CONNECTING THE DOTS: A NETWORK ANALYSIS OF CKD AND AKI GENES

Student: Katelyn Hur, Red River High School, Grand Forks, ND

Mentor: Junguk Hur, PhD, University of North Dakota, Grand Forks, ND

BACKGROUND

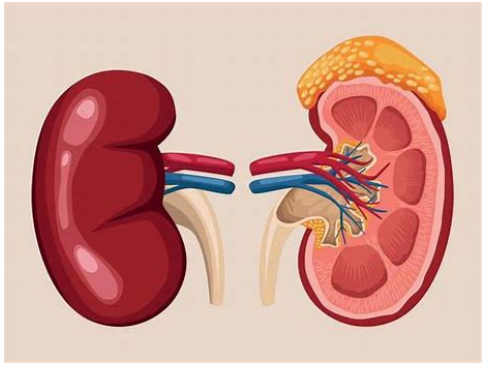
- Was intrigued to learn about the severity of kidney diseases and the fact that we are still trying to find effective cures.
- Kidney diseases are primarily classified into two main types: chronic kidney disease (CKD) and acute kidney injury (AKI).

What is Chronic Kidney Disease (CKD)?

Chronic Kidney Disease is a gradual loss of function in your kidneys often because of diabetes and high blood pressure (long-term conditions), it is uncurable.

What is Acute Kidney Injury (AKI)?

Acute Kidney Injury is a sudden loss of function in your kidneys often because of dehydration, blood loss, or urinary tract infection, it is curable once the underlying cause is cured.



Kidney

https://www.vecteezy.com/free-vector/kidney

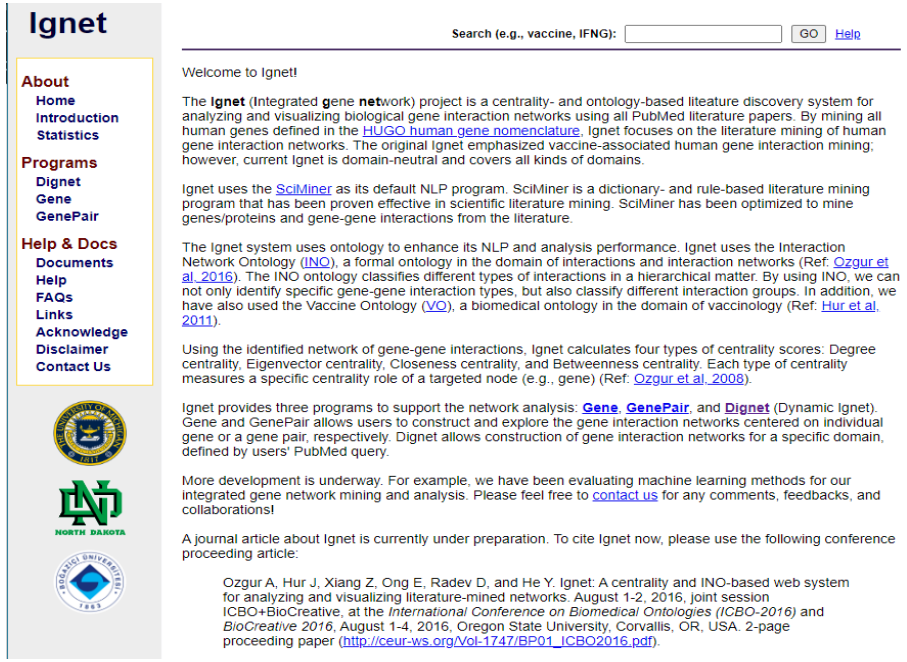
WHY ARE CKD & AKI IMPORTANT?

- 800 million people (10% of the world's population) are affected by Chronic Kidney Disease (CKD)
- The annual cost of treating CKD is estimated to be over $120 billion
- CKD is a leading cause of death globally, with millions of people dying each year due to complications related to CKD
- Acute Kidney Injury (AKI) affects about 13.3 million people globally each year
- The cost of treating AKI in hospitalized patients in the United States is estimated to be around $10 billion annually
- AKI causes long-term health issues and increased mortality if not treated promptly

How can we better understand the differential gene interactions in CKD and AKI to discover improved treatment options for kidney failure?

Global Facts: About Kidney Disease | National Kidney Foundation

METHODOLOGY (DATASETS)

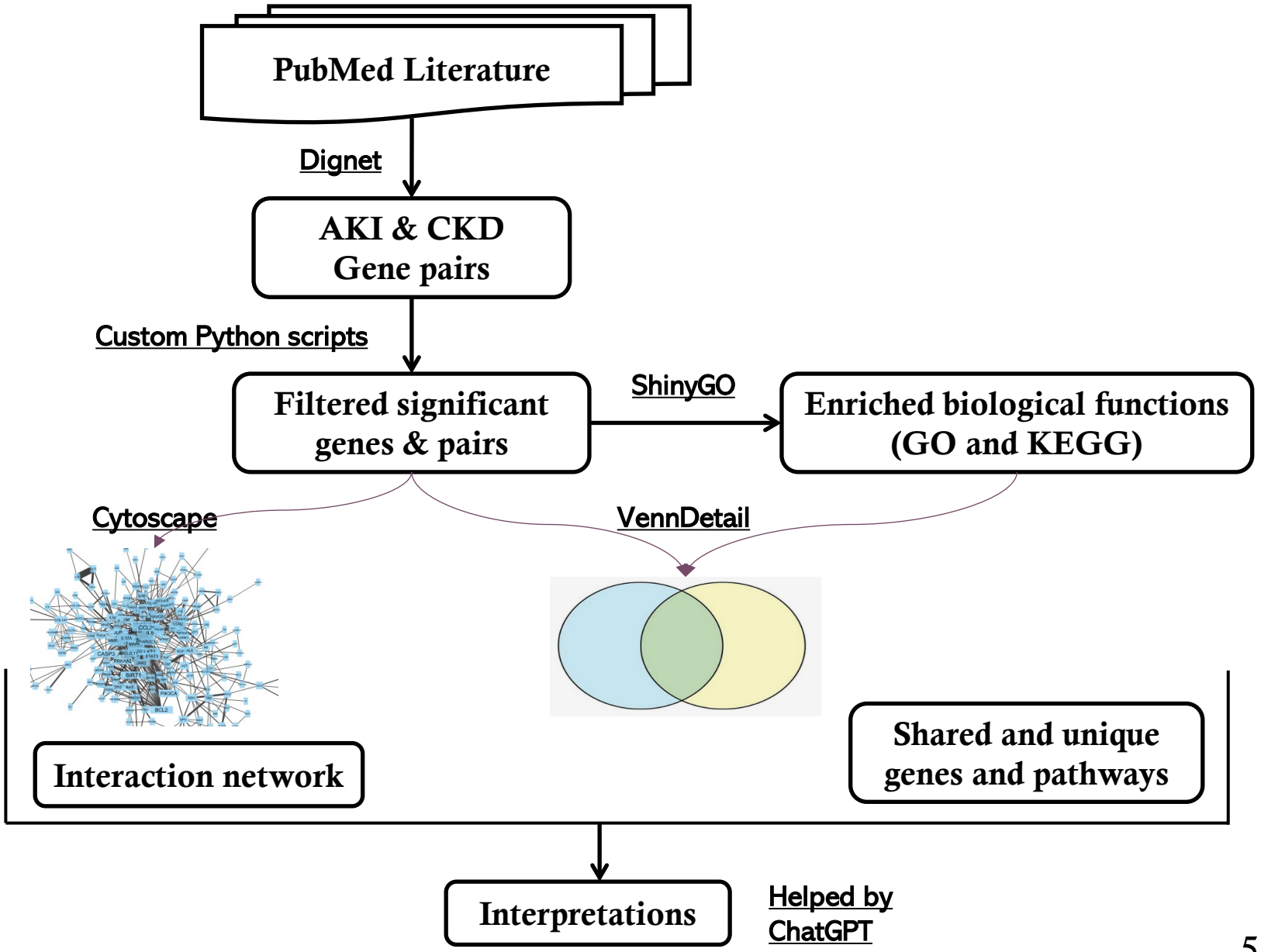


- The abstracts of biomedical literature in **PubMed**
  - "**Acute Kidney Injury**": **77,050 papers**
  - "**Chronic Kidney Disease**": **86,023 papers**
- Gene-pairs downloaded from these articles identified by dynamic Ignet (Dignet)

The **Ignet (integrated gene network; https://ignet.org)** project is an ontology-based system of discovering literature (from PubMed) analyzing and visualizing biological gene interaction networks.

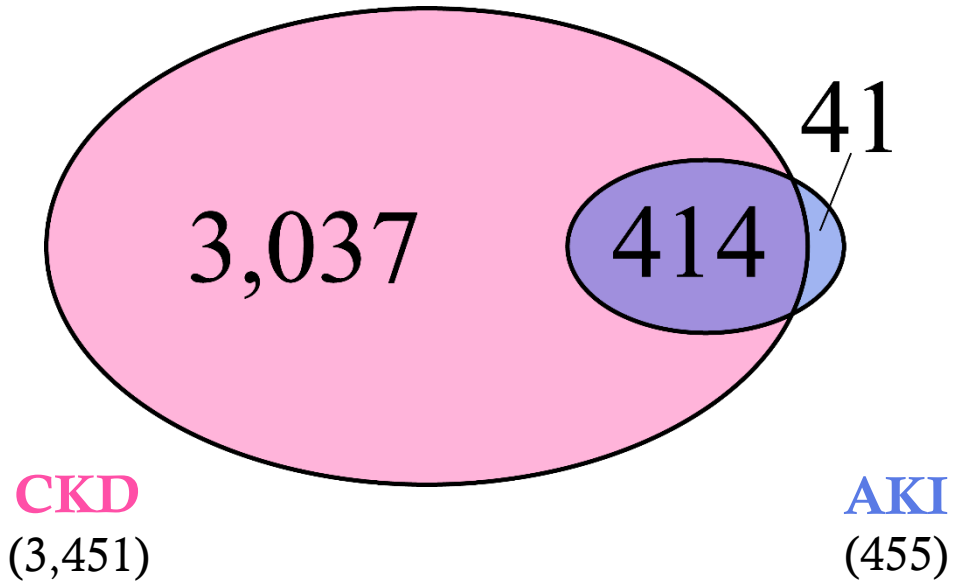
WORKFLOW

- **Dignet**: **Dynamic Ignet** with PubMed search
- **Custom Python scripts**: my own scripts for handling gene-pair files, calculating overlap, generating a network file
- **ShinyGO**: web-based gene set analysis system
- **VennDetail**: web-based overlap analysis (Venn diagram)
- **Cytoscape**: Network visualization tool
- **ChatGPT**: Artificial Intelligence (AI) ChatBot

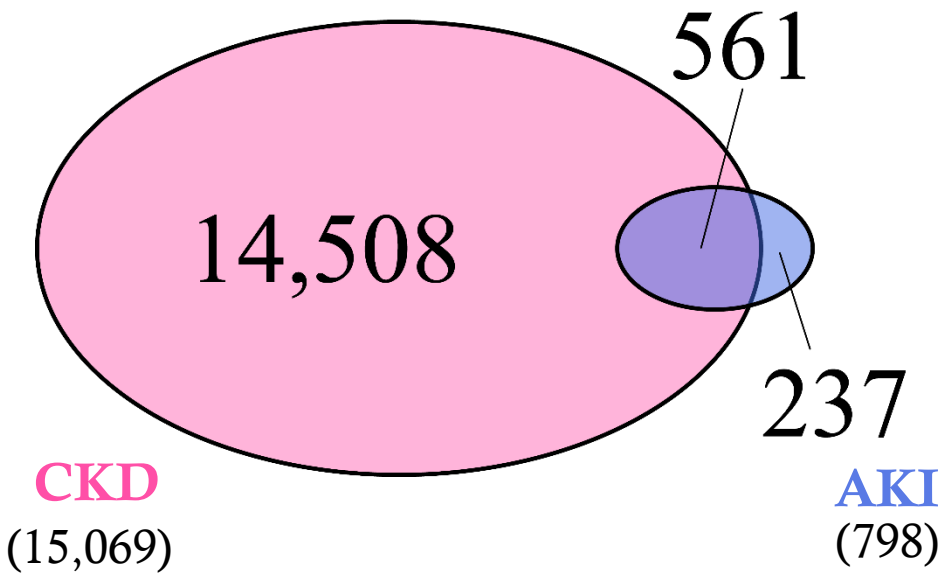


OVERLAP - VENN DIAGRAMS

Genes



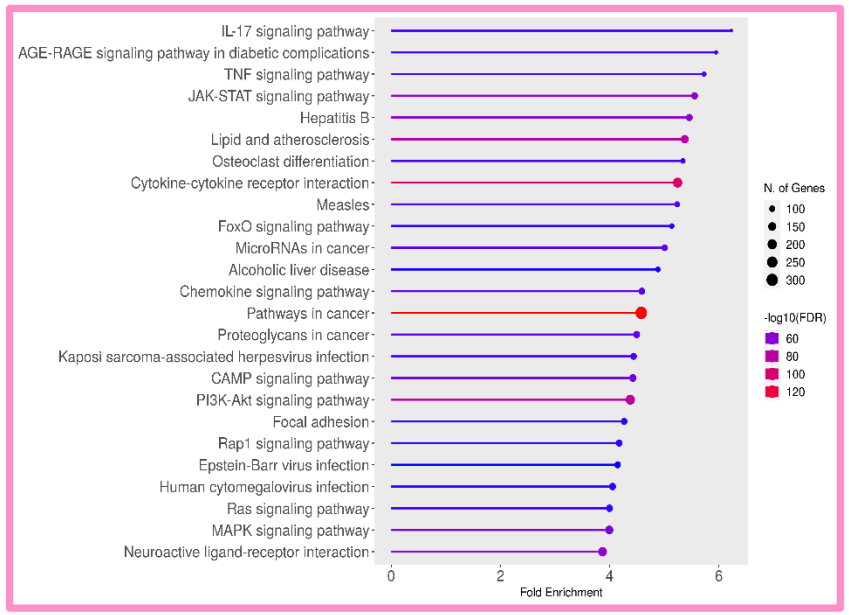
Gene Pairs



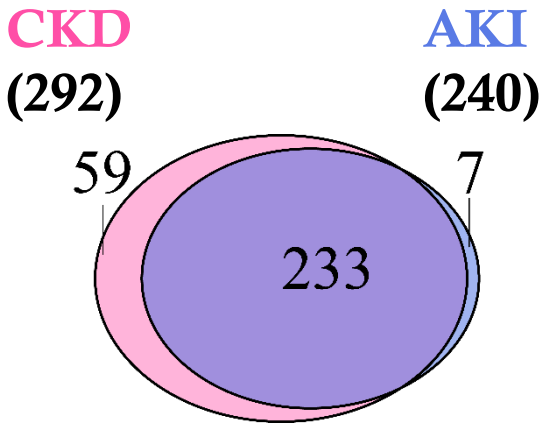
A lot more genes and gene-pairs in CKD than AKI

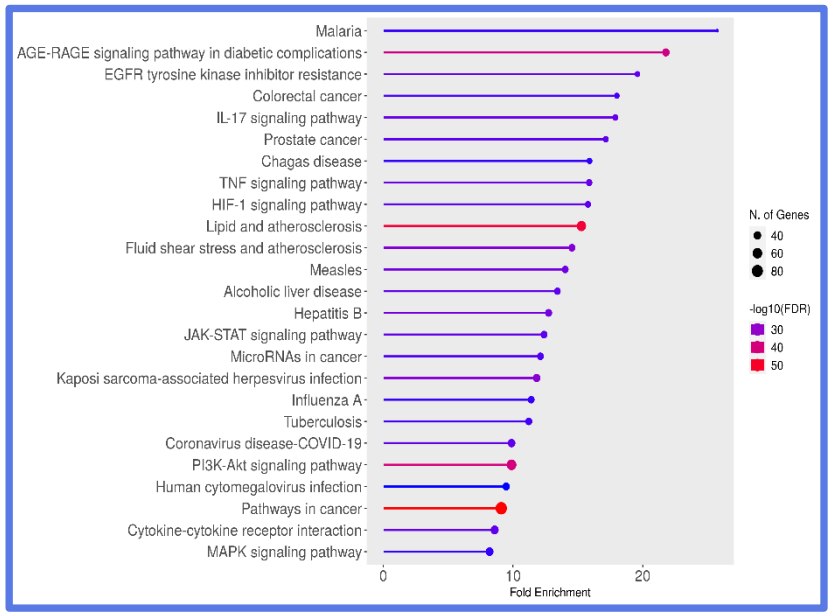
VennDetail (http://hurlab.med.und.edu:3838/VennDetail/)

KYOTO ENCYCLOPEDIA OF GENES AND GENOMES (KEGG) PATHWAYS – TOP 25



All shared except cAMP signaling pathway





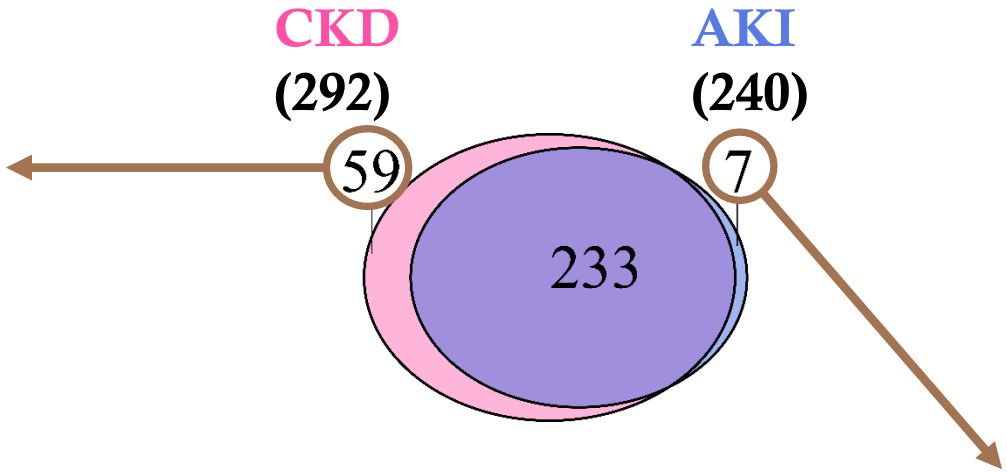
All shared

ShinyGO (http://bioinformatics.sdstate.edu/go/) & VennDetail

UNIQUE KEGG PATHWAYS

hsa04911 Insulin secretion
hsa00010 Glycolysis/Gluconeogenesis
hsa00980 Metabolism of xenobiotics by cytochrome P450
hsa00620 Pyruvate metabolism
hsa01230 Biosynthesis of amino acids
hsa04972 Pancreatic secretion
hsa04971 Gastric acid secretion
hsa05204 Chemical carcinogenesis-DNA adducts
hsa04970 Salivary secretion
hsa00140 Steroid hormone biosynthesis
hsa00830 Retinol metabolism
hsa00230 Purine metabolism
hsa05032 Morphine addiction
hsa04142 Lysosome
hsa00983 Drug metabolism-other enzymes
hsa05033 Nicotine addiction
hsa04330 Notch signaling pathway
hsa04340 Hedgehog signaling pathway
hsa04727 GABAergic synapse
hsa04721 Synaptic vesicle cycle
hsa04120 Ubiquitin mediated proteolysis
hsa01232 Nucleotide metabolism
hsa00071 Fatty acid degradation
hsa04978 Mineral absorption
hsa00591 Linoleic acid metabolism
hsa00270 Cysteine and methionine metabolism
hsa00910 Nitrogen metabolism
hsa01040 Biosynthesis of unsaturated fatty acids
hsa04961 Endocrine and other factor-regulated calcium reabsorption
hsa04975 Fat digestion and absorption
hsa03250 Viral life cycle-HIV-1

hsa01212 Fatty acid metabolism
hsa00500 Starch and sucrose metabolism
hsa00600 Sphingolipid metabolism
hsa03430 Mismatch repair
hsa02010 ABC transporters
hsa04392 Hippo signaling pathway-multiple species
hsa01210 2-Oxocarboxylic acid metabolism
hsa03420 Nucleotide excision repair
hsa00603 Glycosphingolipid biosynthesis-globo and isoglobo series
hsa00100 Steroid biosynthesis
hsa00430 Taurine and hypotaurine metabolism
hsa00640 Propanoate metabolism
hsa00564 Glycerophospholipid metabolism
hsa04962 Vasopressin-regulated water reabsorption
hsa04130 SNARE interactions in vesicular transport
hsa04742 Taste transduction
hsa03460 Fanconi anemia pathway
hsa00280 Valine leucine and isoleucine degradation
hsa00053 Ascorbate and aldarate metabolism
hsa00565 Ether lipid metabolism
hsa04136 Autophagy-other
hsa00240 Pyrimidine metabolism
hsa00650 Butanoate metabolism
hsa00232 Caffeine metabolism
hsa00130 Ubiquinone and other terpenoid-quinone biosynthesis
hsa00515 Mannose type O-glycan biosynthesis
hsa00120 Primary bile acid biosynthesis
hsa04070 Phosphatidylinositol signaling system



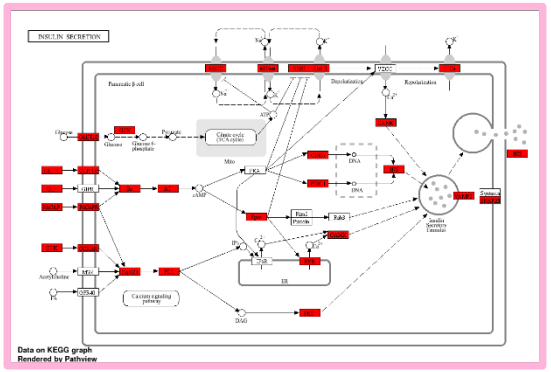
ChatGPT found the pathways highlighted in red to be the most relevant.

hsa00470 D-Amino acid metabolism
hsa00730 Thiamine metabolism
hsa00061 Fatty acid biosynthesis
hsa00520 Amino sugar and nucleotide sugar metabolism
hsa00524 Neomycin kanamycin and gentamicin biosynthesis
hsa05322 Systemic lupus erythematosus
hsa00750 Vitamin B6 metabolism

ShinyGO (http://bioinformatics.sdstate.edu/go/) & VennDetail & ChatGPT

KEY KEGG PATHWAYS

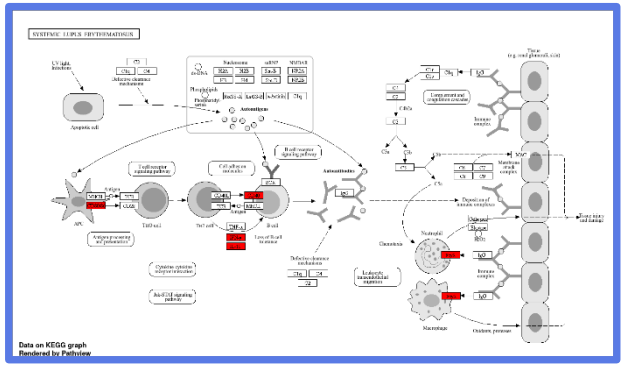
hsa04911 Insulin secretion



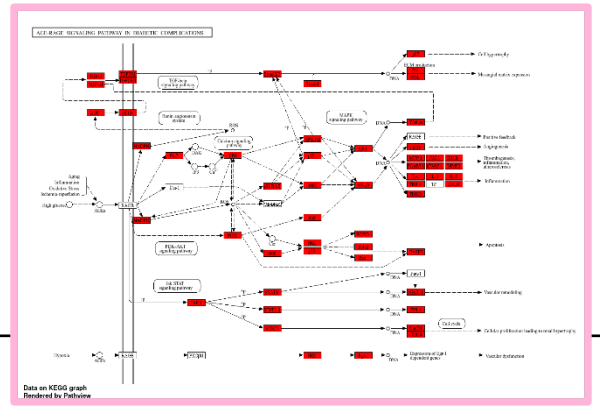
Unique

: genes from CKD (for pink outline) and AKI (for blue outline)

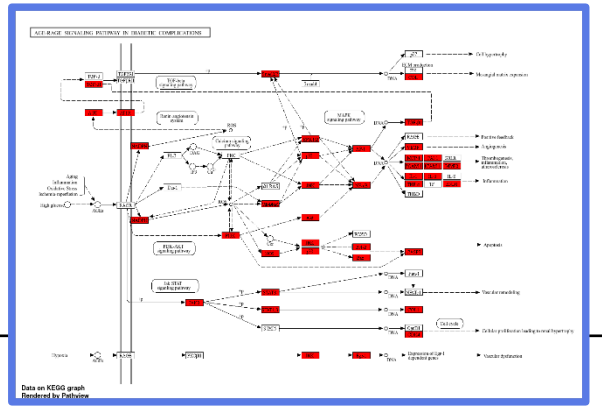
hsa05322 Systemic lupus erythematosus



Common Key Pathway: hsa04933 AGE-RAGE signaling pathway in diabetic complications

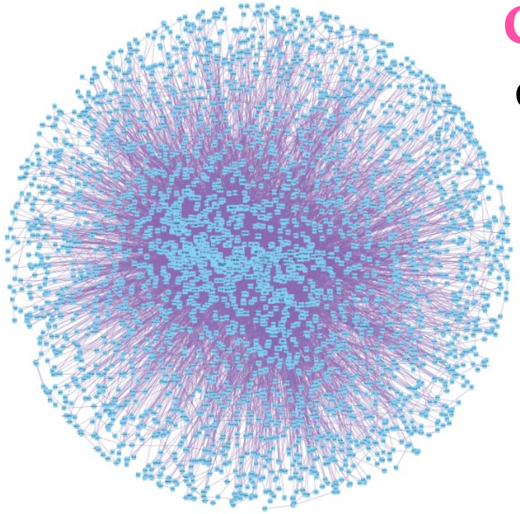


Very high overlap between CDK and AKI

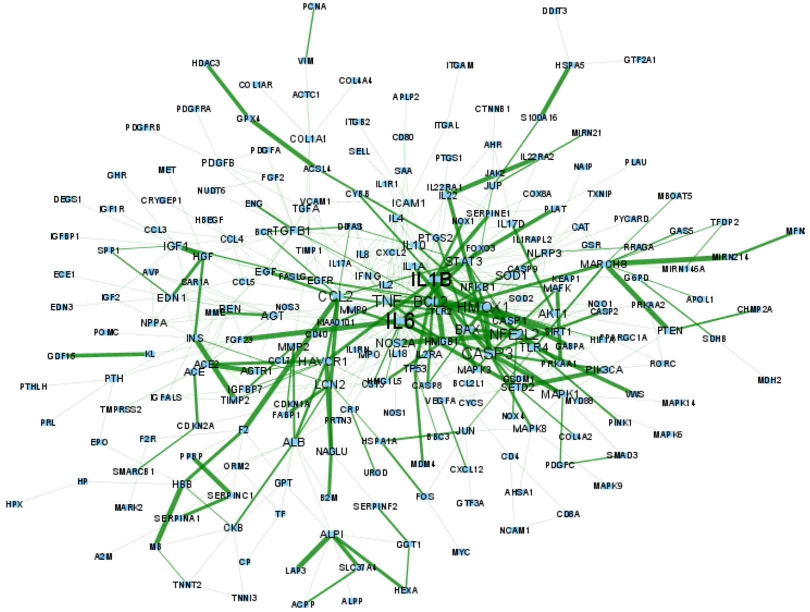


GENE PAIR NETWORK

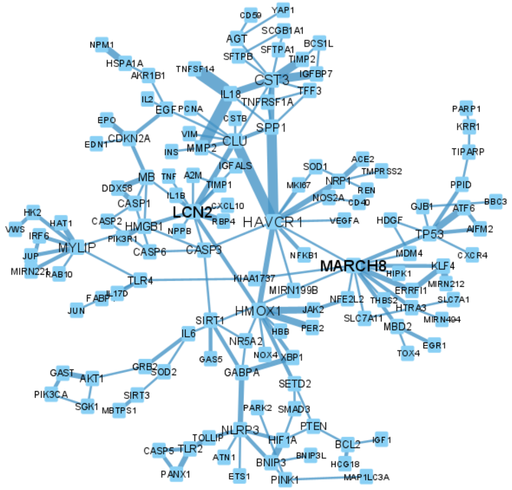
- Using Cytoscape to visualize the gene pair networks
- Three networks
  - Common: centered around IL1B, IL6, …
  - CKD-unique: too big. Top edges around TNF, AKT1, INS, IFNG, …
  - AKI-unique: LCN2, MARCH8, …



CKD only



Common



AKI only

CONCLUSIONS & DISCUSSION

- **Major findings**
  - Substantially more genes and pairs in CKD because there are much more publications on CKD than AKI
  - AGE-RAGE is the top common enriched biological function of CKD and AKI
  - Insulin secretion is a unique enriched biological function of CKD
  - Systemic lupus erythematosus is a unique biological function of AKI

- **What are the best treatment targets for kidney failures (CKD and AKI)?**
  - The three enriched biological functions mentioned above could be important potential targets.

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