Adjustment of p-Value Expression To Ontology Using Machine Learning For Genetic Prediction, Prioritization, Interaction, And Its Validation In Glomerular Disease

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RESEARCH

Adjustment of p-value expression to ontology using machine learning for genetic prediction, prioritization, interaction, and its validation in glomerular disease

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Abstract

Background: The selection of gene expression mixed to multiple similarity scores of their gene ontology terms (GO), were adjusted by our algorithm as essential prediction tasks for evaluating the regulatory pathways. Moreover applying machine learning techniques, in order to link the gene products into networks that prioritize candidate genes as classification. Finally detecting some significant genetic interactions by applying our algorithm model as validation of the results.

Results: Experimental validation of all associations facilitates the discovery of causative genes known to be related to glomerular diseases (GD). As well as EGR1, IL33, BMP2, SLAMF8. In which their GO annotations related to this gene include kidney vasculature development, regulation of cell activation/inflammatory/immune effector/adaptive immune/glomerulus/glomerular mesangial cell proliferation development, etc. Other genes as TNXA, FCER1A, NME3, FMOD, BTG2, PTGER4, AXL, CYP1A2, CYTL1, BHLHE40, IFI16, SPON1, ETNPPL, COL14A1, ITGAV, MYOZ2, CAMK2A, SORT1, RANBP1, in which their variants information include complement a set of C3, C4, and C7 measurement, serum IgE/IgA measurement, c-reactive protein measurement, nephrotic syndrome, immune system disease, tuberculosis, glomerular filtration rate, chronic kidney disease, etc. The lasts enable a rapid interpretation of complex gene expression studies. As well, other high-throughput genomics assays illustrate an overview of a computational model for gene prioritization and their genetic interactions.

Conclusions: The furtherance of combining and adjusting the genes expression to multiple similarity scores of their gene ontology (GO) and interacting all possible cross-association of the results reported classification of genes between among to the subject category and validated the abstracts.

Keywords: Glomerular diseases; Gene expression; Gene ontology; Machine learning; omics sciences; Gene prediction; Gene prioritization; Gene interaction

Background

The term C3 glomerulopathy (C3G) is a group of related conditions that cause the malfunction of the kidneys [1], characterized by the presence of glomerular deposits composed of C3 [2]. These glomerular diseases (GD) include many conditions with a variety of genetic/environmental causes [3]. C3G is associated with changes (mutation) in many genes. Most of these genes provide instructions for making

proteins that help to regulate a part of the body's immune response known as the complement system [4]. This system works together as a group of proteins to destroy foreign invaders/trigger/inflammation. A specific mutation in the complement system-related genes, like C3, ADAM19, ADAMTS13, C3AR1, C8A, CD46, CFB, CFD, CFI, CFHR(1-5) and as well as other complement system-related genes [5, 6], risk haplotypes of CFH and CD46 have been identified that modify disease penetration and severity [7, 8]. In most cases, the cause of the C3G is unknown.

Many kinds of research are still devoted to discovering new gene selection techniques. Likewise, the confidence of using a single criterion for genes selection is not always adopted, considering which criterion should be good. This question has inspired us with the idea of taking into account the ranking of evaluating p-value expression and proposing a novel gene selection for the transcriptomics data, focusing on the adjustment of gene expression to the similarity score. Furthermore, our solution can be considered the most informative and stable method for gene prediction/selection. Also, the gene expression results consist of the input of normalized gene expression measurements [9]. From this, a linear model fit for all genes is computed to find genes with significant differential expression (DE) between different conditions from understudied raw data (as a set of binary files in CEL format), accessible via the public repository of microarray data NCBI Gene Expression Omnibus (GEO) [10]. Moreover, the first step in the pre-processing is the quality control of the data because this latter is an essential step in any analytical process as a relative concept that depends on the nature of the biological sample, the experimental settings, and other factors. The full Robust Multi-array Average (RMA) was also performed to background-correct, normalize and summarize the process [11, 12]. The organization of this article consists of two large sections. The first one (methods) includes gene signature identification of Differential Expressed (DE) genes, then a followed step leading to construct the workflow and their structure, prioritizing and interacting gene products on each cluster. Finally, a result section covers a set of interpretations of the biological/clinical results of our hypothesis.

Methods

A major focus of this follow-up study was demonstrated in (Fig. 1), proposing and validating a novel matrix-Expression-Similarity-Frequency; consisting of a new scoring scheme; based on a given combined/adjusted linear DE measurement selection in diverse experimental conditions of individual samples. Machine learning tasks [13, 14, 15] then were used focusing on combining mathematical algorithms to our gene products by clustering this last as unsupervised learning first based on their normalized matrix-Expression-Similarity-Frequency scores of occurrence to find out the structure as groups of a similar category. The data, in this case, contains only inputs and no desired output labels. Then a classification as the second step where the algorithm contains both the inputs and the desired outputs (limited to a set of outputs), used to construct co-regulation, and link them into networks that prioritize candidate genes as a logistic regression tool. In addition, significant genetic interactions were detected for a specific tissue type, genetic background, experimental stimulus, or clinical variables as validation of the results.

Experimental Data

Five datasets (Table. 1) consisting of human kidney biopsies of patients are used in our analysis, defining a comparison of glomerular transcriptome profiles of adult-onset steroid-sensitive focal segmental glomerulosclerosis and minimal change disease [16]. Transcriptomic and proteomic profiling, revealing insights of mesangial cell function in patients with IgA nephropathy [17]. Glomerular transcriptome from subjects in the NEPTUNE cohort [18]. Shared molecular targets in the glomerular transcriptome from patients with nephrotic syndrome and ANCA-associated vasculitis. Glomerular transcriptome from European renal cDNA bank subjects and living donors [19].

A computational algorithm for gene adjustment

The statistical methods used to detect DE genes were as moderated t-statistics for the microarray data based on a linear model fit; by fixing a P-value as 0.0001, estimated as a prior probability that a gene is DE [20, 21]. Then the semantic similarity computation was assumed based on Wang method [22], and using GOSemSim [23] package among gene products, based on the information's content (IC), and a directed acyclic graph (DAG) [24]. The IC-based measures depend on the frequencies of two GO terms involved on their closest common ancestor term in a specific corpus of GO annotations [25, 26]. The similarity computation was assumed for the three distinct aspects molecular functions (MF), biological processes (BP), and cellular components (CC). The best-match average strategy (BMA) was also used to calculate the average of all maximum similarities on each row and column for the similarity computation. Furthermore, a new scoring for the gene similarity measures for every pair of genes is demonstrated here (Formula. 1). Through which the matrix evaluates whether the means and normally distributed score within each independent pair of genes of samples evaluates an important significance or not by introducing the matrix-Similarity-based.

$$M_{simsc}(g_1, g_2) = \sum_{n=1}^{Lengthx} \sum_{n=n+1}^{Lengthx} \left(\sqrt{\frac{1}{2} * \left(\frac{\delta_1^2}{\delta_2^2} + \frac{\delta_2^2}{\delta_1^2} \right)} \right) * \left(\frac{\mu_1 + \mu_2}{2} \right)^2 \quad (1)$$

- Only the paired groups can be used to perform the paired test.
- The sample means are denoted as μ_1 and μ_2 for each score of similarity.
- Each score is sampled independently and randomly.
- The sample standard deviations δ_1 and δ_2 are normally distributed within each of the two rows.

Gene prediction results consist of a matrix-Expression-Similarity-Frequency-based as a new adjusted scoring for the DE measurement mixed with their scores and frequencies of occurrence of matrix-Similarity-based, which yield the final association score. These statistic scores are used for the candidate's genes as demonstrated here (Formula. 2). The genes with the highest scores will be selected and improved first then to serve as inputs to the machine learning steps.

$$M_{CombSc} = n_{expr} * M_{expr} + n_{sel} * M_{simsc} \quad (2)$$

- A number of expressed genes provided with fixed P-value was combined to the expression matrix.
- A number of correlated genes combined to semantic similarity matrix.

Prioritization of candidate genes based Machine Learning

Machine learning techniques [27, 28, 29] were performed first by clustering our gene products; from the normalized final scores (results of Formula. 2), segmenting their into k clusters to understand biological processes as well as molecular functions [30, 31]. Each cluster represents a group of similar observations performed using the ward method and Euclidean distance. Whereas, objects from different clusters are as dissimilar as possible. The algorithm can stop when the assignment of genes to clusters has no longer changed [32, 33]. Further, each genes cluster list has been exposed to the hgu133a,hgu133plus2 database of homo sapiens, as a direct mapping of gene symbol [34, 35], then implemented into a hypergeometric model to assess whether the number of selected genes are linked/associated with the pathogenesis of the diseases [36, 37]. Moreover, all enriched terms are associated with their enrichment scores, allowing the possibility to cross from high-level concepts to detailed pathway diagrams showing bio-molecular events using GroupGO(), EnrichGO() function [38, 39]. Genetic variation was also studied, based on the genome-wide association study (GWAS) Catalog to tag variation across the genome, and enable investigations of causal variants [40, 41, 42, 43]. The most promising conserved non-coding regions of the promoters/enhancers [44] based oPOSSUM [45]; were also used to select the interaction between our gene products. Whose interactions between genes and transcription factors (TFs) are important for understanding gene regulation and the origin of protein complex components [46].

To facilitate the prioritization of causative genes as the second step of machine learning and based on supervised learning algorithm tools. A new gene prioritization algorithm tools were explained based on a logistic regression method [47, 48, 49, 50]. The gene prioritization boosts the power of identifying the most promising phenotype-associated among those clusters in normal conditions in different tissues (in which each gene can have a normalized score of expression in Tissue expression database [51]).

$$Score_{prioritization}(Gene_i|Tissue_t) = \mu_0 + \mu_1 X_1 + \mu_2 X_2 + \mu_3 X_3 + \dots + \mu_n X_n \quad (3)$$

- μ_0 is the means of expression-tissue-specific for a given gene with fixed tissues.
- $\mu_1, \mu_2, \mu_3, \dots, \mu_n$ represents the means of (frequencies of occurrence) for target genes for each process.
- $X_1, X_2, X_3, \dots, X_n$ represents the normalized expression values of biological processes, GWAS, and TFs, etc.

Following the hypothesis that genes underlying similar tissues will share functional and phenotype characteristics, we incorporate logistic regression for any given training genes which needed to be prioritized (formula. 3). The gene prioritization model could be formulated by arranging the candidate genes (i) in the order of their tissues (t) first; to be sure to be associated with the pathology. Our gene prioritization algorithm takes two inputs: a collection of evidence sources defining a phenotype/trait of interest, and enhancer/promoter interactions information, extracted for a given gene, linked to each other with a normalized score; reflecting the “likelihood” for each gene to be responsible for the phenotype. Then a second factor represents a prioritization mean factor (frequencies of occurrence of each entire). The output of the algorithm is a list of candidate genes arranged according to calculated scores for each tissue.

Overall, a full process of extracting transforming, and loading (ETL) data from homogeneous or heterogeneous sources [52, 53] was established to access our data. In short, it’s an essential component in cleansing, customization, reformatting, integration, and insertion of our prerequired data [54, 55, 56]. In this paper, we tried to navigate through our adjusted genes to conceptualize the ETL processes, as shown in (Fig. 2); modeling a prioritization tool first, then modeling genetic interaction constructs into proper storage (format/structure) for querying and analysis.

Genes Interaction

Genetic interactions of omics data refer to a combination of pairs of genes into different tissues of fixed clusters as shown in (Fig. 3), whose contribution to a phenotype between specific variants in complex traits and tissues remains a major challenge [57, 58, 59]. Moreover, as the number of interacting genes increases, and because the traditional statistical methods are limited to their ability to identify interacting genes in high dimensions data [60, 61, 62]. We developed a novel algorithm-based model; called mixed-gene tissues interaction (MGTI) using our previous data. It first calculated gene prioritization scores and then identifies significantly interacted mixed-gene between the selected tissues using (formula. 4), reflecting strengths of regulatory interactions, aimed to understand etiology for our glomerular disease as a use case.

$$Score_{inter}(g_1, g_2) = \frac{\log_{10}(S_p(g_1)) + \log_{10}(S_p(g_2))}{2 + \log_{10}(\max(S_p(g_1, g_2)))} \quad (4)$$

- S_p represents a score of genes prioritization.
- The interaction scores are between [0,1].
- When the interaction scores are $\cong [0.31, 1]$, the MGTI model reflects an increased regulation of diseases.
- When the interaction scores are $\cong [0.1, 0.3]$, the MGTI model reflects a decreased regulation of diseases, in which we should interact more with other possible genes.

Results and Discussion

The spectrum of glomerular diseases is an abnormal control of complement cascade activation, whose actions are considered as part of the innate immune system,

procuring an immune complex deposition of fragments of C3 in glomeruli [63]. In most cases, GD is often resulting in damage to the kidneys, of which the cause is unknown. The first thing we do to measure the transcriptional levels was the validation of the information stored in raw data measurements [64, 65]. Where, the last was more described in our paper [66]; published of ACM organization, Proceedings of the New Challenges in Data Sciences: Acts of the Second Conference of the Moroccan Classification Society; as validation process of the information stored in expression sets. Each experiment was first analyzed separately, and the results have then combined based on their P-value [67].

Genetic contributions and their statistical impact for estimation of the predictive models of gene

Results of each number of DE genes were extracted, combined, and expected in a uniform distribution of the P-value that corresponds to five different datasets (Table. 1). The semantic similarity results analysis is represented as the distance of (dis)/similarity between our list of genes in the interval of $[0,1]$. In which, when $Sim(g_i, g_j) = 1$ refers that $(i = j)$. Afterwards, when $Sim(g_i, g_j) \cong [0.6, 1]$ means that the precision of semantic similarities over genes in $GO(g_i, g_j)$ is more significant, and related to common pathologies. Then, when $Sim(g_i, g_j) \cong [0, 0.5]$ refers that the precision of semantic similarities over genes in $GO(i, j)$ can be significant or related to other common pathologies. However, many genes had a high score on the expression in parallel to a low score of GO (or the reverse). Whose the classical functional analysis in the literature is based only on the selection of genes from experiments, then to search their dis/similarity score. This problem was inspired us to combine/adjust both scores (expression and similarity) in a single formula, giving more chance to predict genes related to pathologies based on their occurrence frequencies. For that, we propose a novel gene selection method by introducing a novel matrix-Expression-Similarity-Frequency-based. Different threshold values give different levels of sensitivity and specificity, whether the low threshold (with red color) refers to a false positive, and the high threshold (with blue color) refers to true positive, as fixed for the validation of our study. This threshold makes it more likely specific (more high positives) against more sensitive (more low positives); as shown in the figure (Fig. 4) with a given fixed threshold of observations.

Evaluation/Prioritization based tissues using regression model

An estimating results score from formula. 2 for each gene was the input for computing the clustering algorithms. Four clusters were found, each cluster represents a group of similar observations. To search for shared functions, all gene products were linked to different databases as an enrichment, traits (non-coding variants), tissues databases, and conserved transcription factor binding sites selected based on their score of %GC content. These kinds of analyses generate a huge quantity of data, which needs to be given a biological interpretation. Majors of these genes fall under (kidney, blood, urine, immune system, and embryonic) tissues, and in the hypothesis interpretation and validation section for the GD, we were based on a specific entire to generate a list of maximum information of genes related to a specifics biological pathway terms as regulation of inflammatory response, regulation of acute inflammatory response, regulation of protein processing/maturation, positive regulation

of glomerulus development, regulation of glomerular mesangial cell proliferation, regulation of adaptive immune response, complement activation, etc. A circular (Circos) plot (Fig. 6) was the most efficient to visualize genomic data giving us the possibility to easily map information on a single plot. A Heatmap-like functional classification plot (Fig. 5), was used to visualize the most significant terms with the terms expected from the literature, according to some scores for the causative genes as (EGR1, IL33, BMP2, SLAMF8, etc.). In which, we filtered and selected the most dominant GO terms according to GD that include kidney vasculature development, regulation of cell activation/ inflammatory/immune effector/adaptive immune/glomerulus/glomerular mesangial cell proliferation] development, etc. A barplot (Fig. 5) was used to visualize the gene-variant-trait associations among GWAS catalog for the most dominant terms like complement C3, C4, C7 measurement, serum IgE/IgA measurement, c-reactive protein measurement, nephrotic syndrome, immune system disease, tuberculosis, glomerular filtration rate, chronic kidney disease, urinary metabolite measurement, C-reactive protein measurement, glomerular filtration rate, etc. In addition, many genes such as TNXA, FCER1A, NME3, FMOD, BTG2, PTGER4, AXL, CYP1A2, CYTL1, BHLHE40, IFI16, SPON1, ETNPPL, COL14A1, ITGAV, MYOZ2, CAMK2A, SORT1, RANBP1, etc. represented some trait association. Finally, the PieChart plot (Fig. 5) represented the means of expression of genes in the selected tissues; Kidney, Kidney cancer cell, Immune system, Urine, Blood, Blood vessel, Blood plasma, Hematopoietic stem cell, Parenchyma, Uroepithelium, HEK 293 EBNA cell, HEK 293ET cell, HK 2 cell.

The Gene prioritization model could be formulated as follows (which is composed of two parts): arrange candidate genes in the order of their normalized scores and frequencies of occurrence from formula. 2, then to their normalized scores and frequencies of occurrence for categorical tissues, biological process, TFs, and variants. By the same token, the logistic regression model (parametric regression) was performed for categorical data to prioritize the dependent variable using a given set of independent variables for solving Classification problems. In logistic regression, it is not necessary to have a linear relationship between the dependent and independent variable, but there should not be collinearity between the independent variable. As discussed above, logistic regression was used to classify elements of each cluster under various tissues by calculating the mean of normalized expression of each element of the set. A confidence regression line provides a representation of the uncertainty in a sense, we can prioritize among a cluster of genes, the most promising ones based on their prioritization scores on each selected tissue as visualized on (Fig. 7). We notice also in the table (Table. 2), that many redundant genes have been more promising by our applying the priority model for fixed tissues, this has only one interpretation which has a great value of the expression in the different tissue analyzed. The process of arranging all possible prioritizing genes causing disease based on their logistic regression has shown consistent genes may reside in distinct pathways and affect the promoter/regulatory region of location-related, organism-specific.

Based PubMed resource, for information retrieval, summarizing and comparing topics according to their frequencies of occurrence [68, 69, 70], to broaden or/and

narrow a search [71], and to exclude unwanted search terms/concepts from a specific speech as "glomerulopathies", "diabetic kidney disease", "tumor Nephrectomy", "diabetic nephropathy", "focal segmental glomerulosclerosis", "rapidly progressive glomerulonephritis", "minimal change disease", and "membranous glomerulonephritis". In addition, 972 abstracts that were extracted, had 11 genes as COL4A5, EGR1, GDF15, CPE, CASK, NT5E, JUN, AXL, CCL3, IL33, ITGAV from our candidate's genes have already been reported in previous studies with GD.

Genetic interactions bridging transcription factor and pathways in genome-wide association studies

Traditional statistical methods consider gene-gene interactions or estimate interactions among only a small number of phenotype information with significant main effects. However, our MGTI algorithm-based model can be applied especially when the data are high dimensional (many attributes or independent variables) or when interactions between more than two tissues can play a role in the analysis of human disease etiology and regulation data mining. To perform ETL (extract-transform-load) operations, either a vector of SQL commands was used to select data based on a specific entity. Here we were focused to select the best score of gene-gene interaction to support and validate the hypothesis validation. Representative (Table. 3 and 4) have been added to show some randomly gene-gene interaction-algorithm tools based MGTI model. Finally, the gene interaction results encode a superfamily of proteins, playing a role in transcriptional expression. Whether ligands of this family bind various enzyme binding and receptors/initiators; leading to recruitment and activation of family transcription and/or signaling factors that regulate the level and stability of gene expression. The encoded proteins possess an intracellular and/or extracellular domain that is composed of different motifs. This gene may be involved in several cellular functions including multiple cell types and various tissues. Alternative splicing results in multiple transcript variants of these candidate genes.

The early diagnosis and prognosis of any disease type have more necessity of using of bioinformatics tools. As it can facilitate the subsequent clinical management of patients. This follow-up analysis can be applied also to other types of data such as cancer data, etc. Finally, our global objective was to incorporate/develop a Shiny web-based application as an R framework designed to help and facilitate users to navigate under "Shiny apps" as tutorials, about us, and test our algorithms tools: gene prediction, prioritization, and interaction.

Conclusions

The linked resources of biological/clinical data-based expression profiles (adjusted score), were used to validate molecular biology research. Moreover, the result of the highest expression is in most cases; a list of genes, defining a comparison of glomerular transcriptome profiles established to investigate the underlying disease mechanisms; as a representative knowledge of focal segmental glomerulosclerosis, minimal change disease, insights into mesangial cell function in patients with IgA nephropathy. Majors of our prioritized genes fall under the transcription co-factor

binding, regulation of glomerular mesangial cell proliferation, regulation of adaptive immune response, complement activation, etc. Furthermore, that achieves and validates the target of the best-represented gene-gene interactions findings.

List of abbreviations

- Gene Ontology (GO)
- Glomerular Diseases (GD)
- C3 Glomerulopathy (C3G)
- Differential Expression (DE)
- NCBI Gene Expression Omnibus (GEO)
- Robust Multi-array Average (RMA)
- Information Content (IC)
- Directed Acyclic Graph (DAG)
- Best-Match Average (BMA)
- Genome-Wide Association Study (GWAS)
- Transcription Factors (TFs)
- Extracting Transforming, and Loading (ETL)
- Mixed-Gene Tissues Interaction (MGTI)

Availability and Requirements

- Project name: GenePPI
- Project home page: <https://github.com/boutaina-ettetuani/Glomerular-Diseases-Analysis>
- Programming language: R
- Any restrictions to use by non-academics: None.

Declarations

Ethics approval and consent to participate

Authors confirm that all experiments were performed in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

All raw data accession are accessible via the public repository of microarray data NCBI Gene Expression Omnibus: (www.ncbi.nlm.nih.gov/geo/query/acc.cgi), with an accession: (GSE69814, GSE93798, GSE108113, GSE104948), in which the data input expected during the current GenePPI project after applying our algorithms are included in the R Shiny application, and linked as available in the GitHub repository: <https://github.com/boutaina-ettetuani/Glomerular-Diseases-Analysis>, in which the data supporting can be found as CSV files.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

BE contributed to R-scripting for the development of GenePPI structural analyses, statistics, implementation of the method. All authors have read and approved the final manuscript including results, figures shaping, manuscript formatting, and manuscript writing. RC contributed to the interpretation of results. AM contributed to the interpretation implementation of the method, and structural analysis. AM and RC contributed equally in literature research.

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Tables

Table 1 Description of the five datasets, in which all types of data was transcription profiling by array, with their fixed P-value when annotated to the human databases, and selected matrix-Expression-Similarity-Frequency-based.

Id	Statut	number of samples	number of genes	Selected genes
E-GEOD-69814	4-Jan-17	11	32321	71
E-GEOD-93798	3-Jul-17	42	54675	34
GSE108113/E-GEOD-104066	26-Jun-19	76	1416100	53
GSE108113/E-GEOD-108109	17-Jul-18	111	1416100	68
E-GEOD-104948	24-Jan-18	196	76958	183
Total of genes				415
Not duplicated				412
Annotated				209
Selected				100

Figure 5 Highest threshold visualization: GWAS Catalog presentation used with retrieval important traits, whose the color of bar plot indicates the occurrence frequency of each entities. The second plot represent the top pathways displayed for all enriched terms with specifics scores visualizing the linkage of genes and biological concepts as a network for the literature genes; C3, ADAM19, ADAMTS13, C3AR1, C8A, CD46, CFB, CFD, CFI, CFHR (1-5), CFH, CD46, and candidates genes. Then a PieChart plot used to represent the means expression of genes in the selected tissues.

Table 2 The most promising genetic head data prioritization-model-based for the four clusters

Cluster N 1				
kidney	urine	Immune system	blood	Embryonic dev
IL33	SPON1	SPON1	SPON1	SPON1
RANBP1	IL33	IL33	IL33	IL33
ANK1	RANBP1	RANBP1	RANBP1	RANBP1
MYOZ2	ANK1	ANK1	MYOZ2	ANK1
MEOX1	MYOZ2	MYOZ2	PALB2	PALB2
CACNA1G	MEOX1	MEOX1	CACNA1G	MYOZ2
PALB2	CACNA1G	CACNA1G	ANK1	MEOX1
Cluster N 2				
kidney	urine	Immune system	blood	Embryonic dev
BMP2	BMP2	COL15A1	BMP2	BMP2
COL15A1	COL15A1	ITGAV	COL15A1	COL15A1
ITGAV	ITGAV	BMP2	ITGAV	ITGAV
ATP13A3	ATP13A3	ATP13A3	ATP13A3	ATP13A3
TNFSF10	TNFSF10	TNFSF10	TNFSF10	TNFSF10
FGF7	FGF7	FGF7	FGF7	FGF7
Cluster N 3				
kidney	Urine	Immune system	Blood	Embryonic dev
SPON1	SPON1	SPON1	SPON1	SPON1
RET	RET	RET	RET	RET
FOS	FOS	FOS	FOS	FOS
SFRP4	SFRP4	SFRP4	AXL	AXL
AXL	NME3	P2RY14	SFRP4	SFRP4
NME3	CA10	NME3	GDF15	GDF15
CA10	BTG2	CA10	NME3	CCL4
Cluster N 4				
kidney	urine	Immune system	blood	Embryonic dev
SPON1	SPON1	SPON1	SPON1	SPON1
MYOZ2	MYOZ2	MYOZ2	TDG	TDG
PALB2	PALB2	PALB2	PALB2	PALB2
SORT1	RAP1B	RAP1B	SPRY1	MYOZ2
RAP1B	NME3	P2RY14	MYOZ2	SORT1
TDG	SORT1	NME3	RAP1B	SPRY1

Table 3 Global summary of mixed-gene tissues interaction (MGTI) model based on gene prioritization results as well as randomly selected genes from the results.

Cluster N 1		
	Genes 1: IL33	Genes 2: RANBP1
Mean-coExp(adjusted)	0.17	IL33
Mean-tissues	5.8	SPON1
Description-tissues	"Immune system"	"Kidney"
Mean-BP	0.59	-
Description-BP	"regulation of inflammatory response" "regulation of immune effector process" "positive regulation of response to external stimulus" "positive regulation of cytokine production" "positive regulation of inflammatory response" "adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains" "positive regulation of proteolysis" "regulation of adaptive immune response" "regulation of neuroinflammatory response" "positive regulation of cell activation"	-
Mean-TFs	0.77	1.54
Description-TFs	"Myc", "CEBPA", "USF1", "TBP", "FOXO3", "Arnt::Ahr", "Sox5"	"Zfx", "MYC::MAX", "Mycn", "RXRA::VDR", "ZNF354C", "Myc", "Egr1"
Mean-GWAS	4.75	0.4
Description-GWAS	"Acute kidney injury"	"urinary metabolite measurement" "chronic kidney disease" "blood protein measurement" "platelet count" "serum IgG glycosylation measurement"
prioritization score	16.53	16
Interaction score: 0.75		
	Genes 1: SPON1	Genes 2: CYP1A2
Mean-coExp	2.13	1.66
Mean-tissues	0.1	5.3
Description-tissues	"Immune system"	"Urine"
Mean-BP	0.1	-
Description-BP	"regulation of inflammatory response" "regulation of protein processing" "regulation of protein maturation" "regulation of protein binding" "positive regulation of proteolysis" "positive regulation of protein processing"	-
Mean-TFs	0.77	-
Description-TFs	"Pax6", "PBX1", "Evi1", "NR3C1", "Sox17", "NFATC2", "MIZF", "EBF1"	-
Mean-GWAS	0.7	0.0022
Description-GWAS	"Acute kidney injury"	"glomerular filtration rate" "hypertension" "urinary albumin to creatinine ratio" "serum albumin measurement" "Microalbuminuria"
prioritization score	16.53	4.42
Interaction score: 0.56		

Table 4 Table 3 (continued)

Cluster N 2		
	Genes 1: ITGAV	Genes 2:FCER1A
Mean-coExp	1.05	1.69
Mean-tissues	3.35	1.9
Description-tissues	"Hematopoietic stem cell" "Parenchyma"	"Kidney"
Mean-BP	0	0
Description-BP		
Mean-TFs	1.18	0.96
Description-TFs	"IRF2", "Sox17", "Esrrb", "ARID3A", "RORA1", "SOX9"	"NFYA", "NHLH1", "Gata1", "Myf", "FEV"
Mean-GWAS	2.38	0.003
Description-GWAS	"urinary albumin to creatinine ratio" "Microalbuminuria"	"C-reactive protein measurement", "leukocyte count", "serum IgE measurement"
prioritization score	16.01	6.6
Interaction score: 0.63		
Cluster N 3		
	Genes 1: PHLDA2	Genes 2: BTG2
Mean-coExp	0.96	0.23
Mean-tissues	2.4	3.15
Description-tissues	"Kidney"	"Blood" "Blood vessel"
Mean-BP	-	-
Description-BP	"regulation of binding" "regulation of protein binding"	-
Mean-TFs	1.19	1
Description-TFs	"GABPA", "NFE2L2", "IRF1", "ELK4", "Egr1", "FEV", "RELA"	"INSM1", "NFYA", "Tcfcp2l1", "CREB1", "Zfx", "Klf4"
Mean-GWAS	-	0.49
Description-GWAS	-	"mean corpuscular hemoglobin" "red blood cell distribution width" "immunoglobulin isotype switching measurement" "multiple sclerosis"
prioritization score	10.17	9.26
Interaction score: 0.65		
Cluster N 4		
	Genes 1: MYOZ2	Genes 2: SORT1
Mean-coExp	1.8	3.15
Mean-tissues	1.5	1.7
Description-tissues	"Kidney"	"Urine"
Mean-BP	-	-
Description-BP	-	-
Mean-TFs	1.08	1.5
Description-TFs	"PLAG1", "MEF2A", "ELF5", "Myb", "FOXD1"	"RORA2", "MEF2A", "RREB1" "NFYA", "CREB1", "Gfi"
Mean-GWAS	2.27	0.06
Description-GWAS	"body height" "glomerular filtration rate" "serum IgE measurement" "renal transplant outcome measurement" "donor genotype effect measurement"	"blood protein measurement" "C-reactive protein measurement" "glomerular filtration rate" "C-reactive protein measurement" "creatinine measurement" "body height" "chronic kidney disease"
prioritization score	13.9	11.7
Interaction score: 0.7		