International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 6 Issue 5, July-August 2022 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Gene Expression and Pathway Detection for Diabetic Nephropathy using Computational Intelligence in Bioinformatics

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ABSTRACT

It has been observed that in high blood sugar levels over time these high glucose level can damage various area of the body including cardiovascular system and kidneys. The kidney damage that results is known as “Diabetic nephropathy “.

Diabetes plays a critical role in public health concern with rates of diabetes increasing globally and approximately 40% of affected individuals developing diabetic nephropathy. We have taken bioinformatics and computational approach to studying identification of diabetic nephropathy associated genes by literature mining for gene expression and how the genes affected the pathways (DN).

Numerous datasets has been evaluated for Diabetic nephropathy occurs only in a minority of subjects with either type 1 or type 2 diabetes and seems to result from the interaction between genetic susceptibility and environmental insults and risk factors for the development of diabetic nephropathy includes ethnicity and inherited genetic differences and Hyperglycemia and arterial hypertension and other risk factors are smoking dyslipidemia proteinuria, glomerular hyperfiltration and factors.

Our result have been evaluated how the pathways are been affected in diabetic nephropathy, the pathogenesis of diabetic nephropathy and gene mapping also the development of diagnostic.

How to cite this paper: Dr. Brijendra Gupta | Tanvi Shinde | Aarti Pundalik | Poonam Kedari "Gene Expression and Pathway Detection for Diabetic Nephropathy using Computational Intelligence in Bioinformatics" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-6 | Issue-5, August 2022, pp.48-54, URL: www.ijtsrd.com/papers/ijtsrd50423.pdf

IJTSRD50423

OUTLINE:

We have been working on top genes of diabetic nephropathy, on based of their score we also gone through pathways involved in (DN). And also worked on how gene mapping process is usefuls for identify exactly which chromosome has which gene and exactly pinpointing where that gene lies on that particular chromosome. And the protein misfolding for diabetic nephropathy.

INTRODUCTION:

- Diabetes results in high blood sugar levels over time these high glucose level can damage various area of the body including cardiovascular system and kidneys. The 0kidney damage that results is known as “Diabetic nephropathy “.
- We are working on diabetic nephropathy (DN) and also its top involved genes based on their score the pathways affecting the gene for (DN).It has been seen that their multiple factors involved in the pathogenesis of (DN) while the molecular mechanism that leads to (DN).
- Numerous risk factors for the development of diabetic nephropathy including ethnicity and inherited genetic differences and hyperglycemia and arterial hypertension. Other risk factors are smoking dyslipidemia proteinuria, glomerular hyperfiltration and dietary factors. Diabetic nephropathy is the leading cause of chronical renal disease. Diabetic Nephropathy has been categorized into stages microalbuminuria. Diabetic Nephropathy (DN) is a lethal microvascular complication associated with type 1 and type 2 diabetes mellitus.We have to determine signalling pathways pathogenesis of diabetic nephropathy at DNA level, RNA level, MRNA level at epigenetic level and also its transmission factors at gene level.

And also which pathways affect the genes for diabetic nephropathy.

Methodology or Materials and Methods:

We have collected over genes based on scores of gene-disease (GDA) for diabetic nephropathy using DISGENET and the common pathway (from GENCARD) for those ten genes, which is responsible for affecting the gene in DN and also the other factors.

The pathogenesis and progression of diabetic nephropathy are likely to be as a result of interaction between metabolic and hemodynamic pathways. It is likely that the metabolic and hemodynamic abnormalities seen in diabetes interact with each other and pathways linked to reactive oxygen species (ROS) generation.

Gene regulation and activation of transcription factors are influenced by interactions among metabolic stimuli hemodynamic factors and various ROS in diabetes.

We have used cytoscape for making network of genes and DN we have made a network by 10 genes of DN. Pathways form KEGG database are also added this.

We have gone through different databases and website to collect our data for our paper are as follows:

DATABASE USED
GOOGLE
KEGG
PUB-MET.GOV
DISGINET
CYTOSCAPE
NCBI
GENECARD
MDPI(FREE DATABASE)
STRING
KARGER

Table 1.0

Figure 1:

This image is obtain by CYTOSCAPE we have collected ten genes associated with diabetic nephropathy form GENCARD those ten genes share common pathway

Diabetic Nephropathies-**Signal Transduction** (pathway)- REACT:R-HSA-162582

18 genes: AGT | AXL | CDKN1A | COL4A1 | DGKH | ELMO1 | FN1 | INS | KDR | LEPR | MDK | NOS3 | PRKCE | RELA | SERPINE1 | TGFB1 | TGFBR2 | VEGFA

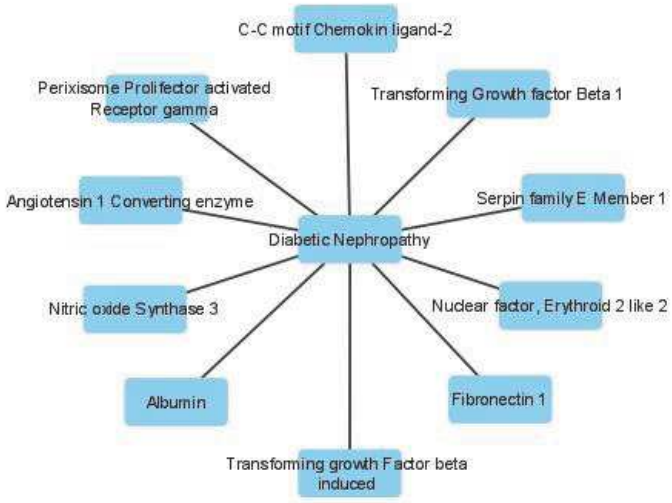

Figure1:

RESULT:

We have collected 10 genes associated with Diabetic Nephropathy using cytoscape we had made network for Diabetic Nephropthy and find out different pathways which are affecting genes for DN. Using different database we have find out which genes are responsible for DN. Form KEGG we got pathways and diagrammatic representation of it. We have gone through protein misfloding process for diabetic nephropathy and gene mapping process for future scope.

Also gone through different factors for the development of diabetic nephropathy.

HYPERGLYCEMIA AND ADVANCED GLYCOSYLATION END PRODUCTS

- Hyperglycemia is a crucial factor in the development of diabetic nephropathy because of its effects on glomerular and mesangial cells, but alone it is not causative. Mesangial cells are crucial for maintenance of glomerular capillary structure and for the modulation of glomerular filtration via smooth-muscle activity. Hyperglycemia is associated with an increase in mesangial cell proliferation and hypertrophy, as well as increased matrix production and basement membrane thickening.

Glycosylation

- Glycosylation of tissue proteins contributes to the development of diabetic nephropathy and other microvascular complications. **Protein kinase C**
- Other proposed mechanisms by which hyperglycemia promotes the development of diabetic nephropathy include activation of PKC.31 Specifically, activation of this enzyme leads to increased secretion of vasodilatory prostanoids, which contributes to glomerular hyperfiltration. By activation of TGF-β1, PKC

might also increase production of extracellular matrix by mesangial cells **CYTOKINES**

- Activation of cytokines, profibrotic elements, inflammation, and vascular growth factors such as VEGF might be involved in the matrix accumulation that arises in diabetic nephropathy. 40–42 Although some evidence suggests that VEGF increases permeability of the glomerular filtration barrier to proteins,22 levels of this growth factor can be low in patients with diabetic nephropathy. Thus, the role of VEGF in the pathophysiology of nephropathy is unclear.

PRORENIN

- Initial clinical studies in children and adolescents suggest that increased plasma prorenin activity is a risk factor for the development of diabetic nephropathy. 36, 37 The prorenin receptor in the kidney is located in the mesangiumand podocytes, and its blockade has a beneficial effect on kidneys in animal models of diabetes. This effect is mediated by intracellular signals that are both dependent on and independent.

LIPID MEDIATORS

- Small lipids derived from arachidonic acid have been implicated in the pathogenesis of diabetic nephropathy. Cyclo-oxygenase 2 breaks down arachidonic acid into several different prostanoids. In a rat model of streptozotocin-induced diabetes, levels of inflammatory prostanoids, such as prostaglandins E2 and I2, were raised of the renin–angiotensin system. Prorenin binds to a specific tissue receptor that promotes activation of p44/p42 MAPK.38.

NEPHRIN

- Podocytes (specialized visceral epithelial cells) are important for the maintenance of the dynamic functional barrier.66 Nephrin, a protein found in these cells, is crucial for maintaining the integrity of the intact filtration barrier. The renal expression of nephrin might be impaired in diabetic nephropathy. Patients with diabetic nephropathy have markedly reduced renal nephrin expression and fewer electron-dense slit diaphragms compared with patients without diabetes and minimal nephropathic changes or controls.

GENETIC SUSCEPTIBILITY

- Genotype seems to be an important determinant of both incidence and severity of diabetic nephropathy.9,31,70 The increase in risk cannot be explained by the duration of diabetes or hypertension, or the degree of glycemic control. Environmental and genetic factors must, therefore, have roles in the pathogenesis of diabetic nephropathy. In patients with type 1 or type 2 diabetes, the likelihood of developing diabetic nephropathy is markedly increased in those who have a sibling or parent with diabetic nephropathy.

Schematic analysis workflow for delineating molecular DN disease presentations. With the phenotype at the center, data are gathered from the scientific literature as well as from different omics studies in order to generate a phenotype molecular feature set.

Bioinformatics analyses on the level of GO term enrichment analysis, molecular pathways as well as via identification of process units leads to the identification of deregulated molecular processes and pathways as well as the construction of molecular models for the given disease.

OBSERVATION:

We have seen for few databases related Diabetic Nephropathy that there are susceptible genes are involved in it which are difficult to identify exact responsible genes. We have tried to collect all the data and from that we try to figure out get all the susceptible genes for diabetic nephropathy and pathways affecting the genes.

Protein misfolding disorders (PMDs) are disease where at least one protein or peptide has been shown to misfold aggregate an tissues where the disease specific damage occurs. F or future scope to identify that genes and its location on DNA and chromosome.

This process will help to find out exact which genes is responsible for diabetic nephropathy and its location also is that genes are hereditary or not ? By the help of gene mapping process.

Artificial intelligence (AI) based machine learning techniques with respect to DN are nephropathy. AI-based machine learning models can even provide actionable prediction models for faster and accurate diagnosis of complications associated with DN. The integration of AI-based analytical techniques, like machine learning and deep learning in clinical medicine, will result in improved disease management through faster disease detection and the cost reduction for the treatment.

CONCLUSION:

Diabetic Nephropathy is not clinically detectable until significant kidney damage has developed, highlighting the need to identify early-stage biomarkers.

Figure 2 shows the table of the present study; Some of these associated genes function as pivotal

regulators in the pathogenesis of DN, such as those related to glycometabolism and lipid metabolism.

However, the functions of most of these genes remain unclear.

Some of these genes function as pivotal regulators in the pathogenesis of DN, such as those related of glycometablism and lipid metabolism.

In our future scope for Diabetic Nephropathy to identify exact which genes are susceptible for DN using GENE MAPPING process.

A graphical representation of the arrangements of genes or DNA sequence on chromosome. The human genome map completed in 1996 locates 5264 markers for gene. A genome map are used to identify and record the location of gene and distances between genes on chromosome

Types of gene mapping are:

Physical mapping: A physical map provides detail of the actual physical distance between genetic markers, as well as exact location of the genes.

Genetic mapping: Genetic mapping looks how genetic information is shuffled between chromosome or between different regions in the same chromosome.

The susceptibility genes in diabetic nephropathy

Gene	SNP	MAF	Study type	Phenotype	DM type	Race	Sample size	OR/HR	*p* value	Ref.
Lipid metabolism-related genes										
ACACB	rs2268388	A = 0.1631/817	meta	T2DN	T2D	Japanese	1,312	1.61 (additive)	1.4×10^{-6}	[8]
			meta	T2D-ESRD	T2D	European	908	1.61 (additive)	0.0006	[8]
ADIPOQ	rs2241766	G = 0.1514/758	CC	T2DN	T2D	Korean	708	1.96 (GG)	0.049	[19]
			cohort	T2DN, male	T2D	Taiwanese	556	1.81 (recessive TT vs. GT+GG, HR)	0.019	[18]
	rs1063537	T = 0.1442/722	cohort	T2DN, male	T2D	Taiwanese	556	1.89 (recessive CC vs. CT+TT, HR)	0.013	[18]
Glucose metabolism-related genes										
GCKR	rs1260326	T = 0.2933/1469	AA	estimated GFR	T2D	European	2,097	1.12 (β)	4.27×10^{-12}	[25]
TCF7L2	rs7903146	T = 0.2278/1141	CC	T2DN	T2D	Caucasians	1,355	1.97 (T)	<0.001	[31]
	rs1196218	A = 0.2500/1252	CC	T2DN	T2D	Chinese	898	1.37	0.0051	[30]
Angiogenesis-related genes										
EPO	rs1617640	C = 0.3253/1629	meta	DN	total	European	2,572	1.47	<0.05	[42]
			meta	PDR+ESRD	T1D	European	7,007	1.31	2×10^{-8}	[39]
VEGFA	rs833061	C = 0.3698/1852	meta	T1DN	T1D	European	543	0.67	<0.00001	[38]
Genes related to renal structure and function										
FRMD3	rs10868025	G = 0.2800/1402	meta	albuminuria with ESRD	T1D	9 white	1,705	1.45 (A [G])	5×10^{-7}	[81]
	rs1888747	C = 0.1979/991	meta	albuminuria with ESRD	T1D	white	1,705	1.45 (G [C])	6.3×10^{-7}	
SHROOM3	rs17319721	A = 0.2238/1121	meta	eGFR	T2D	Tayside, Scotland	3,028	1.02 (A, HR)	3.18×10^{-8}	[25]
Inflammation and oxidative stress-related genes										
ELMO1	rs10951509	G = 0.4289/2148	CC	T2D-ESRD	T2D	American Indians	772	2.42 (A)	0.002	[78]
				T2DN	T2D	Chinese	200	1.76 (A)	0.02	[49]
	Intron 18+9170 A/G	ND	CC	T2DN	T2D	Japanese	732	2.67 (GG vs. GA+AA)	0.000008	[46]
	rs1345365	G = 0.4347/2177	CC	T2D-ESRD	T2D	American Indians	772	2.42 (A)	0.001	[78]
			CC	T2DN	T2D	Chinese	200	3.27 (A)	0.004	[49]
TGF-β1	rs1800470	G = 0.4547/2277	CC	T2D	T2D	Mexico inhabitants	439	1.818	0.016	[58]
	915 G>C	ND	CC	T2DN	T2D	Mexico inhabitants	439	4.073	0.008	[58]
Genes related to the RAAS system										
ACE I/D	rs1799752	ND	CC	persistent micro-albuminuria	T1D	Caucasians	1,365	0.62 (DI/II)	0.009	[64]
			CC	T2D-ESRD	T2D	Chinese Han	432	2.23 (DD vs. II+ID)	0.005	[70]
AGTR1	rs5186 (A1166C)	C = 0.1178/590	CC	T1DN, male	T1D	Denmark, Finland, France, and Sweden	3,561	1.27 (AA vs. AC+CC)	0.03	[73]
			meta	DN	total	Caucasian, Asian	ND	2.1 (CC vs. AA)	0	[75]
			meta	DN	total	Caucasian, Asian	ND	2.11 (dominant)	0	
Other susceptibility genes										
SLC12A3	rs11643718	A = 0.0799/400	CC	T2DN	T2D	Malaysian	1,417	0.547	0.038	[77]
			CC	T2D-ESRD	T2D	Chinese	372	2.2 (GA+AA)	0.019	[76]
			CC	T2D-ESRD	T2D	Koreans	358	2.295	0.003	[79]
RAB38/CTSC	rs640529	T = 0.4846/2427	GWAS	UACR	T1D	European	7,787	0.14 (β)	5.8×10^{-7}	[82]

MAF, global minor allele frequency; OR, odds ratio, the words in brackets mean contrast alleles or genotypes; HR, hazard ratio; β, β value; ND, no data; DN, diabetic nephropathy; T1D, type 1 diabetes; T2D, type 2 diabetes; ESRD, end-stage renal disease; T2D-ESRD, patients with T2D and end-stage renal disease; T1D-ESRD, patients with T1D and end-stage renal disease; T2DN, type 2 diabetes-related nephropathy; T1DN, type 1 diabetes-related nephropathy; PDR, proliferative diabetic retinopathy; eGFR, estimated glomerular filtration rate; UACR, urea albumin creatinine ratio; GWAS, genome-wide association study; CC, case-control study; cohort, prospective cohort; AA, association analysis; dominant, dominant model; recessive, recessive model; additive, additive model.

Fig. 2.

The susceptibility genes in diabetic nephropathy. As shown in the figure, the susceptibility genes in diabetic nephropathy are divided into different categories according to their main functions.

The pathophysiology of diabetic nephropathy. As a consequence of prolonged hyperglycaemia, diabetic nephropathy (DN) typically initiates as renal cellular hypertrophy and hyperfiltration, followed by progressive albuminuria and a decline in glomerular filtration rate (GFR). Microalbuminuria (urinary albumin excretion rate of 30–300 mg per day) develops 10–15 years after the onset of diabetes followed by macroalbuminuria (urinary albumin excretion rate of >300 mg per day) 15–25 years after diabetes onset. A combination of hyperglycaemia,

inflammation, and hypertension drive the development and progression of DN. Presently, it is unclear why some diabetics are susceptible and others appear protected against the development of DN. Currently unknown causal and protective genetic variants have been suggested as one possible mechanism. At the cellular level, high glucose, Ang II, ROS, and profibrotic cytokines including TGF-β1, VEGF and CTGF have been identified as important modulators driving renal fibrosis. More recently, miRNA-mediated regulation and histone modifications have also been implicated in DN pathogenesis. Mutations in one or more key signaling pathways implicated in DN may act to suppress or drive DN progression

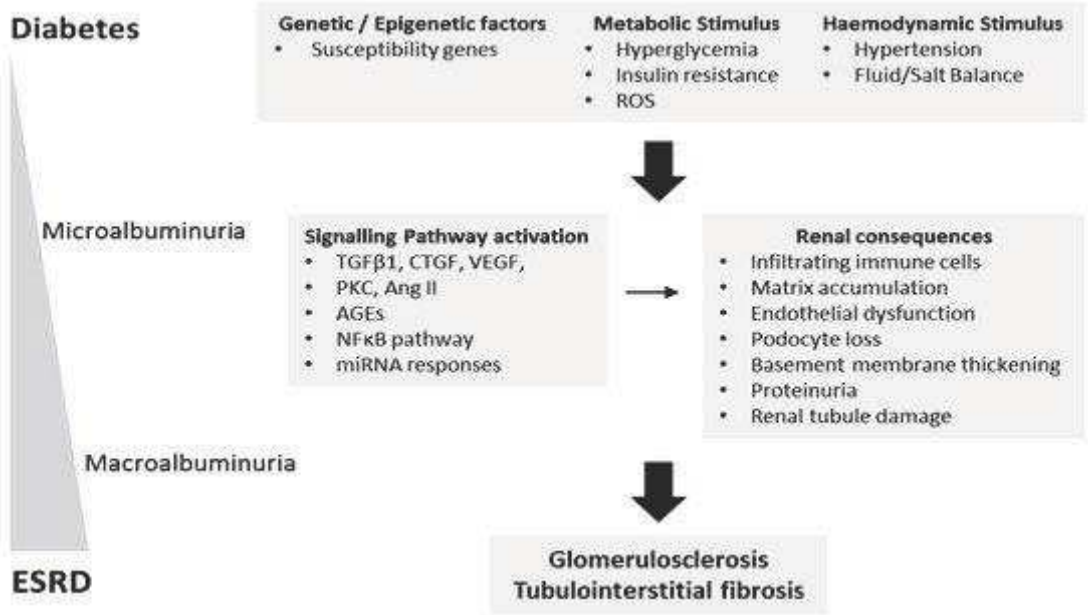

Figure 3:

Table 3:

The results of pathway enrichment analysis for the down-regulated genes:

SSS Category	Pathway Name	Count	*p-value*	Genes
KEGG_PATHWAY	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	11	1.41E-04	*ACTG1, ATP2A2, ACTN4, DMD, DAG1, CACNB2, ITGB5, ITGA3, CTNNA1, CTNNB1…ACTN4, ROCK1, ITGB5, RDX, ITGA3, ARPC5, MYL12A, MYH9, MYL9, ACTG1…*
KEGG_PATHWAY	Regulation of actin cytoskeleton	19	1.65E-04	
KEGG_PATHWAY	Hypertrophic cardiomyopathy (HCM)	9	0.00575	*TNNT2, ACTG1, ATP2A2, TNNC1, DMD, DAG1, CACNB2, ITGB5, ITGA3*
KEGG_PATHWAY	Complement and coagulation cascades	8	0.00641	*CD55, F3, CD46, CD59, C1R, SERPING1, C1S, F2R*
KEGG_PATHWAY	Dilated cardiomyopathy	9	0.00920	*TNNT2, ACTG1, ATP2A2, TNNC1, DMD, DAG1, CACNB2, ITGB5, ITGA3*
KEGG_PATHWAY	Pathogenic Escherichia coli infection	7	0.00956	*ACTG1, EZR, ROCK1, TUBB2A, YWHAQ, ARPC5, CTNNB1*

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