Supplemental Table 1: Associations of identified pathways with CKD. Results from the LitMiner literature search confirmed by individual PubMed review are displayed.

Pathway or group of pathways	Citation	Known implication in CKD
Aldosterone Signaling in Epithelial Cells	[33]	Aldosterone promotes podocyte loss and a consequent decrease in slit–pore membrane integrity, with consequent proteinuria.
Fatty Acid Biosynthesis, Fatty Acid Elongation in Mitochondria, Fatty Acid Metabolism	[16]	Podocytes are especially vulnerable to Fatty acid accumulation, which leads to apoptosis and glomerulosclerosis.
NRF2-mediated Oxidative Stress Response	[14]	Nrf2 mediates protection against tissue injury via antioxidant and detoxification responses to oxidative stress and inflammation in chronic renal failure.
Arginine and Proline Metabolism	[10]	Reduced GFR is associated with reduced arginine/ADMA ratio.
Agrin Interactions at Neuromuscular Junction	[19]	Agrin is a main component of the glomerular basement membrane
Altered T Cell and B Cell Signaling in Rheumatoid Arthritis, B Cell Development, Leukocyte Extravasation Signaling, T Helper Cell Differentiation, Calcium-induced T Lymphocyte Apoptosis, iCOS-iCOSL Signaling in T Helper Cells, Leukocyte Extravasation Signaling, T Helper Cell Differentiation	[36]	Increased neutrophil and decreased lymphocyte numbers are associated with increased CKD incidence.
PI3K Signaling in B Lymphocytes	[39]	Podocyte apoptosis is induced by activation of the phosphatidylinositol 3-kinase/Akt-signaling pathway.
Fructose and Mannose Metabolism	[3]	Low-fructose diet decreases blood pressure and inflammation in CKD.
Glutathione Metabolism	[15]	Gluthathione peroxidases are increased in patients with CKD
Glutamate Metabolism, Glutamate Receptor Signaling, D-glutamine and D-glutamate Metabolism	[24]	Animal data show that increased levels of glutamate lead to downregulation of 1α-hydroxylase expression, a mechanism for secondary HPT in CKD.
Arginine and Proline Metabolism	[30]	Symmetric dimethylarginine (SDMA) is a uraemic retention solute. It stimulates reactive oxygen species production by monocytes in CKD.
Autoimmune Thyroid Disease Signaling	[12]	Autoimmune thyroid disorders are more common in hemodialysis patients.
Bile Acid Biosynthesis	[21]	Bile acid receptor activation prevents the

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		development of vascular calcification in ApoE-/- mice with CKD.
Caveolar-mediated Endocytosis Signaling	23	Endocytosis by proximal tubule cells of glomerularly filtered proteins increases cell stress responses resulting in increased tubulointerstitial inflammation and fibrosis.
CD28 Signaling in T Helper Cells	20	Animal data show that CD28-specific monoclonal antibodies ameliorate mesangial cell proliferation and extracellular matrix expansion in glomerulopathies.
Cdc42 Signaling, Rac Signaling	22	Activation of Cdc42 and Rac1 in podocytes causes foot process effacement and subsequent proteinuria.
Complement System	4	Renal complement activation sustains proinflammatory and profibrotic cellular changes and thereby leads to progression of CKD.
Crosstalk between Dendritic Cells and Natural Killer Cells, Dendritic Cell Maturation	11	T and NK cells contain RAS elements and are potentially capable of producing and delivering AngII to inflammation sites in CKD.
D-arginine and D-ornithine Metabolism	18	Elevated plasma ADMA level was associated with low GFR and macroalbuminuria.
fMLP Signaling in Neutrophils	28	CKD patients show an increased fMLP-stimulated apoptosis rate of polymorphonuclear cells.
Folate Biosynthesis, One Carbon Pool by Folate	5	CKD leads to down-regulation of folate transporter in the intestine, heart, liver and brain.
Glycine, Serine and Threonine Metabolism	17	Inhibition of protein serine/threonine phosphatases prevents renal tubulointerstitial fibrosis in CKD
Glycolysis/Gluconeogenesis	35	HIF targets glycolysis genes. Activation of HIF in CKD is evaluated as a new therapeutic approach.
Glycosaminoglycan Degradation, O-Glycan Biosynthesis	38	In CKD due to diabetic nephropathy, glycosaminoglycans are investigated as a therapeutic approach through protein kinase C (PKC) inhibition.
Glycosphingolipid Biosynthesis	2	Fabry disease a X-linked disorder of glycosphingolipid metabolism leads to CKD and renal failure in adulthood.
Glyoxylate and Dicarboxylate Metabolism, Alanine Metabolism	6	Primary hyperoxaluria type 1 results from alanine:glyoxylate aminotransferase deficiency leading to CKD.
Histidine Metabolism	37	Low serum concentrations of histidine are associated with inflammation, oxidative stress, and increased mortality in CKD.
Intrinsic Prothrombin Activation Pathway	1	Increased prothrombin fragment 1+2 were found in CKD, consistent with a hypercoagulable state in these patients.

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Lysine Degradation	[31]	Serum carboxymethyl-lysine is associated with CKD.
Metabolism of Xenobiotics by Cytochrome P450, Xenobiotic Metabolism Signaling	[26]	Uremic toxins affect drug transporters and metabolizing enzymes in CKD.
Methionine Metabolism	[34]	SNPs of genes encoding for methionine synthase reductase and methionine synthase were found in CKD patients.
Mitochondrial Dysfunction	[8]	Mitochondrial dysfunction plays a role in various chronic kidney diseases.
NF-kappaB Signaling	[29]	CKD is characterized by chronic inflammation. One feature of chronic inflammation is activation of NF-κB.
Nitrogen Metabolism, Urea Cycle and Metabolism of Amino Groups	[13]	Blood urea nitrogen (BUN) is elevated in CKD.
NRF2-mediated Oxidative Stress Response	[25]	The synthetic triterpenoid, bardoxolone methyl induces the transcription factor Nrf2 and improves kidney function in CKD patients.
Oxidative Phosphorylation	[7]	Whole transcriptomic analysis of peripheral blood mononuclear cells of CKD patients demonstrated that several regulated genes were involved in the oxidative phosphorylation system.
Pyruvate Metabolism	[32]	In CKD oxidative stress impairs glucose metabolism through reduction in pyruvate generation and/or transamination.
Serotonin Receptor Signaling, Tryptophan Metabolism	[9]	Plasma serotonin levels increase with declining renal function.
Tyrosine Metabolism	[27]	Tyrosine kinase inhibitor imatinib is beneficial on the progression of renal failure.

REFERENCES FOR TABLE

1. Adams, MJ, Irish, AB, Watts, GF, Oostryck, R & Dogra, GK: Hypercoagulability in chronic kidney disease is associated with coagulation activation but not endothelial function. *Thromb Res*, 123**:** 374-80, 2008.
2. Andrade, J, Waters, PJ, Singh, RS, Levin, A, Toh, BC, Vallance, HD & Sirrs, S: Screening for Fabry disease in patients with chronic kidney disease: limitations of plasma alpha-galactosidase assay as a screening test. *Clin J Am Soc Nephrol*, 3**:** 139-45, 2008.
3. Brymora, A, Flisinski, M, Johnson, RJ, Goszka, G, Stefanska, A & Manitius, J: Low-fructose diet lowers blood pressure and inflammation in patients with chronic kidney disease. *Nephrol Dial Transplant*, 2011.

Supplemental Table 1: Associations of identified pathways with CKD. Results from the LitMiner literature search confirmed by individual PubMed review are displayed.

4. Buelli, S, Abbate, M, Morigi, M, Moioli, D, Zanchi, C, Noris, M, Zoja, C, Pusey, CD, Zipfel, PF & Remuzzi, G: Protein load impairs factor H binding promoting complement-dependent dysfunction of proximal tubular cells. *Kidney Int,* 75**:** 1050-9, 2009.
5. Bukhari, FJ, Moradi, H, Gollapudi, P, Ju Kim, H, Vaziri, ND & Said, HM: Effect of chronic kidney disease on the expression of thiamin and folic acid transporters. *Nephrol Dial Transplant,* 26**:** 2137-44, 2011.
6. Fargue, S, Harambat, J, Gagnadoux, MF, Tsimaratos, M, Janssen, F, Llanas, B, Bertheleme, JP, Boudailliez, B, Champion, G, Guyot, C, Macher, MA, Nivet, H, Ranchin, B, Salomon, R, Taque, S, Rolland, MO & Cochat, P: Effect of conservative treatment on the renal outcome of children with primary hyperoxaluria type 1. *Kidney Int,* 76**:** 767-73, 2009.
7. Granata, S, Zaza, G, Simone, S, Villani, G, Latorre, D, Pontrelli, P, Carella, M, Schena, FP, Grandaliano, G & Pertosa, G: Mitochondrial dysregulation and oxidative stress in patients with chronic kidney disease. *BMC Genomics,* 10**:** 388, 2009.
8. Hall, AM & Unwin, RJ: The not so 'mighty chondrion': emergence of renal diseases due to mitochondrial dysfunction. *Nephron Physiol,* 105**:** p1-10, 2007.
9. Hara, K, Hirowatari, Y, Shimura, Y & Takahashi, H: Serotonin levels in platelet-poor plasma and whole blood in people with type 2 diabetes with chronic kidney disease. *Diabetes Res Clin Pract,* 94**:** 167-71, 2011.
10. Hov, GG, Sagen, E, Hatlen, G, Bigonah, A, Asberg, A & Aasarod, K: Arginine/asymmetric dimethylarginine ratio and cardiovascular risk factors in patients with predialytic chronic kidney disease. *Clin Biochem,* 44**:** 642-6, 2011.
11. Jurewicz, M, McDermott, DH, Sechler, JM, Tinckam, K, Takakura, A, Carpenter, CB, Milford, E & Abdi, R: Human T and natural killer cells possess a functional renin-angiotensin system: further mechanisms of angiotensin II-induced inflammation. *J Am Soc Nephrol,* 18**:** 1093-102, 2007.
12. Jusufovic, S, Hodzic, E & Halilcevic, A: Role of renal anemia in the functional, morphological and autoimmune thyroid disorders in patients on chronic hemodialysis. *Med Arh,* 65**:** 228-32, 2011.
13. Kim, HJ, Kim, KM, Koo, TY, Chi, HS, Kim, SH & Kim, SB: Prevalence of abnormal in vitro closure time using the Platelet Function Analyzer-100 in chronic kidney disease patients and analysis of associated factors. *Clin Nephrol,* 76**:** 195-200, 2011.
14. Kim, HJ & Vaziri, ND: Contribution of impaired Nrf2-Keap1 pathway to oxidative stress and inflammation in chronic renal failure. *Am J Physiol Renal Physiol,* 298**:** F662-71, 2010.
15. Kuchta, A, Pacanis, A, Kortas-Stempak, B, Cwiklinska, A, Zietkiewicz, M, Renke, M & Rutkowski, B: Estimation of oxidative stress markers in chronic kidney disease. *Kidney Blood Press Res,* 34**:** 12-9, 2011.
16. Lee, HS: Mechanisms and consequences of hypertriglyceridemia and cellular lipid accumulation in chronic kidney disease and metabolic syndrome. *Histol Histopathol,* 26**:** 1599-610, 2011.
17. Li, Y, Ge, Y, Liu, FY, Peng, YM, Sun, L, Li, J, Chen, Q, Sun, Y & Ye, K: Norcantharidin, a protective therapeutic agent in renal tubulointerstitial fibrosis. *Mol Cell Biochem,* 2011.

Supplemental Table 1: Associations of identified pathways with CKD. Results from the LitMiner literature search confirmed by individual PubMed review are displayed.

18. Lu, TM, Chung, MY, Lin, CC, Hsu, CP & Lin, SJ: Asymmetric dimethylarginine and clinical outcomes in chronic kidney disease. *Clin J Am Soc Nephrol,* 6**:** 1566-72, 2011.

19. Miner, JH: Organogenesis of the kidney glomerulus: focus on the glomerular basement membrane. *Organogenesis,* 7**:** 75-82, 2011.

20. Miyasato, K, Takabatake, Y, Kaimori, J, Kimura, T, Kitamura, H, Kawachi, H, Li, XK, Hunig, T, Takahara, S, Rakugi, H & Isaka, Y: CD28 superagonist-induced regulatory T cell expansion ameliorates mesangioproliferative glomerulonephritis in rats. *Clin Exp Nephrol,* 15**:** 50-7, 2011.

21. Miyazaki-Anzai, S, Levi, M, Kratzer, A, Ting, TC, Lewis, LB & Miyazaki, M: Farnesoid X receptor activation prevents the development of vascular calcification in ApoE-/- mice with chronic kidney disease. *Circ Res,* 106**:** 1807-17, 2010.

22. Mundel, P & Reiser, J: Proteinuria: an enzymatic disease of the podocyte? *Kidney Int,* 77**:** 571-80, 2010.

23. Nakhoul, N & Batuman, V: Role of proximal tubules in the pathogenesis of kidney disease. *Contrib Nephrol,* 169**:** 37-50, 2011.

24. Parisi, E, Bozic, M, Ibarz, M, Panizo, S, Valcheva, P, Coll, B, Fernandez, E & Valdivielso, JM: Sustained activation of renal N-methyl-D-aspartate receptors decreases vitamin D synthesis: a possible role for glutamate on the onset of secondary HPT. *Am J Physiol Endocrinol Metab,* 299**:** E825-31, 2010.

25. Pergola, PE, Krauth, M, Huff, JW, Ferguson, DA, Ruiz, S, Meyer, CJ & Warnock, DG: Effect of bardoxolone methyl on kidney function in patients with T2D and Stage 3b-4 CKD. *Am J Nephrol,* 33**:** 469-76, 2011.

26. Reyes, M & Benet, LZ: Effects of uremic toxins on transport and metabolism of different biopharmaceutics drug disposition classification system xenobiotics. *J Pharm Sci,* 100**:** 3831-42, 2011.

27. Sampson, MG, Coughlin, CR, 2nd, Kaplan, P, Conlin, LK, Meyers, KE, Zackai, EH, Spinner, NB & Copelovitch, L: Evidence for a recurrent microdeletion at chromosome 16p11.2 associated with congenital anomalies of the kidney and urinary tract (CAKUT) and Hirschsprung disease. *Am J Med Genet A,* 152A**:** 2618-22, 2010.

28. Sardenberg, C, Suassuna, P, Andreoli, MC, Watanabe, R, Dalboni, MA, Manfredi, SR, dos Santos, OP, Kallas, EG, Draibe, SA & Cendoroglo, M: Effects of uraemia and dialysis modality on polymorphonuclear cell apoptosis and function. *Nephrol Dial Transplant,* 21**:** 160-5, 2006.

29. Schepers, E, Barreto, DV, Liabeuf, S, Glorieux, G, Eloot, S, Barreto, FC, Massy, Z & Vanholder, R: Symmetric dimethylarginine as a proinflammatory agent in chronic kidney disease. *Clin J Am Soc Nephrol,* 6**:** 2374-83, 2011.

30. Schepers, E, Glorieux, G, Dhondt, A, Leybaert, L & Vanholder, R: Role of symmetric dimethylarginine in vascular damage by increasing ROS via store-operated calcium influx in monocytes. *Nephrol Dial Transplant,* 24**:** 1429-35, 2009.

31. Semba, RD, Fink, JC, Sun, K, Windham, BG & Ferrucci, L: Serum carboxymethyl-lysine, a dominant advanced glycation end product, is associated with chronic kidney disease: the Baltimore longitudinal study of aging. *J Ren Nutr,* 20**:** 74-81, 2010.

Supplemental Table 1: Associations of identified pathways with CKD. Results from the LitMiner literature search confirmed by individual PubMed review are displayed.

32. Sinha-Hikim, I, Shen, R, Paul Lee, WN, Crum, A, Vaziri, ND & Norris, KC: Effects of a novel cystine-based glutathione precursor on oxidative stress in vascular smooth muscle cells. *Am J Physiol Cell Physiol,* 299**:** C638-42, 2010.

33. Sowers, JR, Whaley-Connell, A & Epstein, M: Narrative review: the emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. *Ann Intern Med,* 150**:** 776-83, 2009.

34. Sunder-Plassmann, G, Winkelmayer, WC & Fodinger, M: Genetic aspects of hyperhomocysteinemia in chronic kidney disease. *Semin Nephrol,* 26**:** 8-13, 2006.

35. Tanaka, T & Nangaku, M: Drug discovery for overcoming chronic kidney disease (CKD): prolyl-hydroxylase inhibitors to activate hypoxia-inducible factor (HIF) as a novel therapeutic approach in CKD. *J Pharmacol Sci,* 109**:** 24-31, 2009.

36. Tian, N, Penman, AD, Manning, RD, Jr., Flessner, MF & Mawson, AR: Association between circulating specific leukocyte types and incident chronic kidney disease: the Atherosclerosis Risk in Communities (ARIC) study. *J Am Soc Hypertens,* 2011.

37. Watanabe, M, Suliman, ME, Qureshi, AR, Garcia-Lopez, E, Barany, P, Heimburger, O, Stenvinkel, P & Lindholm, B: Consequences of low plasma histidine in chronic kidney disease patients: associations with inflammation, oxidative stress, and mortality. *Am J Clin Nutr,* 87**:** 1860-6, 2008.

38. Williams, ME: New potential agents in treating diabetic kidney disease: the fourth act. *Drugs,* 66**:** 2287-98, 2006.

39. Xiao, H, Shi, W, Liu, S, Wang, W, Zhang, B, Zhang, Y, Xu, L, Liang, X & Liang, Y: 1,25-Dihydroxyvitamin D(3) prevents puromycin aminonucleoside-induced apoptosis of glomerular podocytes by activating the phosphatidylinositol 3-kinase/Akt-signaling pathway. *Am J Nephrol,* 30**:** 34-43, 2009.

Suppl. Table 2: List of all pathways not previously implicated in CKD ranked in descending order according to the number of original candidate genes the pathway was associated with (# of connections)

Pathway	# of connections
Ascorbate and Aldarate Metabolism	10
Butanoate Metabolism	10
Glycerolipid Metabolism	10
Propanoate Metabolism	10
Valine, Leucine and Isoleucine Degradation	10
Alanine and Aspartate Metabolism	9
Cyanoamino Acid Metabolism	9
Galactose Metabolism	9
LPS/IL-1 Mediated Inhibition of RXR Function	9
Pentose and Glucuronate Interconversions	9
Phenylalanine Metabolism	9
Synthesis and Degradation of Ketone Bodies	8
Starch and Sucrose Metabolism	7
Fcγ-Receptor-mediated Phagocytosis in Macrophages and Monocytes	6
FXR/RXR Activation	6
Maturity Onset Diabetes of Young(MODY) Signaling	6
Pentose Phosphate Pathway	6
Inositol Metabolism	5
Phospholipase C Signaling	5
PXR/RXR Activation	5
Selenoaminoacid Metabolism	5
Virus Entry via Endocytic Pathways	5
14-3-3-mediated Signaling	4
Pantothenate and CoA Biosynthesis	4
Allograft Rejection Signaling	3
Aminosugars Metabolism	3
Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells	3
Regulation of Actin-based Motility by Rho	3
Aminophosphonate Metabolism	2
Antigen Presentation Pathway	2
Glioblastoma Multiforme Signaling	2
Graft-versus-Host Disease Signaling	2
Hepatic Fibrosis/Hepatic Stellate Cell Activation	2
α-Adrenergic Signaling	2
Methane Metabolism	2
MSP-RON Signaling Pathway	2
Neuropathic Pain Signaling In Dorsal Horn Neurons	2
Neuroprotective Role of THOP1 in Alzheimer's Disease	2
Nur77 Signaling in T Lymphocytes	2
OX40 Signaling Pathway	2
Type I Diabetes Mellitus Signaling	2