Cross Talk Between Renal Transporters and Polycystin-1 as a Potential Molecular Target Involved in Autosomal Dominant Polycystic Kidney Disease

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Introduction. The mutational changes in Polycystin-1(PC-1) encoded by *PKD1* gene is the main cause of Autosomal Dominant Polycystic kidney disease (ADPKD). The pathological changes in renal epithelial cells and multiple cyst formation occur due to activation of cascade of signalling pathways and membrane renal transporters (RTs). Our study have focused on the identification, of different RTs, their interactions with Polycystin-1 and other selected target proteins to find out their role in pathogenesis.
Methods. In this study, various RTs protein sequences were identified and retrieved from NCBI's GenBank and UniProt. RTs were categorized according to different nephronal segmenta as per their functional information retrieved from UniProt and Transpoter databases. Further, sequences were subjected for interaction network analysis in String database and Cytoscape 3.7.2. Different interactions including experimentally validated were identified and can be further validated through *in vivo* methods.
Results. The cross talk between different RT, Polycystin-1 and other sequences were analysed. The various pathways of the interaction with PC-1 were categorised. The total number of 119 nodes and 769 edges interactions were generated. The results were visualized and cross verified with other databases in cytoscape.
Conclusion. The cross signalling of PKD1 with SCNN1A, SCNN1G, SLC12A1, AVPR2 shows their importance in the cyst formation and in pathogenesis of ADPKD.

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INTRODUCTION

A hereditary, lethal, autosomal dominant, polycystic kidney disease is caused due to multiple cysts formation in the renal tubular epithelium that affects the normal function of the kidney and leads to End Stage Renal Disease (ESRD). Later affects one in 400 to 1000 live birth globally.[1] PKD1 and PKD2 are the key genes involved in the pathogenesis of kidney disease. The polycystin-1 (PC1) protein is encoded by *PKD1* and polycystin-2 (PC2) is encoded by *PKD2* gene.[2] Both proteins (PC1 & PC2) function as complex to maintain the normal renal architecture. The malfunctioning of polycystin complex results in the pathological changes in the polarity of the tubular epithelial cells leads to the formation of fluid filled cysts inside the renal tubule and collecting duct.[3-5] The mutation in the *PKD1* gene result into the disease and its progression occur at the early phase of life mainly due to bilateral cyst formation with increase in the size/volume of the kidneys, proteinuria/gross hematuria, hypertension and extra-renal

manifestations.[6-9]

PC1 is a, large glycosylated integral membrane protein with a total of 4,303 amino acids.Its sequence is consisting of 11 trans-membrane spanning domains (partially share sequence homology with PC2), a large extra cellular N-terminal domain and a short cytoplasmic tail ~200 amino acids having several phosphorylation sites and a putative binding sequence for heterotrimeric G proteins.[10,11] PC1 is involved in the protein-protein & protein-carbohydrate interactions and can be activated by cleavage of G-protein-coupled receptor proteolytic site (GPS domain).[12,13]

The cellular and sub cellular localization of PC-1 includes primary cilia, endoplasmic reticulum, adherent and desmosomal junctions, apical membranes, plasma membrane and junctional complexes. PC2 (TRPP2) has 968 amino acids with six transmembrane domains with pore loop region between last two domains, a short cytoplasmic -NH terminal region, and a short -COOH terminal portion. TRPP2 is localized to the plasma membrane, endoplasmic reticulum (ER), centrosome, primary cilium and dividing cells of mitotic spindles.[14-16]

The polycystin complex (PC-1 in collaboration with PC-2) mediates the entry of Ca^{2+} inside the cell thereby increases the cytosolic calcium concentration and signal from apical surface senses the Ca^{2+} flow and results into bending of cilia. When this complex becomes malfunctioned either due to non-functioning of PC-1 or PC-2, the cytosolic calcium concentration gets decreased.[17,18] Under normal conditions, PC-2 (TRPP2) represses the PC-1, which results in deactivation of PC-1 mediated G-protein signalling. Both polycystin proteins interacts with themselves at C-terminal cytoplasmic tail and suppresses the G protein activation.[19] Therefore, deletion of PC-2 triggers the activation of PC-1 and leads to aberrant G-protein signalling, which contributes to cyst formation.

Signalling Pathways and Potential Molecular Target

Different signalling pathways gets activated with the binding of PC-1 to G-protein α-subunits as shown in Figure 1. The pathway such as c-Jun N-kinase, AP-1 transcription factor, nuclear factor of activated T-cell (NFAT) and cAMP signalling cascade get aberrantly activated (Figure 2). Under normal physiological condition they regulated cell differentiation, proliferation and apoptosis. Due to clamping or renal injury, the cytoplamic tail of the PC-1 gets cleaved and translocated into the nucleus where it stimulates the activity of signal transducer and activator of transcription-6 (STAT6) and STAT3 transcription factors dependent pathway that aids in inhibition of the canonical Wnt pathway.[20-23] The overexpression of PC-1 tail fragments in ADPKD is thought to be contribute towards cystogenesis. Normally, PC-1 sequesters the STAT6 on cilia to prevent its activation.

The potential drug targets involved in ADPKD also plays important functions in other tissues and organs. Therefore, a drug used for the PKD target my retard the cyst growth but also cause adverse effects on extra-renal tissues. The selected drug

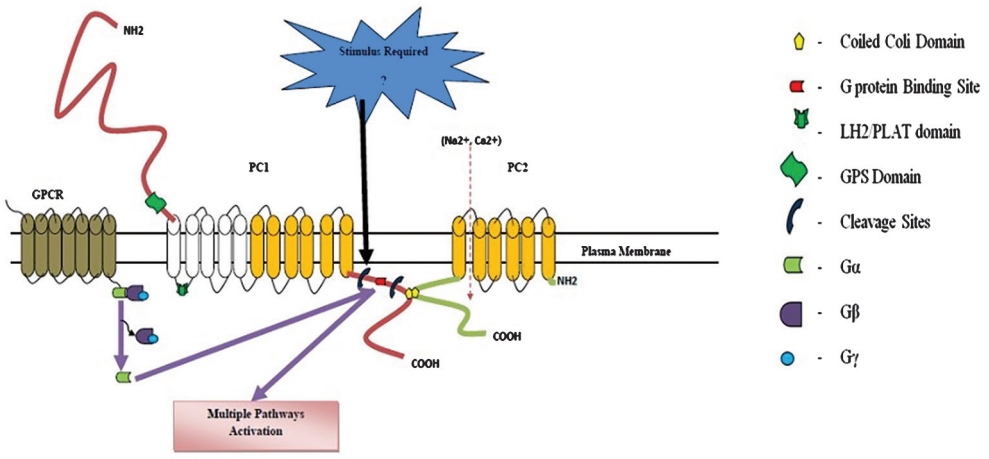


Figure 1. Polycystin-1(PC-1) and Polycystin-2(PC-2) membrane Complex (PC-1&PC-2). A kind of stimulus required for the dissociation of PC-1 from PC-2 at cleavage site and binding of Gα subunit to G-protein binding site. This process leads to the activation of number of pathways involved in the ADPKD.

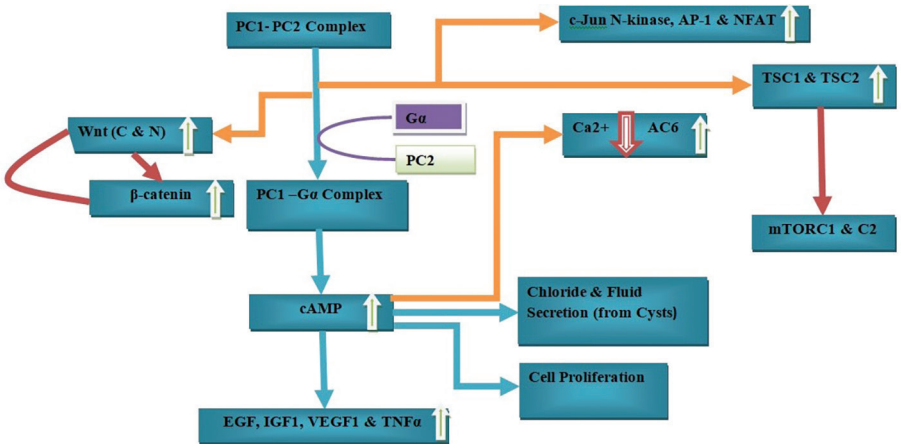


Figure 2. Schematic Representation of pathologically up regulation and down regulation of different signaling pathways in ADPKD after dissociation of PC-1 & PC-2 complex and binding of Gα subunit at PC-1 G-protein binding site.

targets for ADPKD are shown in Table 1 as per literature search.

The mammalian target of rapamycin (mTOR) a key signalling kinase that receives inputs from several upstream pathways and regulates cell growth, proliferation, survival and energy metabolism. The aberrant activity of mTOR is identified in the cyst-lining cells in human ADPKD and also in most rodent models of PKD.[24] But in one of the study, the efficacy of folate conjugated rapamycin slows the kidney cyst growth in mice.[25] PC-1 & PC-2 complex destabilization during the embryonic development result in the severe PKD because of constitutive activation of (β-catenin-dependent) canonical Wnt pathway[26] whereas, the epithelial palner cell polarity (PCP) regulated by β-catenin independent pathway maintains the normal cell function.[27,28]

Vasopressin-2-receptor (V2R) antagonist, Tolvaptan has been reported to slow down the progression of PKD and it also reduces the pain and cause delay of increase in kidney volume in patients.[29] The somatostatin analogue i.e. octeriotide also inhibits the cAMP production and may retard the cyst formation but failed to show beneficial effects in clinical trial[30]. According to recent study, the polycystin dependent calcium influx and nuclear export of histone deacetylase 5 (*HDAC5*), occur simultaneously to maintain the renal epithelial architecture by de-repression of *MEF2C* target genes. The studies on mice have shown that domperidone and loxapine succinate can stimulates the export of *HDAC5* and that results in the reduction of cyst growth and cell proliferation.[31] As *HDAC5* is directly linked to the cyst growth therefore it can be used as a putative target protein. The cyst enlargement is also promoted by a second messenger (cAMP) by stimulating the epithelial cell proliferation through the activation of B-Raf/MEK/ERK pathway by the transepithelial fluid secretion i.e. chloride secretion through the cystic fibrosis transmembrane conductance regulator (CFTR).[32-34] The treatment with Ca^{2+} ionophores inhibits the mitogenic response to cAMP, But Ca^{2+}channel blockers may promote PKD proliferation. It shows the complex role of Ca^{2+} in PKD.[35]

Renal Transporters (RTs)

Renal transporters are involved in ions and solutes transport across the renal tubular epithelial cell membranes via various protein complexes. RTs are expressed on the specific sides of the plasma membranes of renal epithelium. RTs present on blood side called basolateral while

Table 1. Therapeutic Targets from Literature Reference Involved in ADPKD

Target Protein	mTORC1	PI3K	HDAC5	AMPK Activator	V2R	Folate Receptor	PC-1
Accession Number	Q8WTX7.1	CAA72168.1	AAD29047	P54646.2	P30518.1	AAB05827.1	P98161.3
Sequence Length	329	1634	1122	552	371	257	4303

Note. Different selected putative targets were retrieved from NCBI's GenBank/UniProt. PC-1 contain 4303aa is the longest targtet sequence and the key target involved in the pathogenesis of ADPKD.

on the luminal side is called apical. The RTs present on the basolateral membrane function as an excretory transporter whereas transporter present in the apical (luminal side) membrane function as an uptake or reabsorption transporter. So the functioning of RTs is specifically described as uptake transporter (removing substances from the blood i.e. excretion of an ion or solute if it is found in the basolateral membrane) and efflux transporter (returning substance to the blood. However, similar to basolateral membrane, both uptake (reabsorption into the cell) and efflux (excretion into the tubular lumen) transporters are also present in the apical membrane.[36]

In the present study, considering the role of the different RTs in ADPKD, the interactions of different renal transporters with PC-1 and other key proteins involved in the pathogenesis were identified by *In Silico* approach. Later is inexpensive method to predict the interactions but validation by *in vivo* methods can further verify the computationally predicted interactions.

MATERIALS AND METHODS

Identification of Putative Target

The putative target proteins were selected through literature search. The sequences information of targets (Accession numbers) were retrieved from NCBI's GenBank and UniProt Databases as shown in Table 1. The *PKD1* (Polycystin-1) plays key role in the pathogenesis of ADPKD. That's why PC-1 (PKD1) was selected as a potential target protein among others.

Retrieval of Different Renal Transporters (RTs)

Information about different renal transporters, their categorization in different nephronal segments and sequences were retrieved from NCBI's GenBank (https://www.ncbi.nlm.nih.gov/), UniProt database (https://www.uniprot.org/) and transporter databases (http://www.tcdb.org/). The RTs belongs to the SLC (Solute Carrier), ABC (ATP-Binding Cassettes) and aquaporin were categorised according to different nephronal segments and used for further analysis.

Interaction Network Generation

Selected target proteins and different RTs proteins were queried for the interaction analysis using STRING database (https://string-db.org/). Interaction network gives the information of Co-occurrence, Neighbourhood, Text mining and experimentally validated protein- protein interactions (Supplementary Table 1). It will generate the list of protein interactors with the RTs and query proteins. It creates a master network among the queried proteins and their neighbours. Further the interaction network was visualized in the cytoscape version 3.7.2. Sub networks were designed and cross-checked with other interaction databases like BioGrid.

Supplementary Table 1. String Interaction Network Terminology

General Network Terminology	
Node or (Vertices)	Each Protein in Network
Edge or (Link)	Physical or Functional Interactions Between Proteins
Modules	Group of sub networks in which each sub network includes a high number of inside-sub network links and a low number of between- sub network links
String Network	
Text Mining	
Experimental	
Co-Occurrence	
Neighbourhood	
Co- Expression	
Protein Homology	
Gene Fusion	

RESULTS

Different renal transporters (RTs) are listed in the Table 2.[37-94] In the beginning of the table, the RTs localized to the basolateral membranes are involved in the uptake and effulxing of ions or solutes from and back to the blood. Whereas, RTs that are localized to the apical membranes are involved in the reabsorption and effulxing of ions or solutes back and to the lumen of the tubule for urinary excretion are listed later on. RTs from SLC family are listed first for each membrane followed by the ABC family of transporters. Transient receptor poteintial (TRP) cation channels like aquaporins (AQP) and other various ion channels that includes the calcium, chloride, and potassium channels are also listed in the table. There are four sections, in the table i.e. two for basolateral transporters/channels (uptake and efflux from and to the blood) and two for apical membrane transporters/channels (reabsorption and efflux from and to the lumen). These transporters are involved in the interaction

Table 2. List of the Renal Transporters (RTs) in Different Nephronal Segments

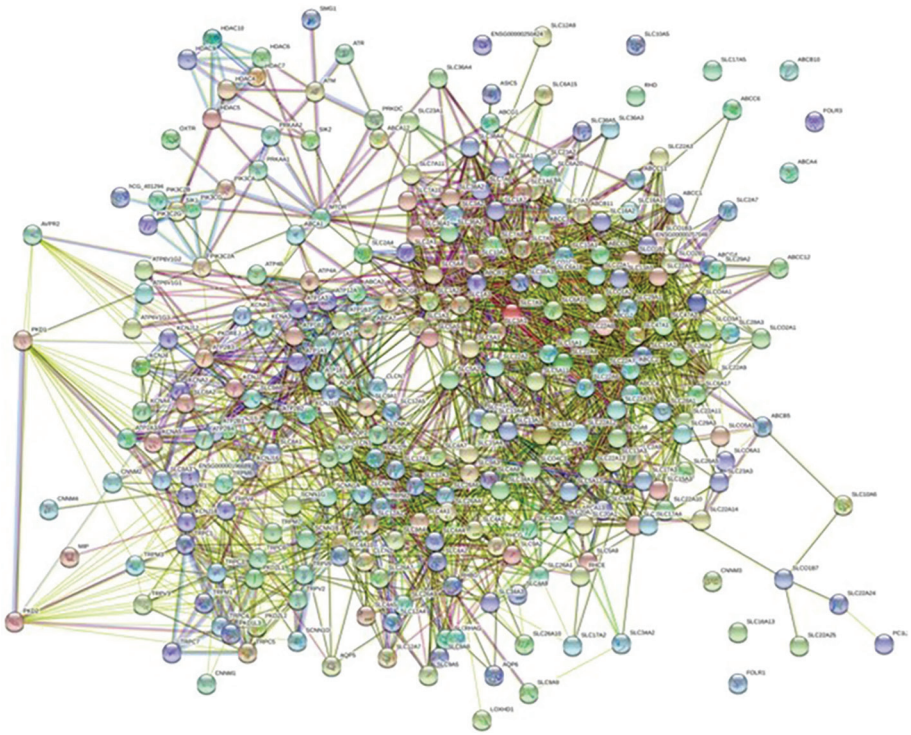
Nephron Segments	Epithelial Membrane	Genes (Transporter/Channels)
PCT Transporters	Basolateral Membrane Uptake from Blood	SLC9A1,[37] SLC9A4,[38] SLC13A3,[39] SLC22A2,[40] SLC22A3,[40] SLC22A6,[41] SLC22A7,[39] SLC22A8,[39] SLC38A3,[42] SLCO4C1[43]
	Basolateral Membrane Efflux to Blood	AQP1,[44] SLC2A9,[40,41] SLC3A2,[42] SLC4A4,[45,46] SLC7A7,[42,47] SLC7A8,[42,47] SLC9A1,[48] SLC9A4,[48] SLC16A10,[42] SLC26A1,[47] SLC38A3,[42] SLC51A,[49] SLC51B,[49] ABCA1,[50] ABCC1,[51] ABCC3,[40,41] ABCC5,[52] ABCC6[53]
	Apical Membrane Uptake from Tubular Lumen	AQP1,[44] SLC1A1,[41] SLC2A9,[40,41] SLC3A1,[54] SLC5A1,[55] SLC5A2,[47,56] SLC5A8,[47,56] SLC5A12,[57] SLC6A15,[58] SLC6A18,[59] SLC6A19,[59] SLC6A20,[60] SLC7A9,[42] SLC9A3,[48] SLC9A8,[48] SLC10A2,[41,56] SLC13A2,[56] SLC15A1,[47,56] SLC15A2,[56] SLC20A2,[61] SLC22A4,[41,56,62] SLC22A5,[40] SLC22A7,[39,40] SLC22A10,[40,41,63] SLC22A11,[40,41] SLC22A12,[40,41] SLC22A13,[40,41] SLC23A1,[47] SLC26A6,[47,64] SLC28A1,[65] SLC28A2,[62,65] SLC28A3,[65] SLC29A1,[65] SLC29A2,[65] SLC34A1,[66] SLC34A3,[66] SLC36A1,[67,68] SLC36A2,[68] SLCO1A2,[69] SLCO1B1,[56,69] SLCO2A1,[63] SLCO2B1,[69] SLCO3A1,[70] SLCO4A1,[71] TRPC1[72]
	Apical Membrane Efflux to Tubular Lumen	SLC9A3,[48] SLC9A8,[48] SLC17A1,[73] SLC17A3,[73] SLC22A4,[40,56,62] SLC26A6,[47,64] SLC47A1,[74] SLC47A2,[75] ABCB1,[75] ABCC2,[40,56] ABCC4,[40] ABCG2[39,56,62]
Thick Ascending Limb (TAL)	Basolateral Membrane Uptake from Blood	SLC9A4,[48] TRPV4[76]
	Basolateral Membrane Efflux to Blood	SLC9A4,[77] SLC12A7,[78] CLCNKA,[79] CLCNKB,[79] KCNJ10,[80] KCNJ16[80]
	Apical Membrane Uptake from Tubular Lumen	SLC9A2,[48] SLC9A3,[48] SLC12A1,[81] SLC26A6,[47,64] TRPP2,[82] TRPV4[76]
	Apical Membrane Efflux to Tubular Lumen	SLC9A2,[48] SLC26A6,[47] KCNJ1[83]
Distal Convoluted Tubule DCT	Basolateral Membrane Uptake from Blood	SLC8A1,[47] SLC12A2,[81] TRPV5[84]
	Basolateral Membrane Efflux to Blood	ATP2B1,[85] SLC8A1,[47] SLC12A7,[78] CLCNKB,[79] KCNJ10,[80] KCNJ16[80]
	Apical Membrane Uptake from Tubular Lumen	SLC9A2,[48] SLC12A3,[41,81] SLC26A6,[47,64] SCNN1A,[86] SCNN1B,[86] SCNN1G,[86] TRPM6,[87] TRPP2,[88] TRPV4,[76,84],\ TRPV5,[84] TRPV6[84]
	Apical Membrane Efflux to Tubular Lumen	SLC9A2,[48] SLC26A6,[47,64] KCNA1[89]
Connecting Tubule and Collecting Duct	Basolateral Membrane Uptake from Blood	SLC4A1,[90,46] SLC8A1,[47] SLC12A2,[81] SLC26A7,[64] RHBG,[91] RHCG[91]
	Basolateral Membrane Efflux to Blood	ATP2B1,[85] SLC4A1,[46,90] SLC4A2,[46] SLC4A3,[46,47] SLC4A9,[47] SLC8A1,[47] SLC12A7,[83] SLC26A7,[64] CLCNKB,[79] KCNJ10,[80] KCNJ16,[80] V-ATPase[92]
	Apical Membrane Uptake from Tubular Lumen	ATP4A,[93] ATP12A,[56] ATP4B,[93] AQP2,[44] SLC26A6,[47,64] SCNN1A,[86] SCNN1B,[86] SCNN1G,[86] SLC4A8,[46] SLC26A4,[64] TRPC3,[94] TRPC6,[94] TRPV4,[76] TRPV5,[84] TRPV6[84]
	Apical Membrane Efflux to Tubular Lumen	SLC4A8,[46] SLC26A4,[64] SLC26A6,[47,64] SLC26A9,[64] KCNJ1,[83] RHCG,[91] V-ATPase[92]

Renal Transporters (RTs) and their sequences were retrieved from UniProt and transporter database. Through literature search their functionality in different renal segments were identified and categorised on the basis of Uptake and Efflux transporters.[37-94]

with different protein in normal as well as disease state like other transporters are involved in the renal tubular transport disease.[95]

Interaction Between Potential Targets and Renal Transporters Through Different Paths

The potential interactions were studied using string database in multi-protein input format using *Homo sapiens* as a search organism. Interaction network shows 119 string nodes and 769 edges with average node degree 12.9, PPI enrichment *P* value: < 1.0 e-16 with avg. local clustering coefficient: 0.438 depicts that the predicted network have more significant interactions than expected. Polycystin-1 (PC-1) region ranges from 275 to 354 where, a PKD1 domain shows interaction with different protein. The interaction between PKD1 & PKD2 complex in string can be observed through multi-coloured edges that represents text mining, experimentally determined, co-expression, protein homology and curated database evidence (Supplementary Figure 1). PKD1 interact with different proteins by various paths. Interaction network were visualized and analysed using cytoscape version 3.7.2 (Figure 3). Subnetwork of 11-node interaction were visualized with



Supplementary Figure 1. String interactions of different renal transporters with potential targets involved in ADPKD. String interaction was performed between selected targets and renal transporters. Interaction shown between 119 nodes and 769 edges. The average node degree and clustering coefficient is 12.9 and 0.438 with *P* value is < 1.0e-16.

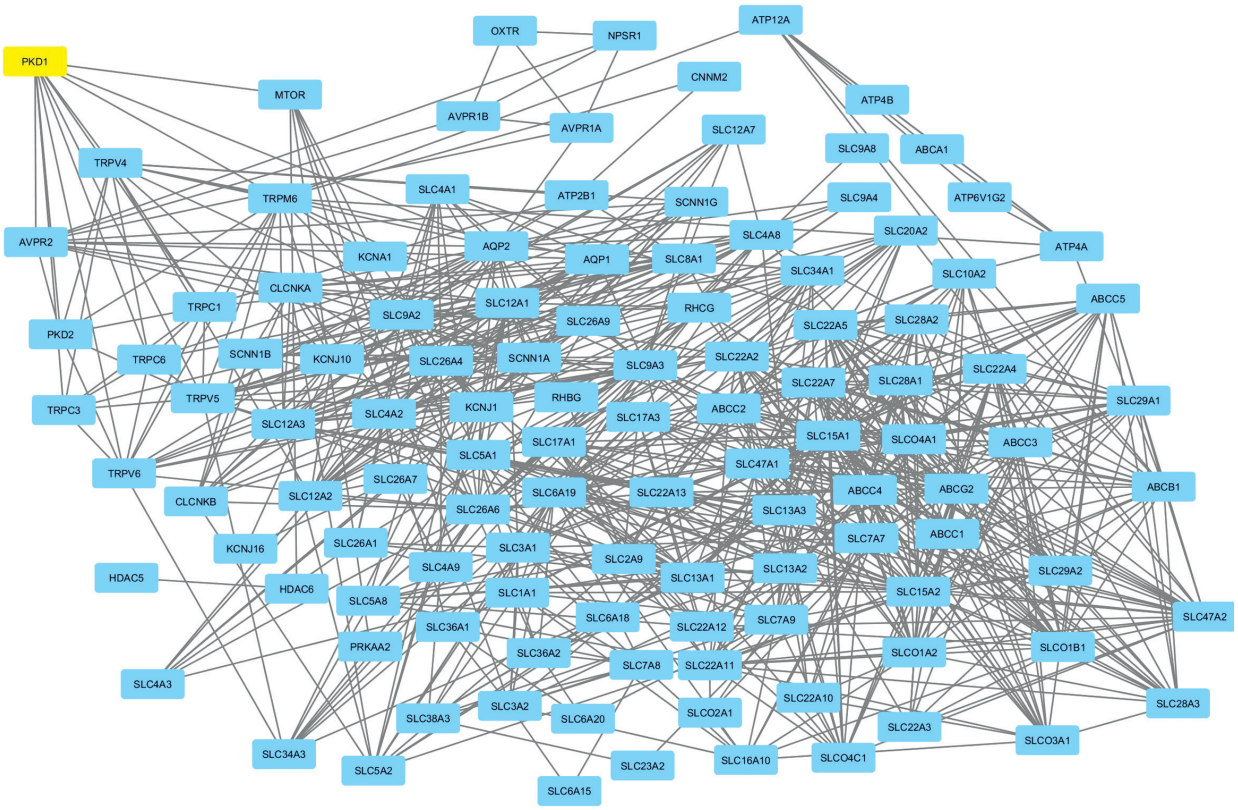


Figure 3. Complete network of the interacting protein retrieved from String and visualized in cytoscape version 3.7.2. This interaction network involves different RTs and selected target protein involved in the pathogenesis.

PKD1 protein as shown in the Figure 4. Further subnetwork of the 30 interacting string nodes were cross checked with other databases i.e. Reactome, BioGrid and visualized in cytoscape (Figure 5).

Path-I

PC-1's PKD1 region interact with AQP2 (Aquaporin-2) i.e. involved in the osmotic gradient maintenance. Other interactions are shown with the different members of Transient receptor potential channels members like TRPM2 (TRP subfamily M member 2) is a cation channel. It mediates Na^+ and Ca^{2+} influx, leading to the increased cytoplasmic Ca^{2+} levels. Other interactions include TRPM6, TRPM7, TRPV1, TRPV5, TRPV4 (subfamily V member 4) TRPC6 (Short transient receptor potential channel 6), TRPC3, TRPC1, TRPC4, and TRPM3 (subfamily M member 3).

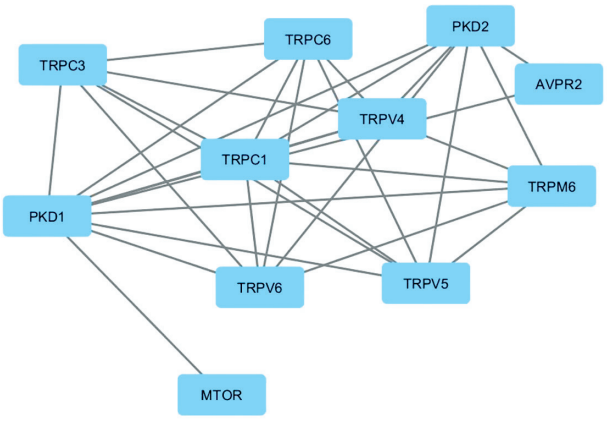


Figure 4. The Sub- Network of 11 interacting nodes. These are the close interacting protein with PKD1 protein. Majority are the member of Transient Receptor Polyprotien (TRP) family and mTOR.

Path-II

PKD1 & PKD2 shows text mining interaction with AKPR2 i.e. vasopressin V2 receptor (from GPCR family) that is mediated by G proteins and activates adenylate cyclase. It is also involved in renal water re-absorption and also used as a potential drug target in ADPKD. Secondly, the aberrant activation of PC1 is also linked with the binding of Gα-subunit with the GPS domain of the PC1. It shows the direct connection of the non-functioning of polycystins complex. AVPR2 shows experimentally determined and text mining interaction with a Solute carrier family 12 member 1 (SLC12A1). Later is electrically silent which

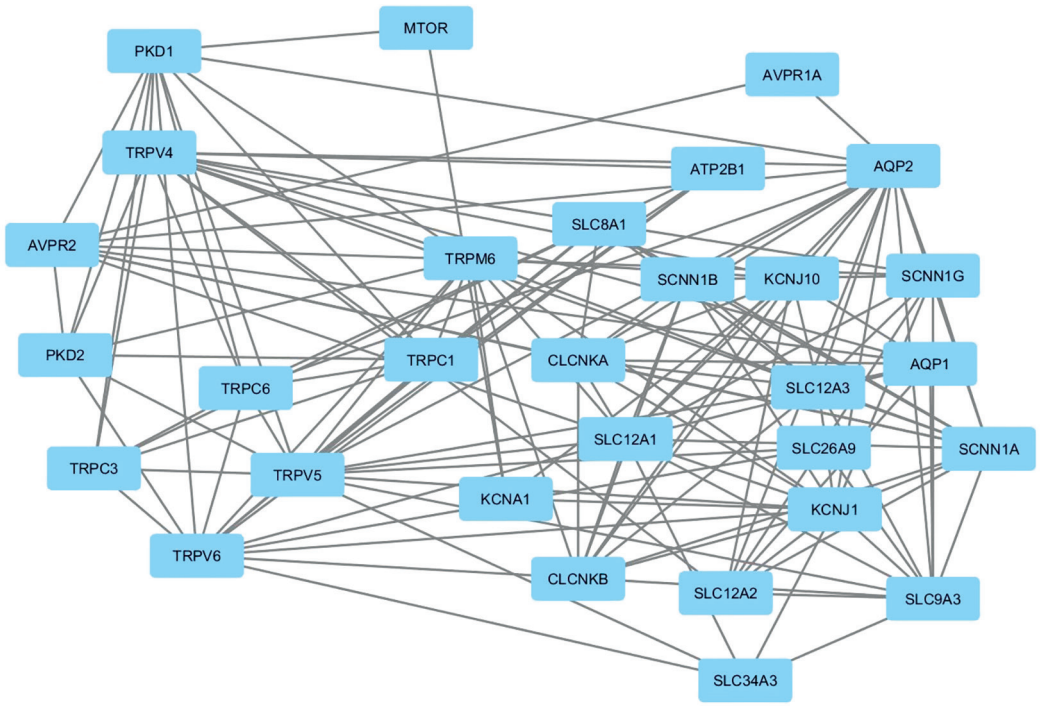


Figure 5. The subnetwork of more elaborated 30 proteins/nodes were created to identify the interacting RTs with PKD1. The network also cross checked with other databases like reactome and BioGrid in Cytoscape. Apart from closed interaction with TRP family of proteins PKD1 shows interaction with Vasopressin 2 receptor (AVPR2) contain G protein coupled receptor 1 family domain and myristoylation sites. So interactions with RTs must be possible through AVPR2.

involves in sodium and chloride re-absorption form apical membrane in the thick ascending limb (TAL) of the nephron that regulates the ionic balance and cell volume. Further, SLC12A1 shows interaction with SLC3A1, involved in the sodium-independent cystine transport and might functioning as an activator of SLC7A9 in PCT. It is also involved in the reabsorption of cystine in the kidney tubule.

Path III

PKD1 through interaction with AVPR2 shows text mining interaction with amiloride-sensitive sodium channel subunit gamma (SCNN1G) and SCNN1A. It involves in electrodiffusion of the luminal sodium through the apical membrane of epithelial cells of DCT nephronal region. This RT control the reabsorption of sodium in kidney.

Path IV

PKD1 shows co-expression and text mining interaction with mTOR i.e. Serine/threonine-protein kinase a central regulator of cellular metabolism, hormonal response and stress signals. Approximately 800 protein phosphorylation are regulated by mTOR. Further prediction of conserved motif, domain, signature and pattern from SLC12A1, SCNN1A, SCNN1G, AVPR2 and PKD1 (PC-1 region 275-354) confirms that they contain Asn-Glycosylation site, myristoylation sites (Table 3) as per prosite prediction (https://prosite.expasy.org/scanprosite/).

Table 3. ScanProsite Prediction Results

Accession Number	ScanProsite Prediction	
P98161 (272-359) PKD1- (88 aa)	PKD Domain	28-88 (PKD)
	Myristoylation Site (MYRISTYL)	16-21 (GQlaAF), 69-74 (GAgsAL)
P30518 (AVPR2) (371 aa)	G-Protein Coupled Receptor Family-1	54-325 (GPRF1)
	N- Glycosylation Site	22-25 (NSSQ)
	Casein Kinase II Phosphorylation Site	23-26 (SsqE), 255-258 (SpgE)
	Myristoylation Site (MYRISTYL)	56-61 (GLvlAA), 122-127 (GMyaSS), 153-158 (GAhwNR), 189-191 (GSgvTD), 188-193 (GVtdCW), 205-225 (GIaaCQ), 259-264 (GAhvSA)
Q13621-SLC12A1 (1099aa)	N-glycosylation Site	4-7 (NNSS), 5-8 (NSSN), 399-402 (NISG), 446-449 (NDTI), 456-459 (NGSA), 583-586 (NFSC), 868-871 (NITK), 881-884 (NTSQ)
	cAMP- and cGMP-Dependent Protein Kinase Phosphorylation Site	1014-1017 (KReT), 1061-1064 (RKgS)
	Myristoylation Site (MYRISTYL)	65-70 (GNqeCY), 208-213 (GIglGV), 227-232 (GIsmSA), 237-242 (GVvrGG) 257-262 (GGsiGL), 261-266 (GLifAF), 314-319 (GIsvAG), 393-398 (GIlaGA), 397-402 (GAniSG), 414-419 (GTmlAI),428-433 (GVaiCV), 452-457 (GMncNG), 457-462 (GSaaCG), 478-483 (GLmnNF), 499-504 (GIfsAT), 612-617 (GAvlCC), 689-694 (GGpmTR),709-714 (GLciCC), 855-860 (GGirGL), 878-883 (GSinTS), 946-951 (GGkiNR), 1089-1094 (GNhkNV).
P37088-SCNN1A (669aa)	Amiloride-sensitive Sodium Channels Signature	411-431 (YTQQVCIHSCFQESMIKECGC)
	N-glycosylation Site	64-67 (NNTT), 65-68 (NTTI), 232-235 (NKSD), 293-296 (NYSH), 312-315 (NNSN), 397-400 (NGSD), 511-514 (NYTV)
	Myristoylation Site (MYRISTYL)	19-24 (GLmkGN), 103-108 (GLIfGE), 199-204 (GArrAR), 303-308 (GNcyTF), 323-328 (GInnGL),372-377 (GVetSI), 388-393 (GGdyGD), 552-557 (GSqwSL), 598-603 (GGrgAQ), 654-659 (GGsaGA), 655-660 (GSagAS), 658-663 (GAssST)
P51170-SCNN1G (649aa)	Myristoylation Site (MYRISTYL)	281-286 (GNcyTF), 301-306 (GSeyGL), 356-361 (GMhlTE), 532-537 (GGqlGL), 536-541 (GLwmSC)
	Amiloride-sensitive Sodium Channels Signature	389-409 (YSLQICLHSCFQTKMVEKCGC)
	N-glycosylation Site	209-212 (NDTS)

ScanProsite (https://prosite.expasy.org/scanprosite/) predict conserved motifs, domain pattern and signatures.The interacting region of PC-1 i.e. PKD1 contain PKD domain and n- N-myristoylation site. Whare as AVPR2 contain region for G-protein coupled receptor family-1domain, N-Glycosylation site and n-myristoylation sites. SLC12A1, SCNN1A and SCNN1G also contain glycosylation and Myristoylation sites involved in signalling. SCNN1A and SCNN1G contain amiloride-sensitive sodium channels signature and SLC12A1 contain cAMP- and cGMP-dependent protein kinase phosphorylation site.

DISCUSSION

Polycystin-1 is the potential target that leads to the activation of number of signalling pathways. So the our study was focused upon the PC-1 interaction with RTs and other protein. The study deciphers the series of interaction that might be possible during pathogenesis of ADPKD. The binding of Gα-subunit with the PC-1 is the key step to pathologically activation of number of signalling pathways. According to the predicted interaction study and ScanProsite results, AVPR2 i.e. Vassopressin 2 receptor contain G-Protein Coupled Receptor Family-1domain that plays key role in the proper functioning of SLC12A1, SCNN1G and SCNN1A under normal condition. These transporters are also involved in the renal tubulopathies.[96] These transporters may play important role in the PC-1 aberrant activation and non-functioning of cilia. Because protein involved in the cyst formation are localized to the primary cilium. The PC-1 region 275 to 354 shows interaction with AVPR2. This region contains mutated residues that are involved in ADPKD. In disease condition, the cross signalling between SLC12A1 and PC-1 through AVPR2 affects the reabsorption of sodium and chloride form thick ascending limb (TAL) of the nephron that leads to the aberrant changes in the architecture of tubular epithelial membrane. SLC12A1 present on the apical side (luminal side) of the tubular epithelial membrane results in the increase in sodium concentration and subsequently affects the functionality of SCNN1G transporter that is involved in the renal homeostasis maintenance. Further, ScanProsite prediction results of SCNN1A, SCNN1G, SLC12A1, AVPR2 and PKD1 (PC-1 region 275-354) also confirms that PC-1 and SLC12A1 also contains myristoylation sites (Supplementary Table 3) i.e. involved in the Protein-Protein interaction, signal transduction, cellular transformation, immune response, viral infection and even oncogenesis. It also regulates phosphorylation/ dephosphorylation by non-receptor tyrosine kinases and Ca^{2+}/calmodulin-dependent protein phosphatise and calcineurin.[97] SLC12A1 is the sodium-potassium-chloride co-transporter that expresses in the renal luminal epithelial membrane. So as per interaction study, SCNN1A, SCNN1G, SLC12A1, AVPR2, and PKD1 cross signalling plays important role in the pathogenesis.

CONCLUSION

The interaction of SCL12A1 with PC1 through AVPR2 affects the reabsorption of sodium and chloride in TAL of nephronal segment that subsequently affects the functionality of SCNN1G and SCNN1A transporters involved in renal homeostasis. The above analysis shows that RTs SLC12A1, SCNN1G and SCNN1A play an important and significant role in ADPKD pathogenesis. The protein interactions predicated by us through *In Silico* approach generate very novel results that needs to be further verified by *in vivo* and clinical studies.

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AUTHOR CONTRIBUTIONS

Gobind Ram as a Ph.D. fellow did this research work. The disease related clinical information was received from Dr. Tarini. Dr. Shiv Kumar Giri has supervised this work. Dr. Anil Kumar and Dr. Gulab Singh has given valuable suggestions in the designing of the study.

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CONFLICT OF INTEREST

Authors declares no conflict of interest.

ETHICS APPROVAL

As this is an *In Silico* based study. No ethical approval is required.

CONSENT FOR PUBLICATION

This is one of kind of interaction study in ADPKD. This work will be beneficial for the research community working on Polycystic Kidney Disease.

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ABBREVIATIONS

SLC12A1: Solute Carrier Family 12 Member 1
SCNN1A: Amiloride-sensitive Sodium Channel Subunit Alpha
SCNN1G: Amiloride-sensitive Sodium Channel Subunit Gamma
AVPR2: Vasopressin V2 Receptor
ABCG1: ATP-binding Cassette Sub-family G Member 1
PKD1: Polycystin-1; Involved in Renal Tubulogenesis
TRPM2: Transient Receptor Potential Channels Subfamily M Member 2
AQP1: Aquaporin-1
SLCO1A2: Solute Carrier Organic Anion Transporter Family Member 1A2
CLCNKA: Chloride Voltage-Gated Channel Ka
KCNJ10: Potassium Inwardly Rectifying Channel Subfamily J Member 10
TRPP2: Transient Receptor Potential Polycystic 2
RHBG: Ammonium Transporter Rh Type B
ATP2B1: Plasma Membrane Calcium-transporting ATPase 1
V-ATPase: Vacuolar-type ATPase