BIOINFORMATICS METHODOLOGY TO REVEALS THE COMMON BIOLOGICAL CONNECTION OF ADULT ONSET STILL'S DISEASE AND ADDISON'S DISEASE

By

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THESIS DECLARATION

This report was written by me, Mst. Nourin Jahan Sonda, under the supervision of Dr Imran Mahmud, Associate Professor & Head In Charge, Dept. of Software Engineering in Daffodil International University. We further attest that no part of this study, or any part of it, has been submitted for a degree anywhere else.

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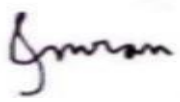

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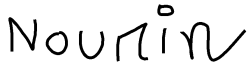

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LIST OF ABBREVIATION

AOSD = Adult Onset Still's Diseases

AD = Addison's Disease

PPIN = Protein Protein Interaction Network

PI = Physical interaction

HG = Hub Gene

GO= Gene Ontology

BP = Biological Process

CC = Cellular Component

MF = Molecular Function

KEGG = Kyoto Encyclopedia of Genes and Genomes

ABSTRACT

In the current world, Adult Onset Still's Diseases and Addison's diseases are diagrammed as more human sicknesses to toss out regular infections for people. Ahead of time works, it is very much clear that Adult Onset Still's infection and Addison's sickness are affected by hereditary elements, and the standard engine technique sickness step by step. In this study we have collected the gene list of AOSD and AD from the DisGeNET database and then our target was to find out the common genes among them by implementing an intersecting program. Then I used those intersected data to construct and analyze the Protein -Protein Interaction Network (PPIN), Enrichment Analysis and others. After the end of this I have got the most common fundamental genes associated with these diseases, the interrelated interaction networks of this two disorder that will help me to better understand the common gene structure of them. From PPIN, 10 most responsible hub genes are obtained. In future by implementing further studies and analyzing those gene structures, it may be able to notify us to take precautionary steps to reduce the risk of those disease and analyzed Protein -drug interaction network.

Keywords Adult Onset Still's disease · Addison disease · Protien-Protien network · Enrichment Analysis · Co-expression. Physical interaction network.

CHAPTER 1

INTRODUCTION

1.1 Background

AOSD is a phenomenal foundational combustible problem of obscure etiology that is responsible for the fundamental proportion of instances of fever of obscure beginning and can likewise have critical musculoskeletal sequelae. AOSD is a rare condition, generally, set forward with high fever related with fundamental investigate. (János Kádár, Edina Petrovicz, 2004)

Monocyclic in 17 patients and polycyclic in 25 got from AOSD and 15 in ongoing. Three passings could be ascribed to AOSD. Corticosteroid reliance happened in 23 patients (45%) as anticipated by low glycosylated ferratin levels. The most youthful patients had the most elevated danger of opposing first-line treatment. (Gerfaud-Valentin M, Maucort-Boulch D, Hot A, et al, 2014)

AD is a rare uncommon disease. A kind of pathological processes can cause AD. In this case, there were several oral as well as systemic manifestations of Addison's disease. (Sarkar, Soumya Brata et al., (2012). Six patients were influenced for tuberculosis (6.6%) in Addison Diseases and In 83 patients (91.2%) were considered for the immune system adrenolytic. Addison's sickness influenced two patients (2.2%) for different reasons. (Sarkar, Soumya Brata et al., (2012))

Six patients were affected for tuberculosis (6.6%) in Addison Diseases and In 83 patients (91.2%) were considered for autoimmune adrenolytic. Two patients (2.2%) were affected by Addison’s disease for other reasons. In 47% of the patients with autoimmune Addison’s disease, at least one other autoimmune disorder was present. Primary hypothyroidism had the highest prevalence (20.5%), followed by vitiligo (9.6%), nontoxic goiter (8.4%), premature menopause (7.3% of the women), Graves’ disease (6%), pernicious anemias (4.8%), Jürgen’s disease (2.4%), hypoparathyroidism (1.2%), type 1 diabetes mellitus (1.2%) and coeliac disease (1.2%). The frequency of autoantibodies in the patients with autoimmune Addison’s disease was:

adrenal antibodies (82.7%), antibodies against microsomal antigens (58%), thyroglobulin antibodies (23.4%), parietal cell antibodies (19.8%), pancreatic islet cell antibodies (6.2%) and ovary antibodies (3.7% of the women). (Pierre M.J. Zelissen, Egbert J.E.G. Bast, Ronald J.M. Croughs,, 1995)

Here this paper discover the commonplace genes for selected diseases after which examine them to discover the hub protein that is notably liable for the sicknesses. This research may also are seeking to discover networks and then pathway analyses done primarily based on the highest performance and then protein-protein interaction (PPI) networks. Phase 2 affords for the given methodology of studies paintings. In Sects 3 and 4 display the results.

1.2Motivation of Research

The reason for AOSD is obscure (idiopathic). Specialists accept that the issue may be brought about by a mix of hereditary components and a strange or misrepresented reaction to diseases or other ecological openings. AOSD is certainly not an innate infection and normally doesn't run in families. We trust that this exploration will assist with identifying the dangerous elements of this kind of uncommon illness. The fundamental inspiration of the examination is to improve the endurance rate and reduction the passing rate however much as could be expected.

1.3 Problem Statement:

Since finding out about past comparative works, I've seen a few shortcomings, which may take this to a higher level of the examination.

- ✓ Limited volumes of information are utilized by two infections.
- ✓ Unable to produced PPI network.
- ✓ Do not work with Enrichment Analysis.
- ✓ Do not work with Pathway analysis.
- ✓ No Co-expression and Physical Interaction.

1.4 Research Question:

An exploration question is a liable investigation into a particular issue or subject. In research, this is the underlying advance. Once, a comprehension of what to investigate, the 'underlying advance' implies that the examination theme is the main significant advance in exploration. A few inquiries are investigated. The rundown of inquiries is given beneath:

- ✓ How to gather the informational index for chosen infections? What's more, where?
- ✓ How to deliver the PPI?
- ✓ How to information mine the informational collection?
- ✓ What sort of devices expected to get the critical outcome?
- ✓ How to examine the Enrichment Analysis?
- ✓ How to add references?

1.5 Research Objectives:

The key goals of this thesis are given below:

- ✓ Identifying genes that are shared by two disorders
- ✓ Generate Generic PPI.
- ✓ Using PPI, Enrichment analysis and pathway analysis.
- ✓ Creating Co-expression & Physical Interaction.

1.6 Research Scope:

The analysis of AOSD is hard to make in light of the fact that there is no particular test or recognizing lab finding that obviously separates the problem from comparative issues. Along these lines, it is critical to figure out how to discover in the beginning phases with the goal that the patients can get by through taking an appropriate treatment ideal.

1.7 Thesis Organization

In this examination, the IEEE referring to a framework has been utilized in this record. The paper has been outfitted with five sections which are depicted underneath:

Part 1: In this section, the examination foundation, inspiration, issue articulation, targets, and exploration degree are given.

Part 2: This section incorporates a conversation of the current related work and sorted out the examination hole.

Part 3: This section contains the examination technique and approaches as follows for the Examination.

Part 4: This section contrasts the tested outcomes and existing methodologies.

Part 5: The examination result and the constraint of this investigation are introduced here.

CHAPTER 2

LITERATURE REVIEW

2.1 CASE STUDY ON THE PPIN OF AOSD AND AD DISEASES

Using some of the prior publications as a starting point, they investigated AOSD & AD there, we did some case study and that in 2006 A paper was released in the BMJ Journal where the authors talked about assessing and synthesis the evidence for optimal diagnosis and management of AOSD (Efthimiou P, Paik PK, Bielory L, 2006). Another paper from 2001 was titled, we discovered that the authors looked at the clinical and pathological aspects of the condition of the adrenal failure AD (Svetlana Ten, Maria New, Noel Maclaren, Addison's Disease, 2001). We're also working here since we believe this forecast, but our major goal is to work with the PPI network and analyze various biological network models and Ontological features. So following this effort could be another step forward in this field.

CHAPTER 3

RESEARCH METHODOLOGY

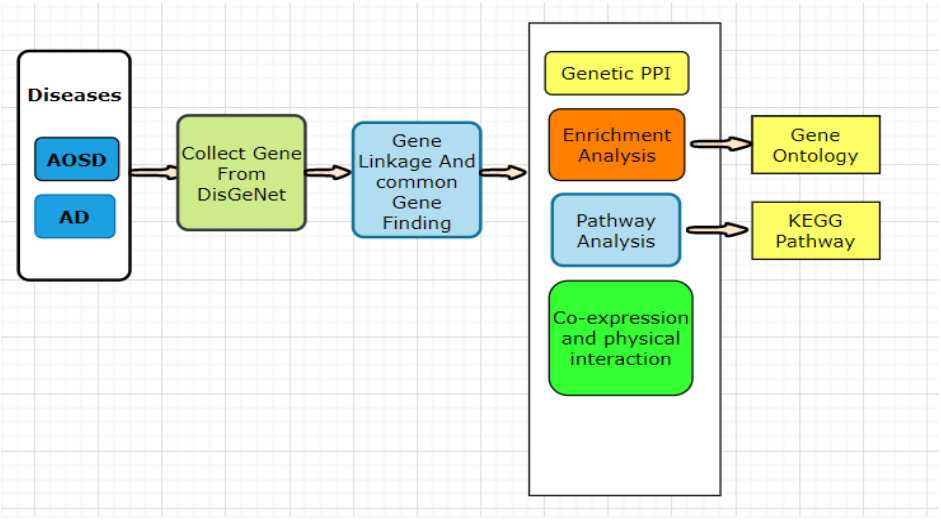

Figure 1: The summary of this research is displayed that includes analyzing Enrichment, gene collection, filtering, Co-Expression, and physical interaction.

3.1 Data Collection

In this study, at first collect dataset from the DisGeNET database (https://www.disgenet.org/program). Here, each passage of the genomic information bases holds a billion bytes of the actuality that that overall umbilicus on biotechnology and bio-informatics. Download a few qualities of the AOSD and an AD issue. At that point, the information is brought into a dominant sheet for each problem that is additionally tested to discover

the regular qualities are polished turmoil.

3.2 Preprocessing and filtering

Preprocessing traces out appointed species-related genes and if any data replicates, expel phase expel the replicated data (Herrero J, Díaz-Uriarte R, Dopazo J , 2003). We have collected Homo sapiens genes only. In this Step downloaded genes. Then downloaded gene imported into Microsoft excel. Then those genes are filtered. Then the imported files are then used to conduct additional gene mining analyses.

3.3 Gene mining and common gene finding

In this investigation, data mining method is expected to understand the overall qualities among AOSD and AD quality mining is essential. For recognizing the linkage of qualities among AOSD and AD, we have parted between a chosen two issues (AOSD and AD). This convergence upholds the investigation to go further examination and capture the basic quality. For insinuating the last regular quality.

3.4 Generic PPI

PPIs network represent two more proteins which are connected with each other's and the organization happens through a few biochemical motives and amongst them hydrophobic impact. PPIs network helps to find a protein complex. (Leung HC, 2009) The protein-protein interaction analysis makes crafted by discovering the point of interest on characteristics easy and the evacuation of the targeted on traits could purpose an organization breakdown. For this examination, planned the PPI network in Network Analyst, which is an electronic instrument in Bioinformatics.

3.5 Enrichment analysis

The portrayal of test natural information is found through enhancement examination. (Alexeyenko A, 2012) Enrichment analysis is estimated utilizing different practical techniques, among them, quality cosmology (GO) stands firm on a critical situation. (Alexeyenko A, 2012) Initially, Gene Ontology was developed for a data set named Fly base yet Gene Ontology terms at last give data on sub-atomic function(MF), An cell component(CC), and natural cycle (BP) (Doms A, Schroeder M, 2005).

3.6 Pathway analysis

For a superior comprehension of excessive-throughput organic records, pathway analysis offers various quantities of gadgets. These apparatuses contain different techniques that give Biomolecular capacities, measurable information, and different calculations). To decipher quality examination related information. Pathways analysis removes the intricacy of differentially communicated qualities, which can be added from excessive-throughput herbal information. (Khatri P, Sirota M, Butte AJ, 2012) In our examination, planned pathway.

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3.7 Co-expression and A physical interaction network

Investigating the usefulness of qualities at the framework level, a co-expression network is utilized for an enormous scope. (Zhang B, (2005)) Exclusive-throughput organic information micro-array dataset is additionally done through co-expression network investigation. (MT, (2011) Gene coexpression networks for the analysis of) This networks for the investigation of Quality co-expression networks take on basic development, where qualities are performed through the hubs and if the qualities are co-expression in a huge way they display an association with different hubs (Zhang B, (2005)). The employer is used to incorporate sensible aspects that are unidentified, and co-expression esteems are the boundary on which the co-articulation network develops for co-articulation community rationalization.

3.8 Summery

In this research, genes dataset of AOSD & AD had been collected from DisGeNet database. After collecting the dataset, built up an intersecting program to find out the common data between these diseases. From these common genes, Find outthe intersection then analyze the Protein-Protein Interaction Network. And by using the hub genes from the PPIN, analyze some Enrichment analysis and pathway analysis.

CHAPTER 4

RESULT AND DISCUSSION

4.1 Gene collection

The qualities answerable for AOSD and AD are gathered from the quality information base of DisGeNet. The quality assortment essentially happens in all species. The quantity of qualities gathered for AOSD and AD is, respectively 76 and 111. Further examination shows that a definitive objective of this exploration is enhancement investigation, pathway investigation.

4.2 Gene mining & common gene finding

In the wake of culling qualities, recognize regular qualities among choose two illnesses utilizing Venny. In the wake of finishing this investigation, then tracked down a few choice sicknesses like AOSD and AD and distinguished 11 normal qualities utilizing the Venny device (accessible at https://bioinfogp.cnb.csic.es/devices/venny/). There are HLA-DRB1, RBM45, HLA-DQB3, TNF, CCL2, HLA-DPB1, HLA-DQB2, IL6, CXCL10, GNA01, and IL15. Research of the Venn chart, get 11 basic qualities Table 1 shows the absolute qualities during the time spent convergence, and The Venn chart showing display the common genes between selected disease.

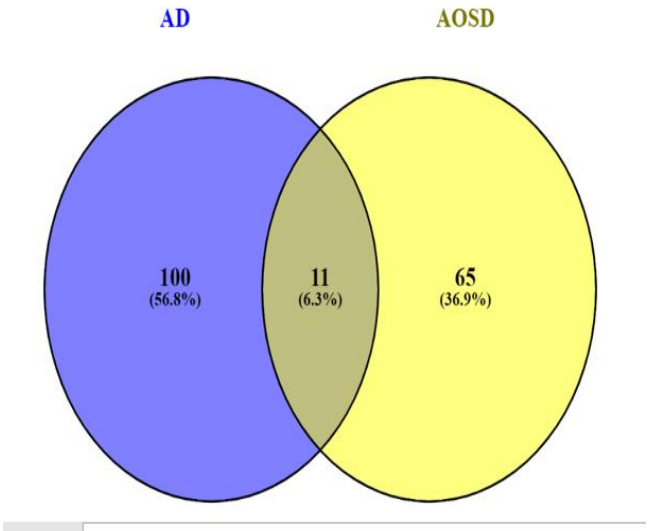


Fig. 2 VENNY diagram for selected two diseases. Here a blue color circle represents Adult Onset Still's Disease and the yellow color represents Addison's disease.

Table 1: Total common gene among selected diseases

Disease	All Gene	Common Gene
AOSD	76	11
AD	111	

4.3 Generic PPI

NetworkAnalyst, which is a web stage for organic information investigation. PPIs network is created by the NetworkAnalyst web interface. NetworkAnalyst gives information concerning quality articulation that references protein-protein collaborations (PPIs) organization. The chief ability of a protein is to have communication with every other in a mobile cycle explicit manner (track XY, 2018). As a contribution to NetworkAnalyst, 11 standard best rundowns for adult-onset still's illness (AOSD) and Addison's contamination (ad) are offered, and it produces final results as shown in Fig 3.

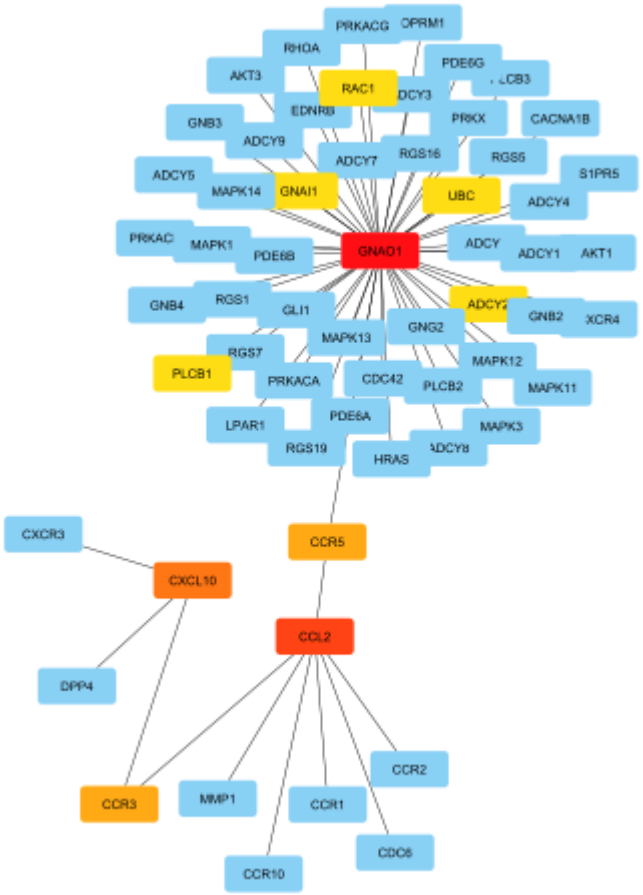


Fig 3. The PPI network is create for the common genes of AOSD and AD. In the PPI network, there are 60 nodes and 61 edges. Here red node declares most number of interactions. In This study, we found 11 nodes

for hub genes among AOSD and AD

4.4 Enrichment analysis

Enrichment Analysis of a quality set is fundamental in investigating pathway organizations, and furthermore investigation of quality articulations. Gene Ontology (GO) is one fundamental term of improvement examination. GO investigation gives cell-based parts and quality handling examination altogether (Lussier Y, 2006). GO examination of our exploration is distinguished utilizing the electronic bio-informatics device STRING. A most unmistakable component of the STRING is quality set can be given as an info and improvement examination is pictured from the delivered actual cooperation organization .Table 4 gives a classifying of hereditary capacity. Fig 6, 7, and 8 give classifying of hereditary capacity by a diagram.

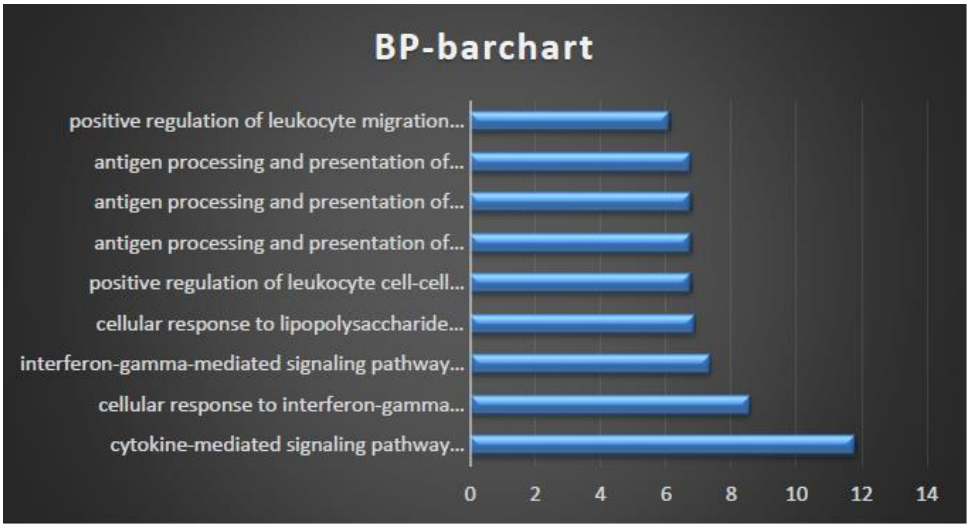


Fig 4 Where *X*-axis represent the term for Biological process (BP) and *Y*-axis represent p-value of this process.

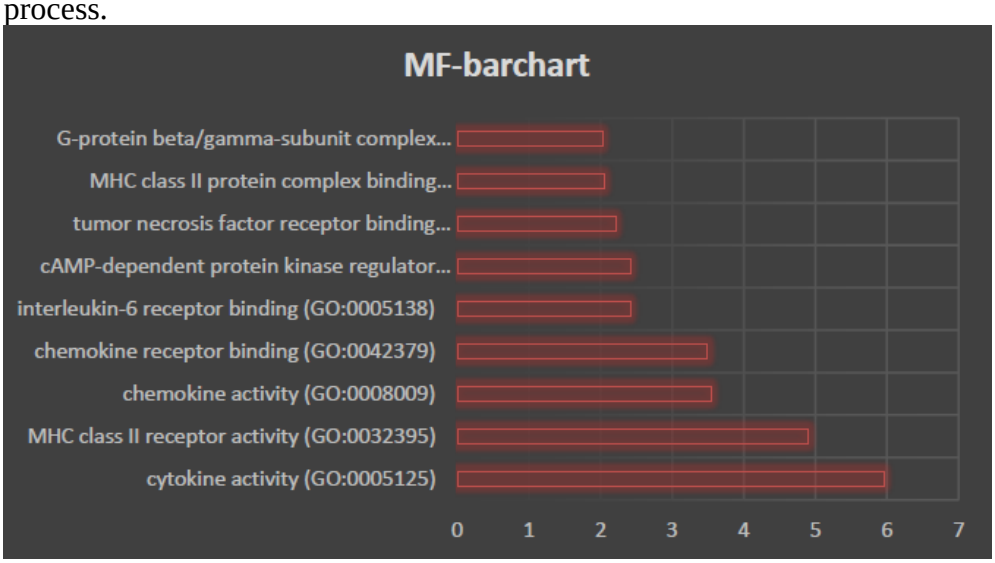


Fig 5 Where *X*-axis represents the term for Molecular function (MF) and *Y*-axis represent p-value of this process.

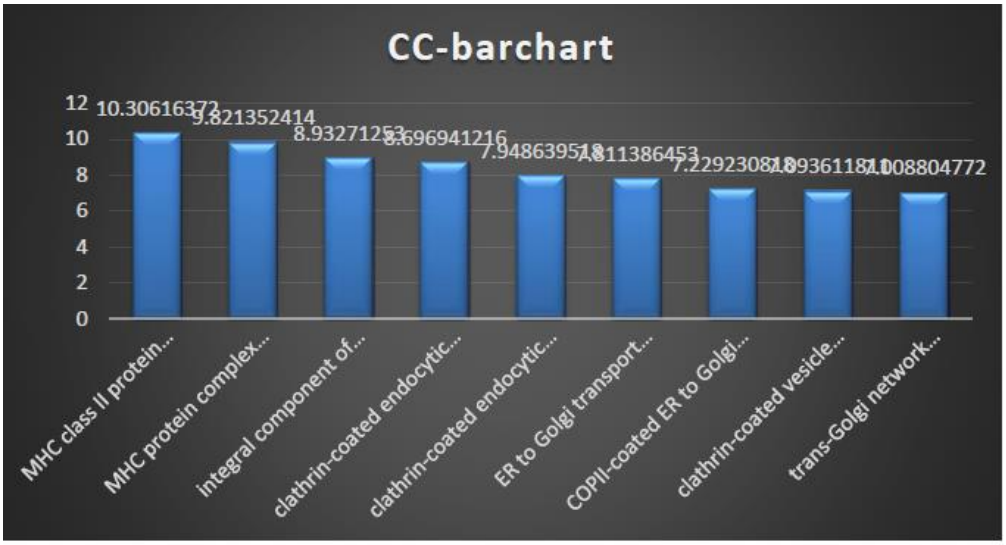


Fig 6 Where *X*-axis represents the term for Cellular component (GO) and *Y*-axis represent p-value of this process.

4.5 Pathway analysis

Pathway analysis got from GeneMANIA, which is an online Bioinformatics data set. The best ten basic qualities (UBC, RAC1, PLCB1, GNAO1, GNAI1, CXCL10, CCR5, CCR3, CCL2, and ADCY2.) GeneMANIA receives a list as a contribution. It delivers the pathway for 10 significant genes. Fig 4 addresses pathway examination of ten normal qualities and KEGG pathway investigation is given in Table 2. The KEGG pathway aids in the interconnection of gene pathways.

Table 2: Pathway analyses for 11 common gene using KEGG database

Term	P-Value	Overlapped Gene
Rheumatoid arthritis	13.98425969	IL6;IL15;HLA-DPB1;CCL2;TNF;HLA-DRB1;HLA-DQB1
Influenza A	12.02396177	CXCL10;IL6;HLA-DPB1;CCL2;TNF;HLA-DRB1;HLA-DQB1
Graft-versus-host disease	10.89044	IL6;HLA-DPB1;TNF;HLA-DRB1;HLA-DQB1
Intestinal immune network for IgA production	10.53232461	IL6;IL15;HLA-DPB1;HLA-DRB1;HLA-DQB1
Inflammatory bowel disease (IBD)	9.850765927	IL6;HLA-DPB1;TNF;HLA-DRB1;HLA-DQB1
Epstein-Barr virus infection	9.373066713	CXCL10;IL6;HLA-DPB1;TNF;HLA-DRB1;HLA-DQB1
Human T-cell leukemia virus 1 infection	9.148551773	IL6;IL15;HLA-DPB1;TNF;HLA-DRB1;HLA-DQB1
Hematopoietic cell lineage	8.962010718	IL6;HLA-DPB1;TNF;HLA-DRB1;HLA-DQB1
Asthma	8.810807799	HLA-DPB1;TNF;HLA-DRB1;HLA-DQB1

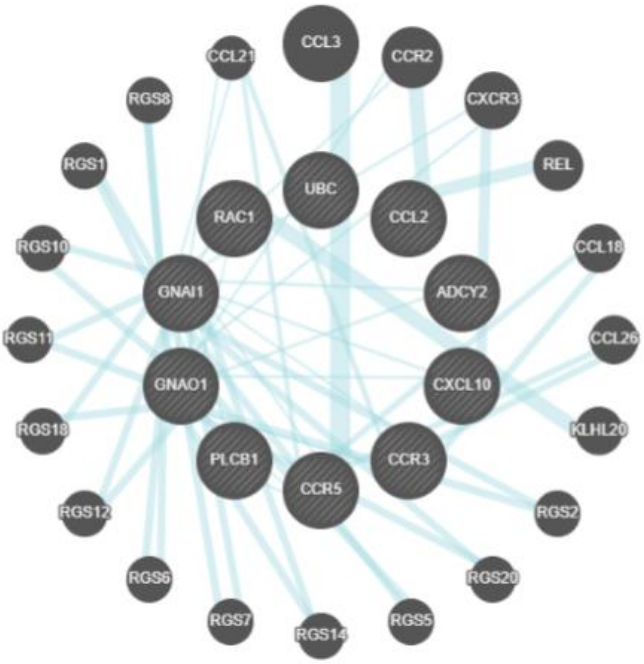


Fig. 7 Pathway analysis for UBC, RAC1, PLCB1, GNAO1, GNAI1, CXCL10, CCR5, CCR3, CCL2, and ADCY2.

4.6 Co-expression, physical interaction network and hub Gene

A Physical interaction and Co-expression are made utilizing GeneMANIA. Among all the unmistakable Bioinformatics instruments, GeneMANIA holds the personality of the most recognizable among every one of them for distinguishing hereditary capacity (). GeneMANIA is the most easy-to-understand interface and it aids different natural explores by demonstrating speculations on quality working, quality rundown investigation, and prioritization of qualities (). Co-articulation and Physical connection for these UBC, RAC1, PLCB1, GNAO1, GNAI1, CXCL10, CCR5, CCR3, CCL2, and ADCY2 qualities are imagined in Fig. 5.

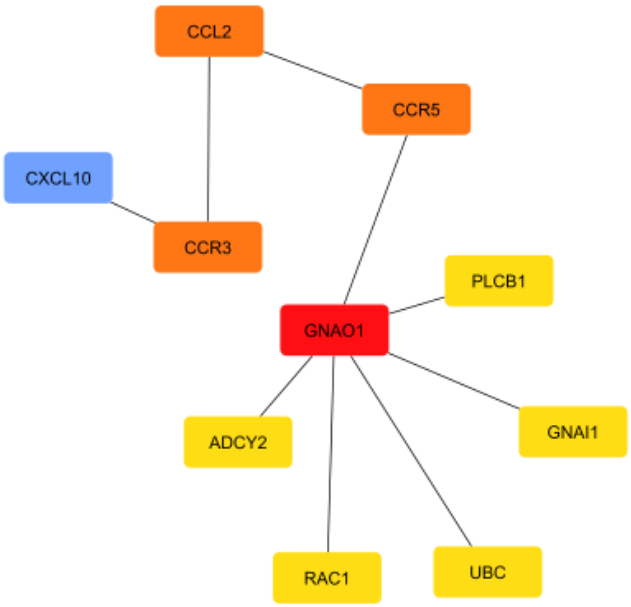
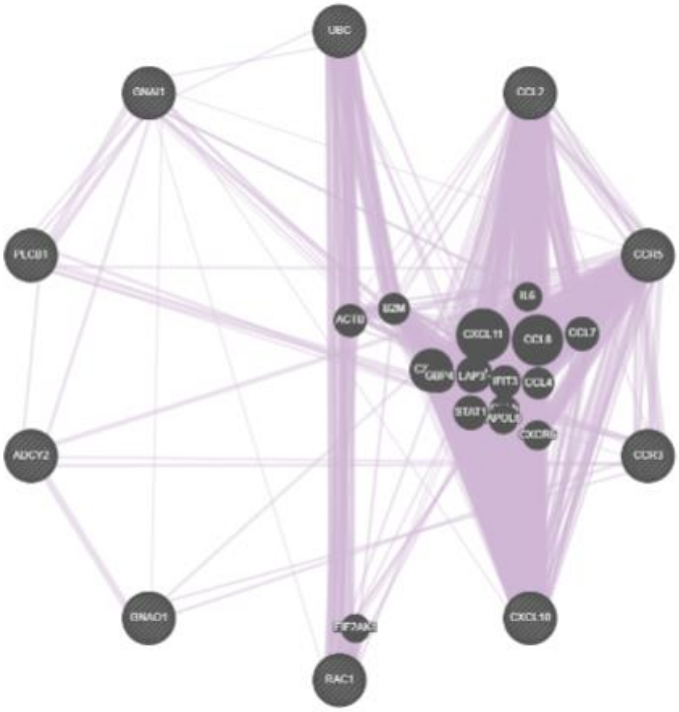


Figure 08: Using Cytohubba in Cytoscape to find hub gene. GNAI1 and CCL2 has most interactions.

(a)



(b)

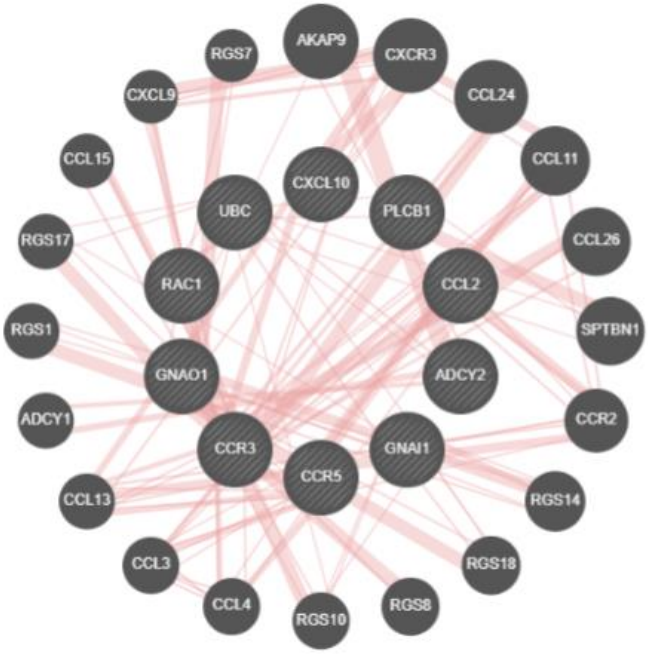


Fig. 9 b represents the physical interaction network and a represents the co-expression network between top 10 genes.

4.7 Summary

By gathering and meeting, we get 11 regular qualities among the related sicknesses. The PIN Network and Hub Gene were made utilizing the regular qualities. From the PPI network, we distinguish 10 center point qualities (UBC, RAC1, PLCB1, GNAO1, GNAI1, CXCL10, CCR5, CCR3, CCL2, and ADCY2). Co-articulation and actual connection network is made utilizing GeneMANIA.

CHAPTER 5: CONCLUSION

5.1 Findings:

This examination has introduced an outline of four sicknesses: AOSD and AD. The two most significant highlights PPI and Enrichment Analysis have been likewise dissected cautiously in this work. Demonstrating incorporates picking the right informational collections, calculations, factors, and techniques for productively organizing information for information mining. To propose a medication for sickness, it is vital to realize the influenced qualities related to the particular infection. Examination with more than one infection, understanding the linkage of the qualities between the related sicknesses is significant. In the ebb and flow study, a cross-conversation sub pathway was developed by planning between qualities to PPI to show the association between the chose illnesses through the natural level. PPI organization, Enrichment Analysis, Pathway examination, co-articulations add to a medication plan for chosen four illnesses. Utilizing GeneMANIA the quality co-articulation and actual communication are set up. Actual Interaction Pathways of at-risk qualities are likewise guaranteeing a typical medication plan to the plan.

5.2 Recommendation for Future works:

It is important to comprehend that the contaminated qualities are associated with every one of these infections to create a medication for more than one illness. It is additionally essential to know the association between the qualities and the related illnesses to arrive at the objective. The current examination did practically every one of the examinations with the help of bioinformatics devices which permit more estimations in the field of bioinformatics utilizing bioinformatics programming. Analysts who willing to improve further can attempt to make a standard medication for sicknesses utilizing a microarray or microRNA informational collection for investigation.

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