

Identification of Potential Biomarkers in IgA Nephropathy and Membranous Nephropathy through miRNA-mRNA bioinformatics analysis

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Abstract

Objective: Immunoglobulin A nephropathy and membranous nephropathy are glomerulus disease. The current study was planned to understand the molecular mechanism of immunoglobulin A nephropathy and membranous nephropathy with discovery of key micro ribonucleic acids and their targetted hub genes.

Methods: The microarray dataset was downloaded from Gene Expression Omnibus database and examined through R package Gene Expression Omnibus 2R. Subsequently, the data was analysed to detect the differential expressed genes. The hub genes were detected using bioinformatics analysis techniques, such as protein-protein interaction network analysis, module analysis and micro ribonucleic acid-messenger ribonucleic acid network construction. The study relied entirely on publicly available datasets conducted in 2021 at COMSATS University Islamabad, Sahiwal Campus.

Results: A total of 949 differential expressed genes were recognised. All of them were upregulated genes. Afterward, 6 overlapped genes (Fos proto-oncogene AP-1 transcription factor subunit, Signal Transducer and Activator of Transcription 3, Forkhead Box O3, Heat Shock Protein 90 Alpha Family Class A Member 1, Heat Shock Protein Family A [Hsp70] Member 5 and Tumour Protein p53) were intersected from cytoHubba plugin, designated as hub genes. One novel micro ribonucleic acid, has-miR-495-3p, was identified as biomarker for diagnosis and therapy of immunoglobulin A nephropathy and membranous nephropathy.

Conclusion: The short, non-coding has-miR-495-3p was found to be proficient in refining personalised diagnosis and treatments for immunoglobulin A nephropathy and membranous nephropathy patients. In vivo and in vitro analyses of micro ribonucleic acids and network interactions may help further explore the processes underlying the disease.

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Introduction

Nephritis, or glomerulonephritis, refers to inflammation of the kidney's functional units, the nephrons, and may progress to nephrotic syndrome or end-stage renal disease (ESRD).¹ Immunoglobulin A nephropathy (IgAN), first described by Jacques Berger in 1968² is a major cause of glomerulonephritis and results from IgA deposition in the glomerular mesangium, leading to mesangial proliferation.^{3,4} Membranous nephropathy (MN) is another common form, characterised by immune complex deposition along the glomerular basement membrane, causing thickening and capillary damage. Glomerular diseases develop through a combination of hereditary and environmental factors, including genetic predisposition, immune dysregulation, infections and toxins.⁵ Given the complexity of their pathogenesis, integrative bioinformatics approaches, such as micro ribonucleic acid-messenger ribonucleic acid (miRNA-mRNA) network

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analysis hold promise for identifying novel biomarkers and therapeutic targets.

In the past few years, microarray gene expression data of thousands of genes from different microorganisms has been studied. It provides strong foundation for the scientific community to study association of genes and metabolic pathways under different conditions, leading to the selection of genes for novel drug therapy.⁶

There is no adequate evidence available to prove the involvement of miRNAs in IgAN and MN disease. The current study was planned to apply bioinformatics approaches to find out the disease-causing genes and their aimed new miRNAs. Also, the study aimed at investigating differentially expressed genes (DEGs), the enrichment of Gene Ontology (GO) terms or pathways, and protein-protein interaction (PPI) in IgAN by using the microarray dataset GSE73953 in order to predict potential targets. The study also planned to analyse the modules and their functions in each PPI network, and to determine possible hub genes. The overall target of the study was to present the connection in miRNA and mRNA network representation for the recognition of core genes.⁷

Materials and Methods

The study analysed data obtained from publicly available open-access National Centre for Biotechnology Information (NCBI) Gene Omnibus Expression (GEO) database (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE73953>) dataset GSE73953. The study relied entirely on publicly available datasets conducted in 2021 at COMSATS University Islamabad, Sahiwal Campus. No patient recruitment, intervention, or animal experiments were planned, and, therefore, approval from any ethics review committee was not required.

The freely available database gives original record and curated microarray datasets. Data of healthy controls was acquired from the Affymetrix GPL4133 platform that was uploaded by Daisuke Okuzaki on October 13, 2015, and updated on February 22, 2018.⁸

DEGs were determined by using clustering analysis of GEO2R package.⁹ Patients and healthy controls were studied for different gene expression. Next, DEGs were distinguished on the statistical criteria of $|\log \text{fold change (FC)}| > 3$ and adjusted $p < 0.01$.¹⁰ Log FC was increased to 3 to avoid noise. Also, the volcano plot of the expressed genes was obtained by using ggplot2 package of R for significant and non-significant genes.

GO enrichment analysis and Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway analysis was done by using Database for Annotation, Visualization and Integrated Discovery (DAVID). Cellular compartments (CCs), biological processes (BPs) and molecular functions (MFs) of DEGs were examined. The ggplot2 is the best option for static bubble map. Bubble map has defined markers as circles with colour and size proportional to the numerical values. The top 10 significantly enriched GO terms and KEGG pathways were identified from the DEG analysis and visualised using bubble plots. In these plots, the size of the bubbles represents the number of genes enriched in each term or pathway, while the colour intensity reflects the level of statistical significance. A threshold of $p < 0.05$ was considered statistically significant for enrichment.¹⁰

The Search Tool for Recurring Instances of Neighbouring Genes (STRING) was utilised for the functional interaction between DEGs on the combined score of > 0.7 .¹¹ The resulted gene network was exported to Cytoscape v_3.9.0. The Molecular Complex Detection (MCODE) plugin was used for network clustering as the tool finds clusters of

highly interconnected regions in the network. In MCODE, modules with nodes > 5 and score ≥ 5 were considered significant. The genes involved in these two selected modules were entered in DAVID for the analysis of KEGG pathways.¹⁰

The CytoHubba plugin was utilised for examining core hub genes between the DEGs. A total of 12 topological analysis methods with different scoring strategies were used in CytoHubba.¹² From the 12 topological analysis methods, four methods were chosen for the recognition of the hub genes from DEGs; degree, Maximum Neighbourhood Component (MNC), betweenness, and closeness. Subsequently, the topmost 25 genes ranked by degree, MNC, closeness and betweenness were chosen for further analysis (10). In the end, the merge network feature of Cytoscape was used to find the intersected genes, designated as the hub genes.

The Encyclopaedia of RNA Interactomes (ENCORI) was utilised for the miRNA-mRNA interaction network. ENCORI has eight different embedded databases for the prediction of miRNAs. Only four databases were chosen for miRNA target forecast; Prediction of Interaction Targets (PITA), PicTar, Targetscan and miRanda(10). The resulted miRNA was chosen as the target of hub genes on the basis of its presence in at least two of the four databases. Next, the interaction network between targetted miRNA and hub genes was visualised using Cytoscape. Also, the degree method of CytoHubba was applied to rank all the hub genes. The interaction frequencies between hub genes and predicted miRNAs were recorded in a spreadsheet, allowing us to identify the miRNA with the highest number of interactions.

Results

The microarray dataset GSE73953 on peripheral blood cells covered 23 patients; 15(65%) IgAN and 8(35%) MN. GEO2R listed all the top DEGs Which were expressed through volcano plot representing the expression level analysis (Figure 1).

Of the 9,880 DEGs generated, 949(9.6%) genes were identified as significant DEGs as per the defined criteria. All the DEGs were upregulated as they had positive log FC value (Supplementary Table 1). The gene symbols of the selected DEGs were noted separately in the supplementary table 1.

GO enrichment analysis of the top 10 considerable

Table-1: The top two modules selected on the basis of nodes > 5 and score ≥ 5 .

Clusters	Score	Nodes	Edges	Node IDs
1	6.8	16	51	HSPA1A, RAN, EIF4E, NUP98, SNRPD1, STIP1, NUP93, HSP90AA1, HSP90AB1, DNAJA1, NUP160, CPSF1, HSPA5, NUP210, NEK9, TOP2A
2	5.6	6	14	PSMC5, PSMC6, PSMA3, PSMD10, PSMC3, PSME3

enriched terms showed that the genes in BP category were more expressed in positive regulation of Inhibitor of nuclear factor kappa B (I-kappaB kinase)/ Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) signalling, cell-cell adhesion, nucleocytoplasmic transport, endoplasmic reticulum (ER) to Golgi vesicle-mediated transport, and protein phosphorylation. GO terms of CC showed that the genes were enriched in nucleoplasm, cytosol, cytoplasm, nucleus, membrane, focal

adhesion, Golgi apparatus and nuclear membrane. For MF, the genes were more tangled in binding of proteins, poly (A) RNA, unfolded protein and adenosine triphosphate (ATP). KEGG enrichment pathway study showed that the genes were substantially enriched in RNA transport, endometrial cancer, pancreatic cancer, chronic myeloid leukaemia, endocytosis, measles, hepatitis C, and fragment crystallizable (Fc) gamma receptor (R)-mediated

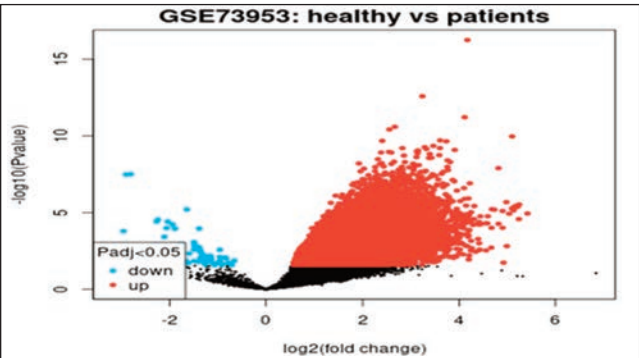


Figure-1:Volcano plot showing expression level of all the genes in the dataset.

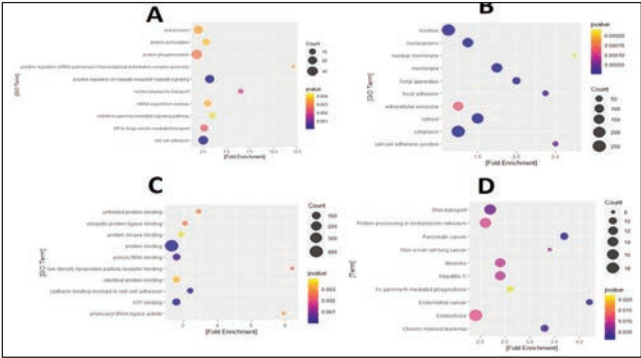


Figure-2:Bubble map showing Gene Ontology in the matter of biological processes (A), cellular compartments (B), molecular functions (C) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis (D).

Supplementary Table: Gene symbols of the selected differentially expressed genes (DEGs).

DEGs	Gene Symbol
Upregulated genes	MSTN, ATPAF1, NLGN4Y, HNRNPA1L2, ETS1, KARS, TIFA, MED22, HNRNPA1L2, HNRNPA1, PSEN2, TTC33, SUPT16H, PPP2CA, SLTM, RAB1A, MTMR12, ENCL, HCFC1, PAPP2A, RNF20, UBFD1, SYF2, CYB5B, EDEM1, ATP6V1E1, TMEM232, CORIN, PRKAR1A, INTS5, NAP1L4, SLC35B3, BRD7P3, SARAF, CSNK1A1, PAQR9, FAM173B, FAM168B, TMEM9B, CLP1, MAF, GIT2, ALDH18A1, CFDP1, SURF6, SNAP23, RPL22, MYCBP, ANKRD11, B4GALNT3, PRKCB, MSANTD2, EIF251, PDIA6, TECPR2, PICALM, ANP32A, RIPK4, SEC23B, ADORA2A, CTSE, NDRG3, EIF4E, IFRD1, RUBCN, DYNC2L1, RBMX2, CAMTA1, IGF2R, HNRNPH3, XRN2, HMGN5, RNF114, GALNT5, COQ8A, JMD1C, RAD17, ADAR, LOC100422526, CACUL1, TSNA, HBP1, BTBD10, ASAH1, TBC1D14, ATP10D, IQCC, USP34, TFCP2, GNB1, CUTC, CTCF, TM2D3, PDCL3, SAT1, CCDC115, RAB9BP1, GPFT2, TRIP12, HERC2, LAMTOR3, MRFAP1, TAOK3, IFI27, KBTBD2, RCC1L, ZNF12, NUPL2, LUZP1, SRP68, CRK, STIP1, THAP11, ABCG5, ATP2C1, SLC2A3, MTM1, LPCAT1, IFI27, RGS14, IFI27, SDHC, ZNF263, ZNF211, CAPZA2, KBTBD2, IFI27, IFI27, PLXNC1, IFI27, PSEN1, IFI27, C9orf78, DECRI1, PTOV1, ACAT1, ETS2, IFI27, FEM1A, IFI27, HMGCS1, DKFZP5861420, GFM2, FOXJ2, IFI27, SESN3, CLK3, ADH5, WNK1, HSPA1A, MINOS1P1, ARHGAP15, NGRN, STIP1, DAPK1, PCMT1, IFI27, ELMO2, TFCP2, MRGPRF, HDAC5, SLC37A3, IST1, AP2A2, ZNF337, TADA2B, MAP1LC3B, VCPKMT, GTF2E2, RAP1GAP2, ZNF285, CRK, CCPG1, SNX17, CD59, EMC2, SON, MRFAP1L1, FAM193A, CAND1, METTL3, FA2H, MCOLN1, PSMD10, ZER1, TCERG1, PRDX3, FER1L6-AS2, STX3, APMA, CPSF1, CD1D, NRBF2, PPP4R1, TERF2, ELL, TUBA1C, RNPEP, ZNF282, CNOT1, ADCK2, DNAJA1, SDF4, CWC25, MRFAP1, TM6IM4, NUP210, WLS, AXIN2, SPTA1, C7orf25, BCR, ASPHD1, BRMS1L, UPE2, PIK3R5, SLC31A1, BST1, PCMT1, RALBP1, SSH1, PPT1, STX11, SRF, ATRNL1, AHSAT1, LOC100132831, FOXK1, HDGFRP2, TPMT, SRP68, GCH1, MAEA, ARPC1B, ZNF44, RAB1A, PIGW, TECPR2, MPRIP, METAP1, TCP1, FBXO18, PI4KB, TPD52L2, UBE2Q1, CD300A, QARS, ANP32C, BLOC1S6, PAGE5, INPP5F, PRKAB1, ATP1A4, ZSCAN21, PSMC5, NOTCH1, PSMC3, L3MBTL3, NOS2, PCDHGA9, SEC16A, TGFA, RAB28, FAM69A, CLK1, CXCR6, NOTCH1, PARG, RAB8A, PDPK1, APIS, CHUK, ZSCAN25, ADM, SVIL, PIK3R5, LLPH, COG3, NOTCH1, LOC105370109, ADM, GSKIP, UPRT, MAN2B2, HSP90AA1, SHQ1, ATP6V1D, AP2M1, ADM, ANXA3, MRM2, HSPA5, CEP120, HDAC3, ANXA2P1, C6orf89, ADM, NOTCH1, SEC23B, NUP93, PDE8A, CTAGE1, WRNIP1, ERMAP, NOTCH1, GABARAPL1, NHS, CDK8, NUP160, NOTCH1, GSP11, TSC22D3, ADM, HSPA1A, UBE230, CENPH, SLC25A37, DDX42, PAGE2, PPFA1, BAP1, IMMT, WDR1, IDH3A, SLC7A6, SRSF1, WHSC1, MPRIP, QSOX2, LRRFIP1, UBE2Q2, NLFCD, GPAT4, CD36, NOTCH1, TCP1, NLFCD, TMEM245, KLHL7, C1orf115, ABHD2, AP3D1, CHERP, ZRSR1, ZNF700, DCTD, STK38, IWS1, LAMP1, NLRP1, LRP3, PLIN3, PBDC1, NAMPT, CIITA, PRUNE1, CAMK1, UHRF1BP1L, MME, EEF1A1, PIK3CD, DDX56, RER1, BLOC1S2, AYLREF, CBX3, ATXN3, TTC5, SNX27, ASAP1, TNPO3, GMPR2, ECHDC1, ANXA2P3, PG51, ATP6V1C1, WBPA, OSGEPL1, CALCOCO2, ZNF487, CASP1, BET1, SACM1L, PIGS, PCCB, DNAJB4, RNF10, MFSO14A, CAMK2N2, GADD45A, TVP23C, KDM1A, PAK1, LRPAP1, ORZW3, FBXW4, SUMO1, TOR3A, TM2D2, SUMO1, LPCAT3, KBTBD4, ZFYVE16, FAM63A, AFG3L2, TRMT11, TMBIM1, CPOX, STAT3, KLF5, PRMT5, SCD, ARV1, CLK1, ZDHHC18, PAQR4, ITPR2, GALNT2, STAT5A, PBDC1, UHRF2, RRP22, SEC24C, MINA, AKTIP, MPZL1, CYLC1, TAF5, BMX, IER3IP1, MTERF3, CYP27A1, TMEM81, ELK1, PROSC, TMOD1, STAT3, ZNF551, RRAGD, MTCH1, UVARG, SUMO1, KIAA0907, SUMO1, HPCA, FGR, LACTB, MLYCD, PITPNA, HLX, LDLRAP1, NDUFA10, MARCKSL1, RAB5B, DOCK2, ARID4A, ITM2C, RAN, STAT3, NADK, RIC8A, STAT3, CDC82, DPM1, AKTIP, PDCD6IP, TBL3, DNTTIP2, FAM118A, DNTTIP2, TRMO, RPRD1A, PPP4R2, MX2, SPON1, RANGAP1, METTL18, DNTTIP2, SMARCA4, JUNB, CTCF, MYLIP, PSMC6, TMCO3, PSMC6, KEL, DNTTIP2, CTNNA1, CLEC12A, TMCO1, TP53, PVR, FCER1A, CKAP5, ACSM3, IL18, ITI2, DCTN5, SGO2, LARP7, CHD4, EIF4H, RNF34, ADGRG3, PPARGC1B, RABEP1, DNTTIP2, HSP90AB1, TRIM10, PHF23, ABCB1, IRF4, SNCA, MKNK2, ALAS1, SUMO1, CTBP2, N4BP1, WTAP, CPA3, LYZ, PABPC4, CBWD5, TTC31, MARS, SNCA, HAT1, NBPF1, IP6K2, PAGE2B, PBRM1, KIAA1211L, CRYZ, RYK, HNRNPAB, SNCA, CTBP2, DNTTIP2, ACAA1, STAT3, SUMO1, 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GNPDA1, ABCB1, ATAD2, SNRPD1, CNDP2, RPL7, AFG3L2, SEMA4D, ZDHHC13, PACSIN2, HOXB2, PGS1, CBWD2, MKRN1, WDFY3, RWDD3, MCFD2, ZNF559, DPP8, XRCC4, WWP2, ADIPOR1, FOS, SNURF, CRISPLD2, H6PD, CLCN3, ABCB1, UBXL4, TPMT, ANKZF1, TXLNA, NUP98, CAV1, SHMT1, ZNF75D, APLP2, TMEM127, DYSE, FASLG, LOC642852, PLXNB2, SLC25A43, PLEKHA3, TRIM62, ZNF564, LRR47, HNRNPCL1, PPM1A, CDR2, BRD4, ABCB1, INO80, APIP, PPP1R15A, SLC35A1, ARL1, TGM2, RTN1, LPP, RAB3IP, EFCAB2, CAR52, WDR26, MICAL3, PSMA3, IL13RA1, CEP152, TRIM25, NFIX, PLXNB2, GBA2, MYD88, NOB1, MFAP2, IL18, KREMEN1, NAGA, NDUFA10, MS4A2, KLF6, SCML4, PRPS2, PPP5C, RABGAP1L, ANXA1, ZNF146, SLC1A5, CAV1, PIN4, CMTM3, FAM120B, TBC1D5, MAPKAP1, SIRPA, USP41, OAS1, BCL2A1, PLXNB2, MKRN9P, C2orf76, AQP3, CHMP5, SMPD4, USP18, MID1IP1, SUB1, RABL3, MANSC1, SLC43A3, F2RL1, TNFSF13, PSAP, WDR82, BCL2L1, MLXIP, C2orf74, CCNT2, ENTDP1, CLIC4, YARS, FAM46C, ARHGAP30

phagocytosis (Figure 2).

Protein-protein network of DEGs was generated (Figure 3), and network analysis led to the detection of top two functional module clusters (Table 1). The genes were mostly involved in RNA transport, antigen processing and presentation, oestrogen signalling pathway, prion disease, protein processing in ER, proteasome and Epstein-Barr

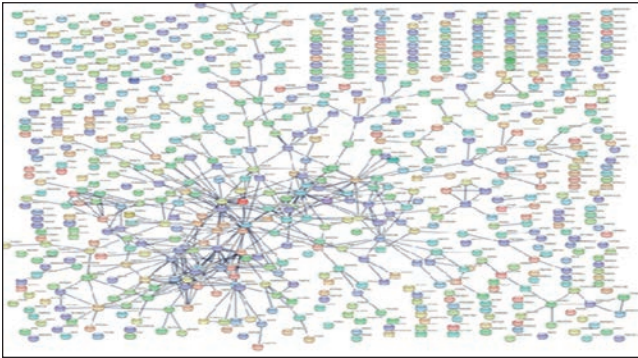


Figure-3:Protein-Protein Interaction (PPI) Network of differentially expressed genes (DEGs) formed by Search Tool for Recurring Instances of Neighbouring Genes (STRING) database.

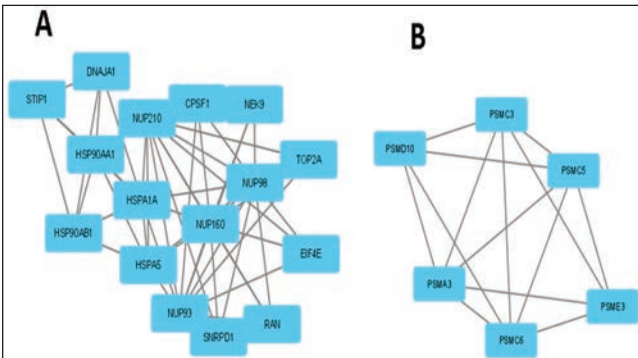


Figure-4:Two modules in Molecular Complex Detection (MCODE) were selected on cut-off criteria of node >5 and score >= 5. (A) The first module consisted of 16 genes. (B) The second module consisted of 6 genes.

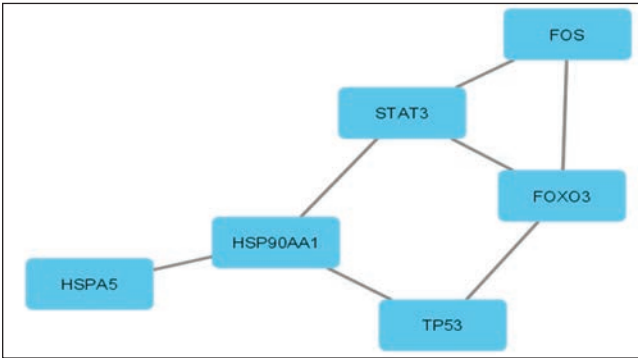


Figure-5:Merged Network from Cytoscape for hub genes showing the intersecting six genes.

FOS: Fos proto-oncogene, AP-1 transcription factor subunit, *STAT3:* Signal Transducer and Activator of Transcription 3, *FOXO3:* Forkhead Box O3, *HSP90AA1:* Heat Shock Protein 90 Alpha Family Class A Member 1, *HSPA5:* Heat Shock Protein Family A (Hsp70) Member 5, *TP53:* Tumour Protein p53.

virus infection (Figure 4).

Hub genes were identified and the top 25 genes were ranked by degree, MNC, closeness and betweenness methods. The ranked genes were also visualised through cluster networks, and the overlapped genes were merged to obtain 6 intersecting genes in the network (Figure 5).

Hub genes and the retrieved miRNA were interacted together, forming a network, with black lines showing the communication of hub genes with their corresponding targeted miRNAs (Figure 6).

The 6 hub genes were ranked using the degree method as Forkhead Box O3 (FOXO3) with score 660, Signal Transducer and Activator of Transcription 3 (STAT3) with score 65, Fos proto-oncogene, AP-1 transcription factor subunit (FOS) with score 50, Tumour Protein p53 (TP53) with score 39, Heat Shock Protein Family A (Hsp70) Member 5 (HSPA5) with score 21, and Heat Shock Protein 90 Alpha Family Class A Member 1 (HSP90AA1) with score 14. The examination of all the targetted miRNAs exposed that hsa-miR-495-3p was

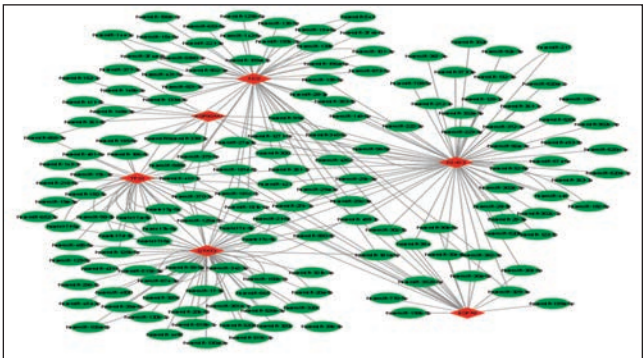


Figure-6:Micro ribonucleic acid-messenger ribonucleic acid (miRNA-mRNA) network. Red diamonds represent hub genes and green ovals represent miRNA.

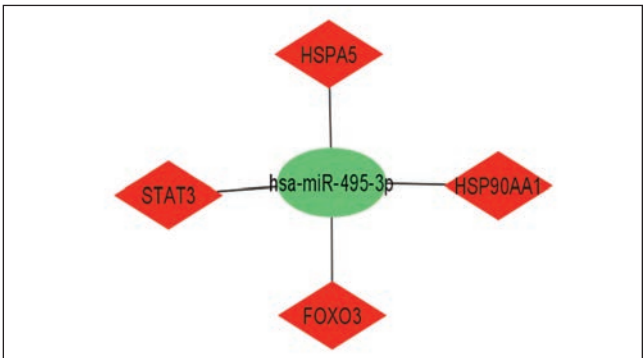


Figure-7:Network showing most targeted micro ribonucleic acid (miRNA) by hub genes. Green colour represents miRNA and red colour represents hub genes.

STAT3: Signal Transducer and Activator of Transcription 3, *FOXO3:* Forkhead Box O3, *HSP90AA1:* Heat Shock Protein 90 Alpha Family Class A Member 1, *HSPA5:* Heat Shock Protein Family A (Hsp70) Member 5.

the top miRNA, and it was affected by four hub genes; HSPA5, STAT3, FOXO3 and HSP90AA1 (Figure 7).

Discussion

With 15 IgAN and 8 MN samples from the GSE73953 dataset, out of the top 9,880 DEGs, only 949 genes were identified as significant DEGs as per the defined criteria. All the DEGs were upregulated as they had positive log FC value. As for GO enrichment, the upregulated DEGs were considerably concentrated in different functions of the body. The current highlighted 6 hub genes in IgAN and MN. More than half of them targeted has-miR-495-3p which is involved in developmental, immunological and inflammatory processes in healthy cells, and invasion, proliferation, metastasis and drug resistance in cancer cells.¹³ Furthermore, has-miR-495-3p could play a crucial role in the pathogenesis of IgAN and MN. The Hub genes are involved in prolactin signalling pathway, FOXO signalling pathway, protein processing in ER and chemokine signalling pathway.

Several studies have shown that the identified six hub genes have significant roles in proteinuria, inducing ER stress in renal epithelial cells. The investigation indicated that HSPA5 may be a promising therapeutic approach to enhance tubular epithelial cells' survival and alleviate the progression of chronic kidney disease.¹⁴ Studies also identify that the expression levels of HSPA5 increased in the kidney tissues of mice.¹⁵ Moreover, researchers found that Heat Shock Protein Family A (Hsp70) Member 1-Like (HSPA1L)-mediated pathways play critical roles in maintaining organellar function of proximal tubular cells in diabetic kidney disease.¹⁶ Similarly, elevated Heat Shock Protein 90-kilodalton alpha (Hsp90α) is identified as a risk factor for cognitive impairment and may serve as a biomarker for mild cognitive impairment in type 2 diabetes mellitus patients without diabetic nephropathy.¹⁷ In tonsil-induced inflammatory syndrome, antibodies against heat shock proteins may contribute to kidney damage.¹⁸ Knockdown of FOXO3 gene increased the oxidative injury and cell apoptosis in kidneys of the mice.¹⁹ Studies showed that FOXO and STAT3 pathways have roles when diabetic kidney disease is treated by Rhizoma Chuanxiong.²⁰ Previous studies showed that STAT3 signalling performs crucial role in the development of renal cancers, as increase in STAT3 activates progression of pathological stages and worsen the survival conditions.²¹

Despite using the same data repository, previous studies, such as those by Hu S-L et al. and Noor F et al., have reported differing sets of novel genes.^{2,10} Such heterogeneity is not uncommon when analysing shared datasets, and may arise from variations in pre-processing

methods, statistical thresholds, analytical pipelines, and pathway enrichment tools. These methodological differences can substantially influence outcomes, and should be acknowledged as a likely reason for the discrepancies observed across studies, with important implications for reproducibility.

The identification of unusual pathways in IgAN and MN patients revealed potential molecular candidates having effective diagnostic and prognostic values. Because of a lack of experimental studies, the current study could not delve into the miRNA-mRNA network's role in IgAN and MN development.

Conclusion

STAT3, FOXO3, HSP90AA1 and HSPA5 were found to be hub genes, while miRNA hsa-miR-495-3p was found to be a biomarker of IgAN and MN. The identified hub genes and miRNA may act as a crucial innovator for research focused on identifying associative pathways in glomerulonephritis.

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List of abbreviations: ATP = Adenosine Triphosphate, BP = Biological Processes, CC = Cellular Compartments, DAVID = Database for Annotation, Visualization, and Integrated Discovery, DEGs = Differentially Expressed Genes, ENCORI = Encyclopedia of RNA Interactomes, ER = Endoplasmic Reticulum, FC = Fold Change, FOS = Fos proto-oncogene, AP-1 transcription factor subunit, FOXO3 = Forkhead Box O3, GEO = Gene Omnibus Expression, GO = Gene Ontology, HSPA5 = Heat Shock Protein Family A (Hsp70) Member 5, IgA = Immunoglobulin A, IgAN = IgA nephropathy, KEGG = Kyoto Encyclopedia of Genes and Genomes, MCODE = Molecular Complex Detection, MF = Molecular Functions, MN = Membranous Nephropathy, MNC = Maximum Neighborhood Component, NCBI = National Center for Biotechnology Information, PPI = Protein-Protein Interaction, RNA = Ribonucleic Acid, STAT3 = Signal Transducer and Activator of Transcription 3, STRING = Search Tool for Recurring Instances of Neighbouring Genes, TP53 = Tumor Protein p53

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Author Contribution:

AI: Performed analysis and drafting.

ZA: Performed analysis.

MI & FJ: Revised the work critically.

MAR: Design and revised the work critically.