC000786	188	0	1	0.0049261		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Acquired Immunodeficiency Syndrome	CC001175	243	0	2	0.0077821		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Acrokeratosis	CC001202	3	0	1	0.0555555		0	0		C0346037
Acral Lentiginous M C0346037		16	2	Acromegaly	CC001206	138	25	4	0.0266666		2	0.08		C0346037
Acral Lentiginous M C0346037		16	0	Acute pancreatitis	CC001339	435	0	2	0.0044543		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Acute periodontitis	CC001342	130	0	2	0.0138388		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Addison Disease	CC001403	111	0	1	0.0079365		0	0		C0346037
Acral Lentiginous M C0346037		16	2	Adenocarcinoma	CC001418	2235	168	11	0.0049107		2	0.0119047		C0346037
Acral Lentiginous M C0346037		16	0	Adenofibroma	CC001422	8	0	1	0.0434782		0	0		C0346037
Acral Lentiginous M C0346037		16	2	Adenoma	CC001430	1183	103	9	0.0075630		2	0.0194174		C0346037
Acral Lentiginous M C0346037		16	0	Adenosarcoma	CC001442	9	0	1	0.0416666		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Adenovirus Infections	CC001486	145	0	1	0.00625		0	0		C0346037
Acral Lentiginous M C0346037		16	2	Adjustment Disorders	CC001546	9	4	1	0.0416666		2	0.5		C0346037
Acral Lentiginous M C0346037		16	0	Tumors of Adrenal Cortex	CC001618	74	0	2	0.0227272		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Adrenal Gland Neoplasms	CC001624	94	0	2	0.0185185		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Primary Myelofibrosis	CC001815	282	0	5	0.0170648		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Agranulocytosis	CC001824	55	0	2	0.0289355		0	0		C0346037
Acral Lentiginous M C0346037		16	0	AIDS related complex	CC001857	100	0	1	0.0086956		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Alopecia	CC002170	491	0	5	0.0099601		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Alopecia Areata	CC002171	114	0	1	0.0077519		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Extrinsic allergic alveolitis	CC002390	65	0	1	0.0125		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Alzheimer's Disease	CC002395	3397	0	7	0.0020551		0	0		C0346037
Acral Lentiginous M C0346037		16	2	Ameloblastoma	CC002448	174	4	3	0.0160427		2	0.5		C0346037
Acral Lentiginous M C0346037		16	0	Amyotrophic Lateral Sclerosis	CC002736	1114	0	2	0.0017730		0	0		C0346037
Acral Lentiginous M C0346037		16	0	anaphylaxis	CC002792	180	0	3	0.0155440		0	0		C0346037
Acral Lentiginous M C0346037		16	2	Anaplasia	CC002793	538	7	9	0.0165137		2	0.2857142		C0346037
Acral Lentiginous M C0346037		16	0	Anemia	CC002871	847	0	7	0.0081775		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Aplastic Anemia	CC002874	238	0	6	0.0241935		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Cooley's anemia	CC002875	144	0	1	0.0062893		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Congenital dyserythropoietic anemia	CC002876	24	0	1	0.0256410		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Anemia, Hemolytic	CC002878	154	0	1	0.0059171		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Autoimmune hemolytic anemia	CC002880	81	0	1	0.0104166		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Anemia, Macrocytic	CC002886	51	0	2	0.0307692		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Refractory anemias	CC002893	340	0	5	0.0142450		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Refractory anaemia with excess blasts	CC002894	49	0	1	0.315625		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Angina Pectoris	CC002962	139	0	1	0.0064935		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Angioid Streaks	CC002982	13	0	1	0.0357142		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Aniridia	CC003076	83	0	1	0.0102040		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Anisometropia	CC003081	7	0	1	0.0454545		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Anorexia	CC003123	242	0	1	0.0038910		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Anoxia	CC003130	287	0	1	0.0033112		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Anthracosis	CC003165	65	0	1	0.0125		0	0		C0346037
Acral Lentiginous M C0346037		16	2	Anthrax disease	CC003175	66	3	1	0.0123456		2	0.6666666		C0346037
Acral Lentiginous M C0346037		16	0	Anus Neoplasms	CC003463	8	0	1	0.0434782		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Anxiety	CC003467	1048	0	4	0.0037735		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Anxiety Disorders	CC003469	840	0	2	0.0023419		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Aortic Aneurysm	CC003486	278	0	3	0.0103092		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Aortic coarctation	CC003492	88	0	2	0.0196078		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Aortic Valve Insufficiency	CC003504	377	0	1	0.0025510		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Aortic Valve Stenosis	CC003507	234	0	1	0.0040160		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Arnold Chiari Malformation	CC003803	53	0	1	0.0147058		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Cardiac Arrhythmia	CC003811	559	0	2	0.0034904		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Arteriosclerosis	CC003850	2006	0	6	0.0029761		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Arteriovenous fistula	CC003855	93	0	1	0.0092592		0	0		C0346037
Acral Lentiginous M C0346037		16	2	Congenital arteriovenous malformation	CC003857	163	23	3	0.0170454		2	0.0869565		C0346037
Acral Lentiginous M C0346037		16	2	Arthralgia	CC003862	248	27	2	0.0076335		2	0.0740740		C0346037
Acral Lentiginous M C0346037		16	0	Arthritis	CC003864	1072	0	8	0.0074074		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Arthritis, Psoriatic	CC003872	450	0	1	0.0021505		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Rheumatoid Arthritis	CC003873	2723	0	9	0.0032967		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Ascites	CC003962	198	0	1	0.0046948		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Asphyxia Neonatorum	CC004045	45	0	1	0.0166666		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Asthma	CC004096	2096	0	7	0.0033254		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Astigmatism	CC004106	148	0	1	0.0061349		0	0		C0346037
Acral Lentiginous M C0346037		16	2	Astrocytoma	CC004114	985	59	9	0.0090725		2	0.0338983		C0346037
Acral Lentiginous M C0346037		16	0	Ataxia	CC004134	868	0	4	0.0045454		0	0		C0346037
Acral Lentiginous M C0346037		16	2	Ataxia Telangiectasia	CC004135	384	698	5	0.0126582		2	0.0028653		C0346037
Acral Lentiginous M C0346037		16	0	Atherosclerosis	CC004153	2044	0	7	0.0034096		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Atrial Fibrillation	CC004238	939	0	4	0.0042060		0	0		C0346037
Acral Lentiginous M C0346037		16	0	Child attention deficit disorder	CC004269	26	0	1	0.0243902		0	0		C0346037

PANTHERDB

Well with the help of DisGeNET gene data were retrieved in which the 16 different kinds of genes which were associated in the acral lentiginous melanoma .

In the panther db we need to give all the gene id or names which taken from DisGeNET

In the select organism we should give HOMO SAPIENS

And in the select analysis we should select what kind of chart we need to produce as output

And Submit

In the Panther db out of 16 genes which were taken from DisGeNET only 14 genes are mapped

Mapped IDs

FASLG

TERT

SNIP1

SLN

CDKN2A

HLA-DQA1

PLD1

BRAF

HLA-DQA1

NRAS

KIT

PDGFRA

PTEN

WRN

Molecular Function



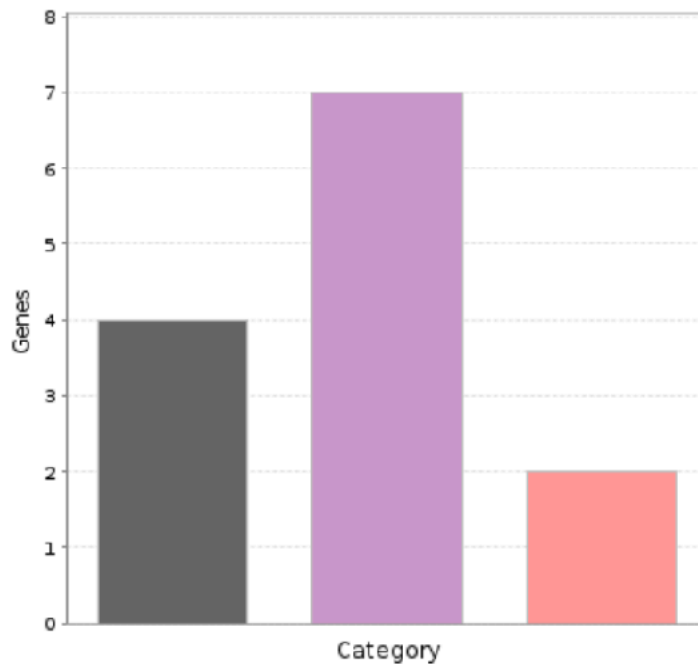
Features:

- ✧ Mouse-over bar chart category to see category name and statistics
- ✧ Click on a bar chart category to drill down to child categories
- ✧ Click on chart legend link to retrieve gene list for each category
- ✧ Click on a color key in chart legend to choose your favorite color for the category **NEW!**

Select Ontology: **Molecular Function** View: **100%**

PANTHER GO-Slim Molecular Function

Total # Genes: 14 Total # function hits: 13



Click to get gene list for a category:

■ [binding \(GO:0005488\)](#)

■ [catalytic activity \(GO:0003824\)](#)

■ [molecular transducer activity \(GO:0060089\)](#)

Color picker powered by



**Chart tooltips are read as: Category name (Accession): # genes; Percent of gene hit against total # genes; Percent of gene hit against total # Function hits

Cellular Component



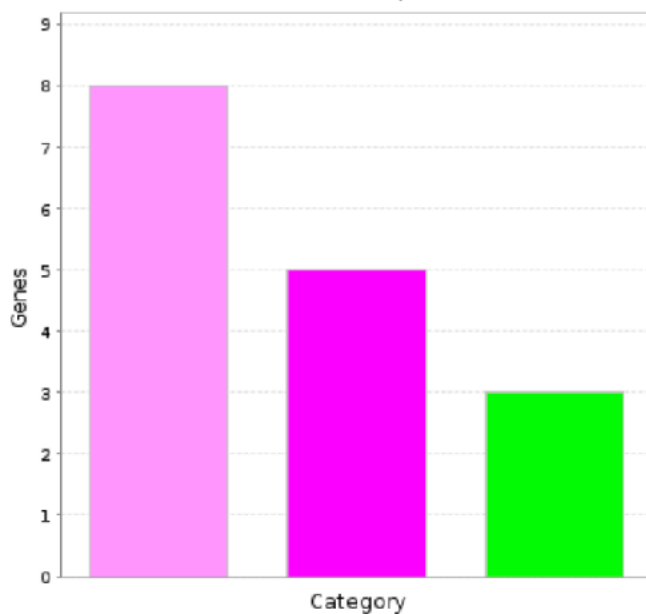
Features:

- Mouse-over bar chart category to see category name and statistics
- Click on a bar chart category to drill down to child categories
- Click on chart legend link to retrieve gene list for each category
- Click on a color key in chart legend to choose your favorite color for the category **NEW!**

Select Ontology: **Cellular Component** View: **100%**

PANTHER GO-Slim Cellular Component

Total # Genes: 14 Total # component hits: 16



Click to get gene list for a category:

- [cellular anatomical entity \(GO:0110165\)](#)
- [intracellular \(GO:0005622\)](#)
- [protein-containing complex \(GO:0032991\)](#)

Color picker powered by Web Colors by VisiBone

**Chart tooltips are read as: Category name (Accession): # genes; Percent of gene hit against total # genes; Percent of gene hit against total # Component hits

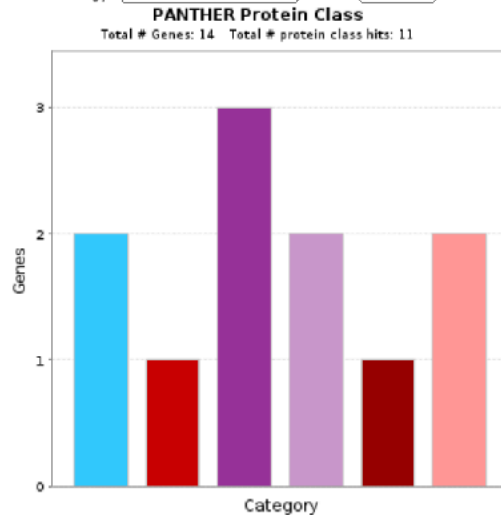
Protein Class

PANTHER BAR CHART

Features:

- Mouse-over bar chart category to see category name and statistics
- Click on a bar chart category to drill down to child categories
- Click on chart legend link to retrieve gene list for each category
- Click on a color key in chart legend to choose your favorite color for the category **NEW!**

Select Ontology: **Protein Class** View: **100%**



Click to get gene list for a category:

- [defense/immunity protein \(PC00090\)](#)
- [metabolite interconversion enzyme \(PC00262\)](#)
- [nucleic acid metabolism protein \(PC00171\)](#)
- [protein modifying enzyme \(PC00260\)](#)
- [protein-binding activity modulator \(PC00095\)](#)
- [transmembrane signal receptor \(PC00192\)](#)

Color picker powered by Web Colors by VisiBone

**Chart tooltips are read as: Category name (Accession): # genes; Percent of gene hit against total # genes; Percent of gene hit against total # Protein Class hits

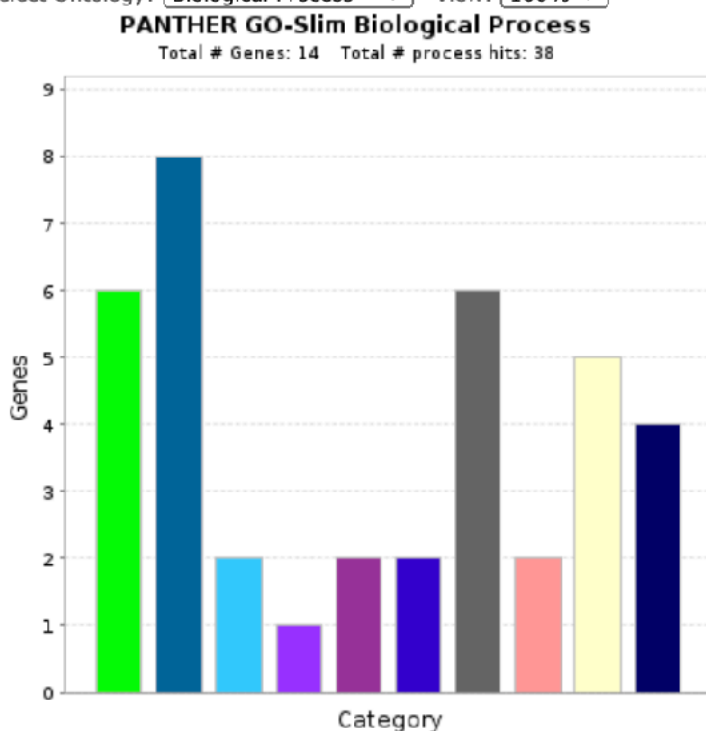
Biological process

PANTHER BAR CHART

Features:

- Mouse-over bar chart category to see category name and statistics
- Click on a bar chart category to drill down to child categories
- Click on chart legend link to retrieve gene list for each category
- Click on a color key in chart legend to choose your favorite color for the category **NEW!**

Select Ontology: **Biological Process** View: **100%**



Click to get gene list for a category:

- [biological regulation \(GO:0065007\)](#)
- [cellular process \(GO:0009987\)](#)
- [developmental process \(GO:0032502\)](#)
- [immune system process \(GO:0002376\)](#)
- [localization \(GO:0051179\)](#)
- [locomotion \(GO:0040011\)](#)
- [metabolic process \(GO:0008152\)](#)
- [multicellular organismal process \(GO:0032501\)](#)
- [response to stimulus \(GO:0050896\)](#)
- [signalling \(GO:0023052\)](#)

Color picker powered by Web Colors by VisiBone

**Chart tooltips are read as: Category name (Accession): # genes; Percent of gene hit against total # genes; Percent of gene hit against total # Process hits

Pathway

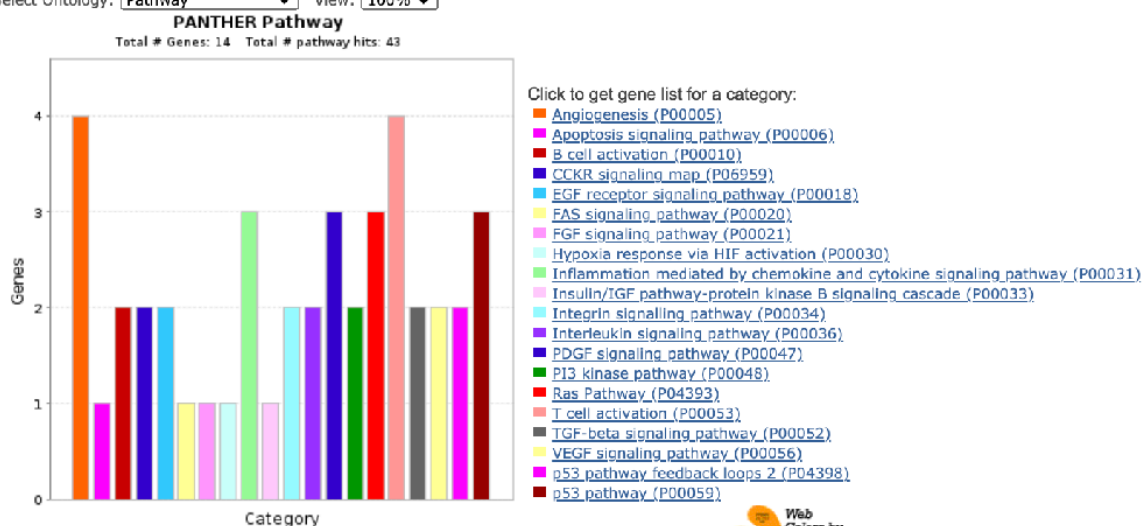
PANTHER BAR CHART

[Pie Chart](#) [Export](#)

Features:

- Mouse-over bar chart category to see category name and statistics
- Click on a bar chart category to drill down to child categories
- Click on chart legend link to retrieve gene list for each category
- Click on a color key in chart legend to choose your favorite color for the category **NEW!**

Select Ontology: **Pathway** View: **100%**



**Chart tooltips are read as: Category name (Accession): # genes; Percent of gene hit against total # genes; Percent of gene hit against total # Pathway hits

NETWORK ANALYST

It is a comprehensive network visual analysis platform for gene expression analysis

In the interface of the network analyst through five different types we can give data input to it

1) GENE LIST INPUT : starting from a list of gene ids with optional expression values

2) GENE EXPRESSION TABLE : starting from a single count table (RNA seq) or intensity table (micro array)

3) NETWORK FILE : Starting with a network file (Sif ,graphml , json)

4) RAW RNA - SEQ DATA : uploading RNA seq fastq files to our galaxy server for mapping & Quantification

5) MULTIPLE GENE EXPRESSION TABLES : Starting with several gene expression tables for meta analysis

In these I used Gene list input

In organism select HOMO SAPIENS

In the Set Id type select OFFICIAL GENE SYMBOL

In the given gene list we should keep the selected genes from DisGeNET

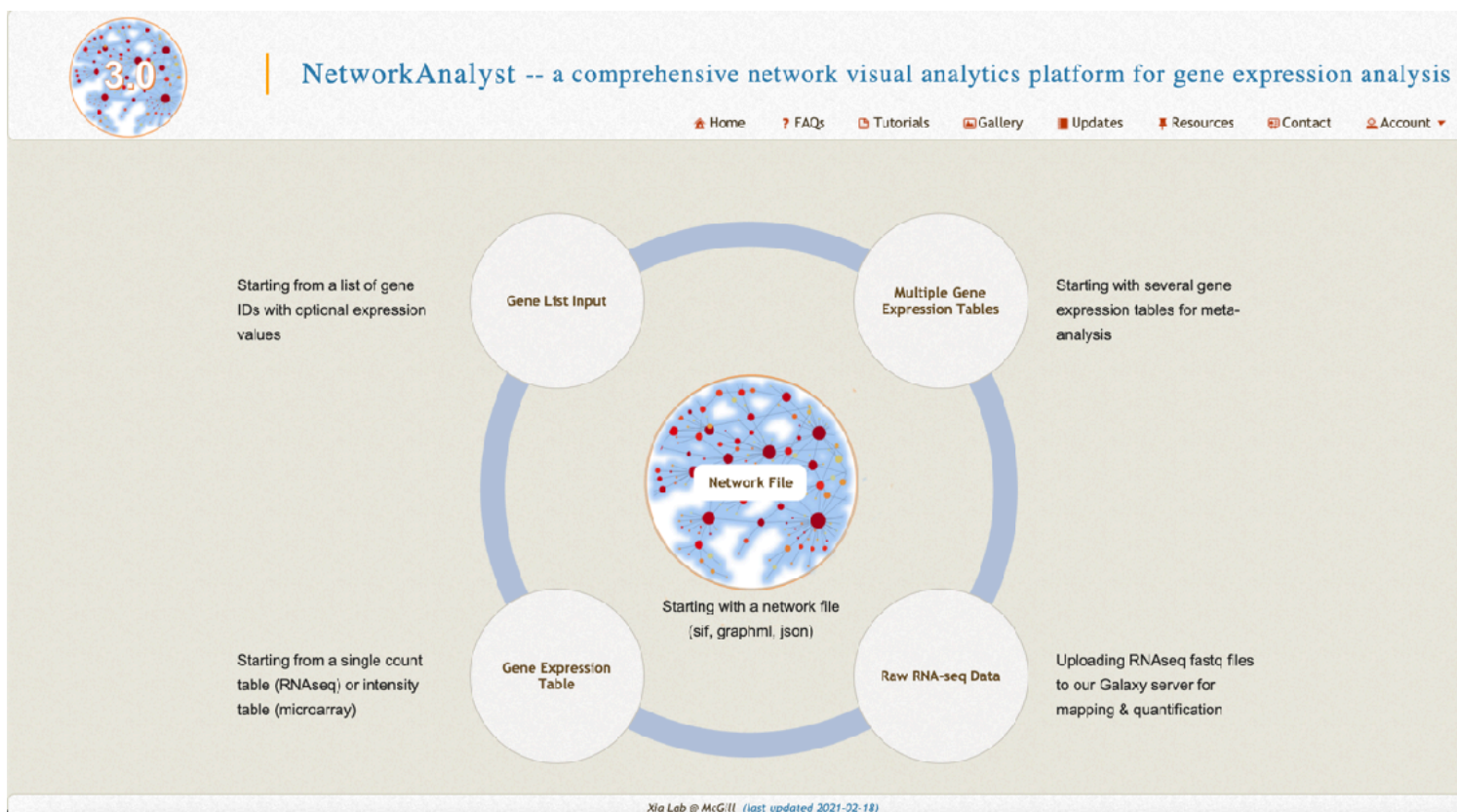
After uploading

The analysis overview will get appear

In the network mapping select any kind of interaction in my study I used Generic PPI (Imex INTERACTOME)

The mapping overview will get appeared in which the networks appears in my case 3 sub networks appeared

NETWORK ANALYST INTERFACE



GENE LISTS



NetworkAnalyst -- a comprehensive network visual analytics platform for gene expression analysis

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[Upload Data](#)
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[Network Customization](#)
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Please upload one or multiple lists of genes/proteins for network-based analysis and other data visualization, with built-in support for various functional enrichment analysis. For first time users, you are advised to explore the features using one of our example data sets.

Specify organism

Set ID type

Copy-and-paste one or more gene lists (Insert a "/" line to indicate the start of a new gene list, or [click here](#) to upload multiple gene list files)

[Try Example](#)

H. sapiens (human)

Official Gene Symbol

TERT
WRN
BRAF
KIT
NRAS
CDKN2A
HSP10
LOC110806263
SLX
PTEN
PI3D1
PDGFRA
FASLG
HLA-DQA1
HFM
SNIP1

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MAPPING OVERVIEW



NetworkAnalyst -- a comprehensive network visual analytics platform for gene expression analysis

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Mapping Overview

The significant genes (seeds) from previous analysis are mapped to the corresponding molecular interaction database. The procedure typically produces one big subnetwork ("continent") with several smaller ones ("islands"). Subnetworks with **at least 3 nodes** are listed below. You can visually explore them in the next step. These subnetworks can be downloaded as SIF (simple interaction format) files to be explored in other tools (i.e. Cytoscape).

Networks	Nodes	Edges	Seeds	Interactions (.SIF)
subnetwork1	298	178	10	Download
subnetwork2	3	2	1	Download
subnetwork3	3	2	1	Download

[Previous](#)

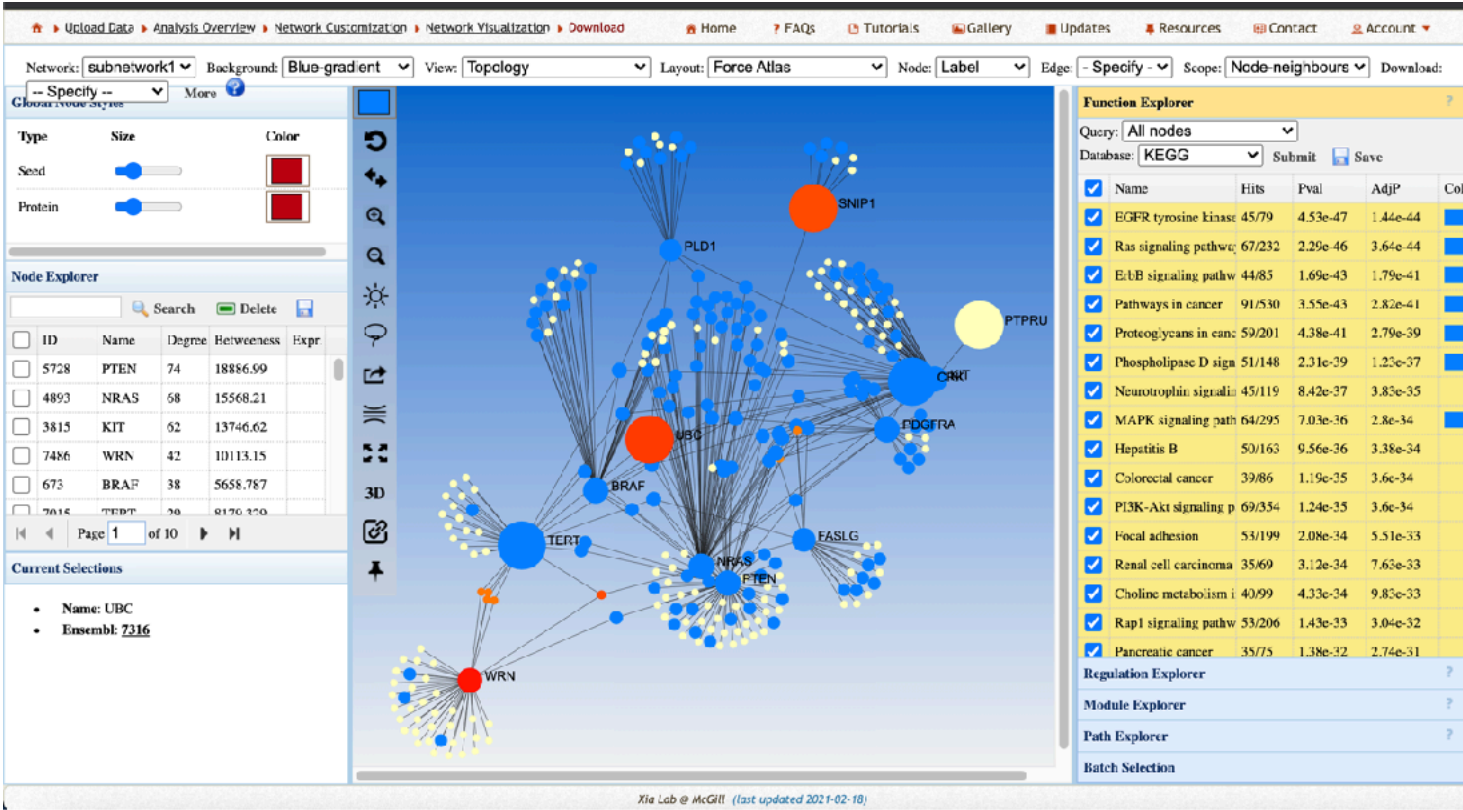
[Proceed](#)

Xia Lab @ MCGill (last updated 2021-02-18)

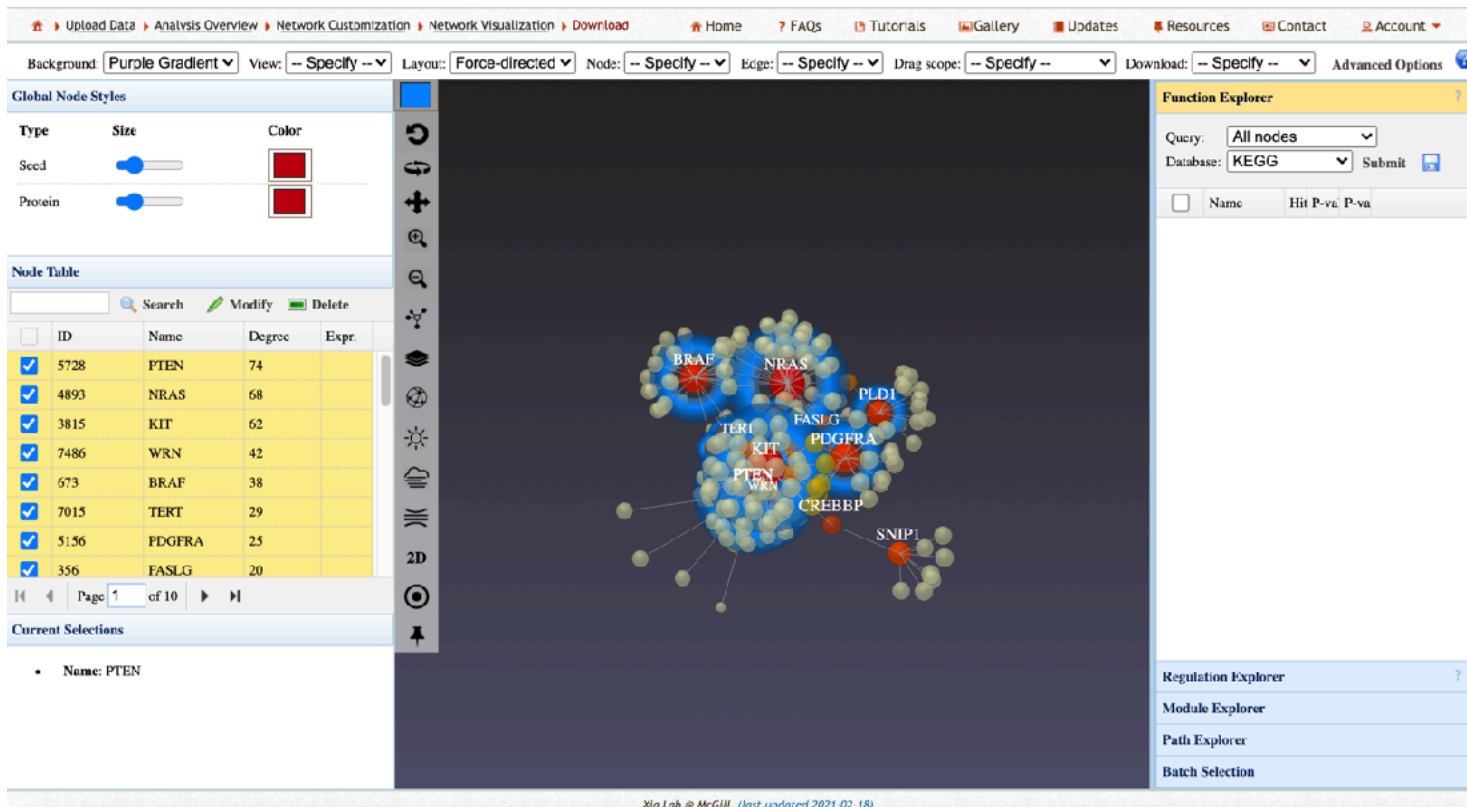
Network Tools:

[Reset Network](#)
[Zero-order Network](#)
[Second-order Network](#)
[Minimum Network](#)
[Steiner Forest Network](#)
[Degree Filter](#)
[Betweenness Filter](#)
[Tissue Filter](#)
[Batch Exclusion](#)

2D NETWORK FOR THE SELECTED GENES



3D STRUCTURE FOR THE SELECTED GENES SPECIFIC GENES IN TABLE



STRING DB

SEARCH TOOL FOR THE RETRIEVAL OF INTERACTING GENES / PROTIENS .

The main purpose of string db is Protein–protein interaction networks are an important ingredient for the system-level understanding of cellular processes.

Such networks can be used for filtering and assessing functional genomics data and for providing an intuitive platform for annotating structural, functional and evolutionary properties of proteins.

In the interface itself contains a different types to provide input . Such as

1. Protein by name
2. Protein by sequence
3. Multiple protein
4. Multiple sequences
5. Protein with Values / Ranks
6. organisms
7. Protein families
8. Examples
9. Random Entry

In these I selected Multiple proteins which are retrieved from the DisGeNET data base

In organism I select HOMO SAPIENS

After searching I got a list of proteins which are being associated with the Targeted genes . We can select the specific genes which we need to add in structural analysis

In the viewers We can select different types like

- I. Network

II. Experiments

III. Data bases

IV. Text mining

V. Fusion

VI. Cooccurrence

VII. Co Expression

VIII. Neighborhood

In this select network

- [Protein by name](#) >
- [Protein by sequence](#) >
- [Multiple proteins](#) >
- [Multiple sequences](#) >
- [Proteins with Values/Ranks](#) New >
- [Organisms](#) >
- [Protein families \("COCs"\)](#) >
- [Examples](#) >
- [Random entry](#) >

SEARCH

Multiple Proteins by Names / Identifiers

List Of Names: (one per line, examples: #1 #2 #3)

TERT
WRN
BRF
KIT
NRAS
CDKN2A

... or, upload a file:

Browse ...

Organism:

auto-detect

[Advanced Settings](#)

SEARCH

The following proteins in *Homo sapiens* appear to match your input. Please review the list, then click Continue to proceed.

[← BACK](#)

[↑ MAPKING](#)

[CONTINUE →](#)

1) "TERT":

- ☒ **TERT** - Telomerase reverse transcriptase; Telomerase is a ribonucleoprotein enzyme essential for the replication of chromosome termini in most eukaryotes. Active in progenitor and cancer cells. Inactive, or very low activity, in normal somatic cells. Catalytic component of the telomerase holoenzyme complex whose main activity is the elongation of telomeres by acting as a reverse transcriptase that adds simple sequence repeats to chromosome ends by copying a template sequence within the RNA component of the enzyme. Catalyzes the RNA-dependent extension of 3-chromosomal termini with the 6-n [...]
- ☐ NF- κ B1 - Transcriptional repressor NF- κ B1; Binds to the X-box motif of MHC class II genes and represses their expression. May play an important role in regulating the duration of an inflammatory response by limiting the period in which MHC class II molecules are induced by interferon- γ . Isoform 3 binds to the X-box motif of **TERT** promoter and represses its expression. Together with PABPC1 or PABPC4, isoform 1 acts as a coactivator for **TERT** expression. Mediates P2-dependent ubiquitination of PHD finger proteins [a.k.a. NF- κ B2, NP_667345.1, A8K6H8]
- ☐ MKRN1 - E3 ubiquitin-protein ligase makorin1; E3 ubiquitin ligase catalyzing the covalent attachment of ubiquitin moieties onto substrate proteins. These substrates include FILIP1, p53/TP53, CDKN1A and **TERT**. Keeps cells alive by suppressing p53/TP53 under normal conditions, but stimulates apoptosis by repressing CDKN1A under stress conditions. Acts as a negative regulator of telomerase. Has negative and positive effects on RNA polymerase II-dependent transcription; Ring finger proteins [a.k.a. RNF61, Q9UHC7, MKRN1-G11]

truncated ... [show all 12 options](#)

2) "WRN":

- ☒ **WRN** - Werner syndrome ATP-dependent helicase; Multifunctional enzyme that has both magnesium and ATP-dependent DNA-helicase activity and 3'→5' exonuclease activity towards double-stranded DNA with a 5'-overhang. Has no nuclease activity towards single-stranded DNA or blunt-ended double-stranded DNA. Binds preferentially to DNA substrates containing alternate secondary structures, such as replication forks and Holliday junctions. May play an important role in the dissociation of joint DNA molecules that can arise as products of homologous recombination, at stalled replication forks or duri [...]

3) "BRF":

- ☒ **BRF** - Serine/threonine-protein kinase Braf; Protein kinase involved in the transduction of mitogenic signals from the cell membrane to the nucleus. May play a role in the postsynaptic responses of hippocampal neuron. Phosphorylates MAP2K1, and thereby contributes to the MAP kinase signal transduction pathway
- ☐ MAP3K1 - Mitogen-activated protein kinase kinase kinase 1; Activates the JUN N-terminal pathway. Required for serum-stimulated cell proliferation and for mitogen and cytokine activation of MAPK14 (p38), MAPK3 (ERK) and MAPK8 (JNK1) through phosphorylation and activation of MAP2K4/MKK4 and MAP2K7/MKK7. Plays a role in mitogen-stimulated phosphorylation and activation of **BRF**, but does not phosphorylate **BRF** directly. Influences microtubule organization during the cell cycle. Belongs to the protein kinase superfamily. STE Ser/Thr protein kinase family, MAP kinase kinase kinase subfamily [a.k.a. PTK1, MLK3, SPRK]
- ☐ RNF149 - E3 ubiquitin-protein ligase RNF149; E3 ubiquitin-protein ligase. Ubiquitinates **BRF**, inducing its proteasomal degradation; Ring finger proteins [a.k.a. DNAPT2, ring finger protein 149, Z81995]

truncated ... [show all 5 options](#)

4) "KIT":

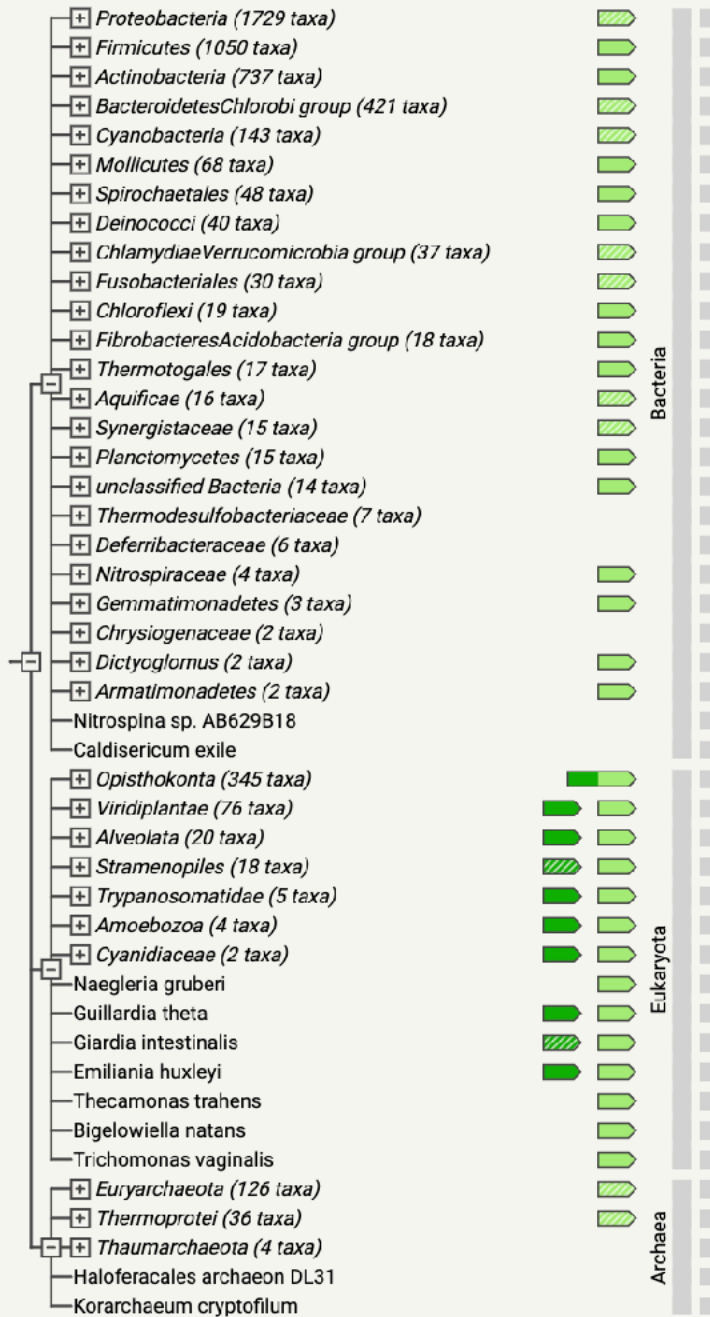
- ☒ **KIT** - Mast/stem cell growth factor receptor **KIT**; Tyrosine-protein kinase that acts as cell-surface receptor for the cytokine KITLG/SCF and plays an essential role in the regulation of cell survival and proliferation, hematopoiesis, stem cell maintenance, gametogenesis, mast cell development, migration and function, and in melanogenesis. In response to KITLG/SCF binding, **KIT** can activate several signaling pathways. Phosphorylates PIK3R1, PLCG1, SH2B2/APS and CBL. Activates the AKT1 signaling pathway by phosphorylation of PIK3R1, the regulatory subunit of phosphatidylinositol 3-kinase. Activat [...]
- ☐ KITLG - **KIT** ligand; Ligand for the receptor-type protein-tyrosine kinase **KIT**. Plays an essential role in the regulation of cell survival and proliferation, hematopoiesis, stem cell maintenance, gametogenesis, mast cell development, migration and function, and in melanogenesis. KITLG/SCF binding can activate several signaling pathways. Promotes phosphorylation of PIK3R1, the regulatory subunit of phosphatidylinositol 3-kinase, and subsequent activation of the kinase AKT1. KITLG/SCF and **KIT** also transmit signals via GRB2 and activation of RAS, RAF1 and the MAP kinases MAPK1/ERK2 and/or MAPK3/ERK [...] [a.k.a. SCF, MGF, BC069797]
- ☐ MAPK1 - Mitogen-activated protein kinase 1; Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated **KIT** and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade plays a [...] [a.k.a. PRKM2, ERK2, PRKM1]

truncated ... [show all 11 options](#)

GENE FUSIONS

-- search within tree --

Go

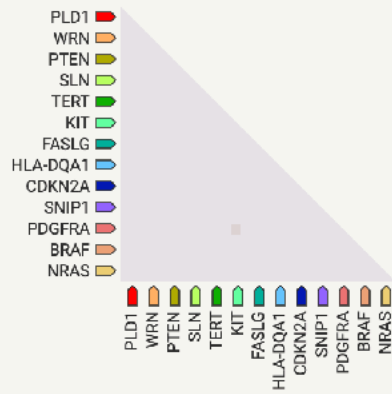


GENE COOCCURRENCE

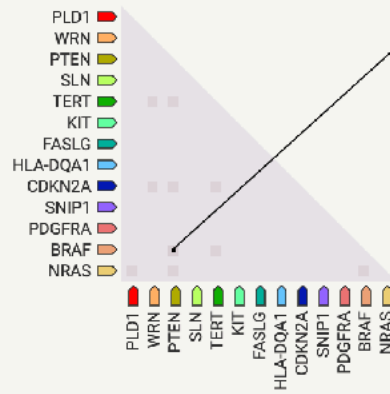


GENE COEXPRESSION

observed Coexpression in
Homo sapiens:



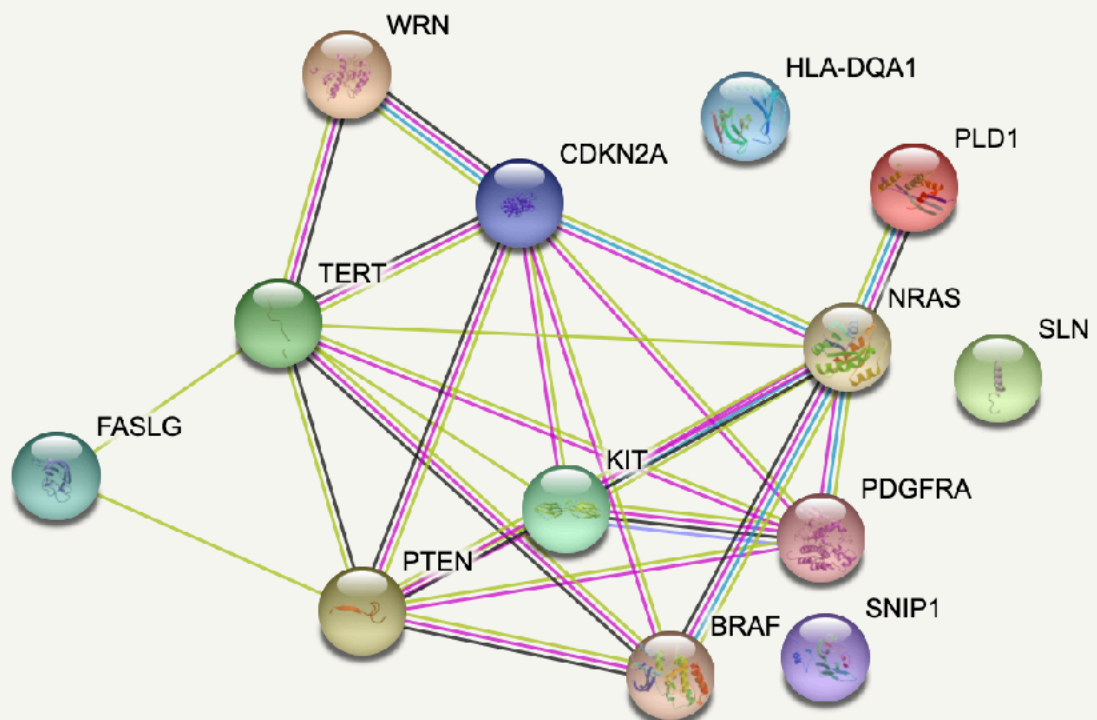
observed Coexpression in
other organisms (transferred):



from D. discoideum
from B. taurus
from M. musculus
from M. domestica
from C. elegans
from P. falciparum
from S. mansoni
from D. rerio

[Show](#)

Coexpression scores based on RNA expression patterns, and on protein co-regulation provided by [ProteomeHD](#)
[click on the heatmap elements for details]



MOLECULAR FUNCTION (GENE ONTOLOGY)	
BIOLOGICAL PROCESS (GENE ONTOLOGY)	
ANNOTATED PATHWAYS	
REACTOME PATHWAYS	
KEGG PATHWAYS	
LOCAL NETWORK CLUSTER (STRING)	
REFERENCE PUBLICATIONS (GENE ONTOLOGY)	
CELLULAR COMPONENT (GENE ONTOLOGY)	
PROTIEN DOMAINS (SMART)	
PROTIEN DOMAINS AND FEATURES	

Network Stats

number of nodes: 13
 number of edges: 24
 average node degree: 3.69
 avg. local clustering coefficient: 0.653

expected number of edges: 5
 PPI enrichment p-value: 4.62e-10
*your network has significantly more interactions
 than expected (what does that mean?)*

CHAPTER 5

(CONCLUSION AND FUTURE WORK)

This Thesis identified that With the assistance of the gene data with the assistance of disease from the CUI code for the acral lentiginous melanoma in order that it'll help in providing the various quite associations which help in understanding the genes have similarity in between one another . Through analysis of the genes which are supported the similarity and gene variants I created Gene analysis from different function like Molecular function , cellular component , protein class , pathway , organic process Which shows the genes network and the way they got interlinked in between the opposite genes . The network analysis is employed to visual analysis platform for the organic phenomenon analysis . The official gene symbol is employed for selected the actual genes . the chosen genes which are used for for the network analysis . The mapping overview of the chosen genes which are projected within the sort of subnetworks I selected the foremost genes which are having linked in between them . The 2d network is came by the highlighted genes WRN , TERT , PTEN , BRAF , FASLG , PDGFRA , PLD1 , SNIP1 . Through the node table I selected Particular genes which are having Highest Degree And created a 3d structure . The genes which formed the during the 3d structure utilized in protein - protein interaction which helps in understanding the system level of cellular process . After getting the chosen list of genes which are being related to targeted genes supported GENE FUSIONS , GENE COOCCURRENCE , GENE COEXPRESSION , AND NEIGHBORHOOD . By selecting the proteins through Homo sapiens through I selected the highlighted Genes in order that helps in protein - protein interactions A 2d structure formed for the highlighted genes But some genes don't have interlinked in between them . HLA DQNA1 , SLN GENE , SNIP1 GENE do not have any bonds in between them So these genes are excluded from the highlighted genes . The genes are Remained plays a serious role within the Acral lentiginous melanoma . Within the 13 genes there are 24 bonds attached in between them the typical of clustering coefficient is 0.653 . Ppi Enrichment value is $4.62e-10$. and therefore the result from the primary selected 16 Genes were right down to 10 Genes which are having Most

bonds in between so these are the genes which are the rationale for formation of acral lentiginous melanoma . WRN , CDKN2A , PLD1 , NRAS , TERT , FASLG , BRAF , PTEN , PDGFRA , KIT GENES Which having highest bonds . The Further studies are often done supported the out come of those genes which helps in thorough study of the disease and therefore the Highlighted genes which may help in Further more discovery of the drug studies and in- silico studies supported these genes around 75 you look after the mutation takes place which shows how important these genes so if the experiments mainly focuses on these genes help within the formation of latest drugs for the acral lentiginous melanoma . These genes helps to see the similarities and differences between the diseases . Till now there are very less differences in between the Cutaneous melanoma and alm supported these genes helps find out more differences and therefore the Drugs are which available now are often altered making it simpler . The Genes from various have potential but only few were investigated .

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