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Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

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Alterations of urinary proteomic profile in patients with chronic kidney disease of uncertain aetiology in Sri Lanka

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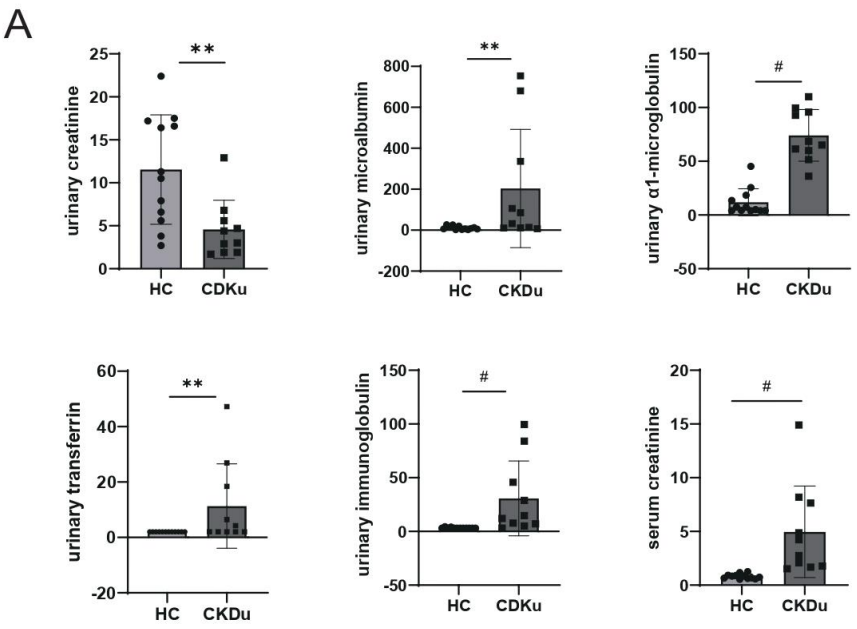
Objectives : Chronic Kidney Disease of Unknown Etiology (CKDu) is characterized by persistent microalbuminuria, reduced glomerular filtration rate, and concurrent renal interstitial fibrosis pathologically, which mainly affected young agricultural workers and caused high mortality in arid regions of Sri Lanka. Urinary biomarkers offer a dynamic reflection of kidney disease progression and there is limited knowledge regarding alterations in the urine proteins among CKDu patients.
Methods : We conducted urine proteomic analysis on 10 CKDu cases and 12 healthy controls (HCs) from Sri Lanka to elucidate novel biomarkers associated with early diagnosis and may offer insights for guiding treatment of the CKDu. Detection of urinary parameters of kidney injury by routine biochemistry methods and inflammatory cytokines of urine by Luminex liquid suspension chip were performed. The differentially expressed proteins (DEPs) of urine between CKDu and HCs were subsequently identified by liquid chromatography-tandem mass spectrometry (LC/MS-MS).
Results : Routine biochemistry indicated a significant increase in urinary microalbumin, urinary α1-microglobulin, urinary transferrin, urinary immunoglobulin, and serum creatinine in CKDu group. Pro-inflammatory factors IL15, IL16, IL18, TNF-α and chemokines CCL7, CXCL8, CXCL9, CXCL12 increased in CKDu group, indicating significant inflammatory response in CKDu group. 1153 DEPs (576 down-regulated and 577 up-regulated) were identified with LC/MS-MS. Bioinformatics analyses, including GO terms and KEGG pathways, revealed that down-regulated proteins were enriched in pathways associated with epithelial-to-mesenchymal transition, such as ECM-receptor interaction. Up-regulated proteins were enriched in pathways related to protein processing in the endoplasmic reticulum, and complement and coagulation cascades. PDIA3 and P4HB, which inhibited the aggregation of misfolded proteins, were further confirmed as hub proteins of up-regulated DEPs in the CDKu group.
Conclusions : Our findings emphasize the pathological processes, including inflammatory cell infiltration and dysfunction of protein processing in the endoplasmic reticulum in the CKDu patients. These observations form the basis for developing potential diagnostic biomarkers for CKDu.

Figure1.jpg


A
urinary creatinine
urinary microalbumin
urinary α1-microglobulin
urinary transferrin
urinary immunoglobulin
serum creatinine
HC
CDKu
CKDu
**
#

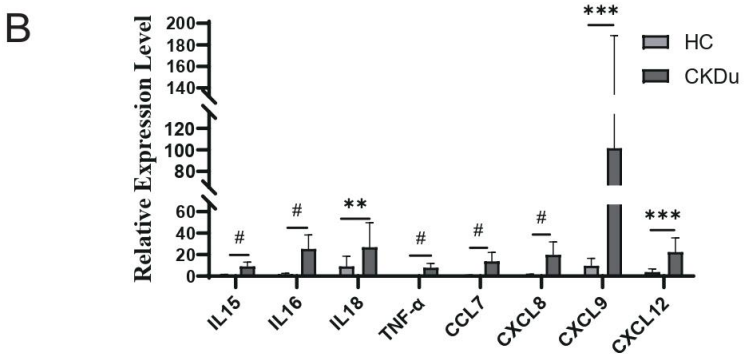

B
Relative Expression Level
HC
CKDu
IL15
IL16
IL18
TNF-α
CCL7
CXCL8
CXCL9
CXCL12
#
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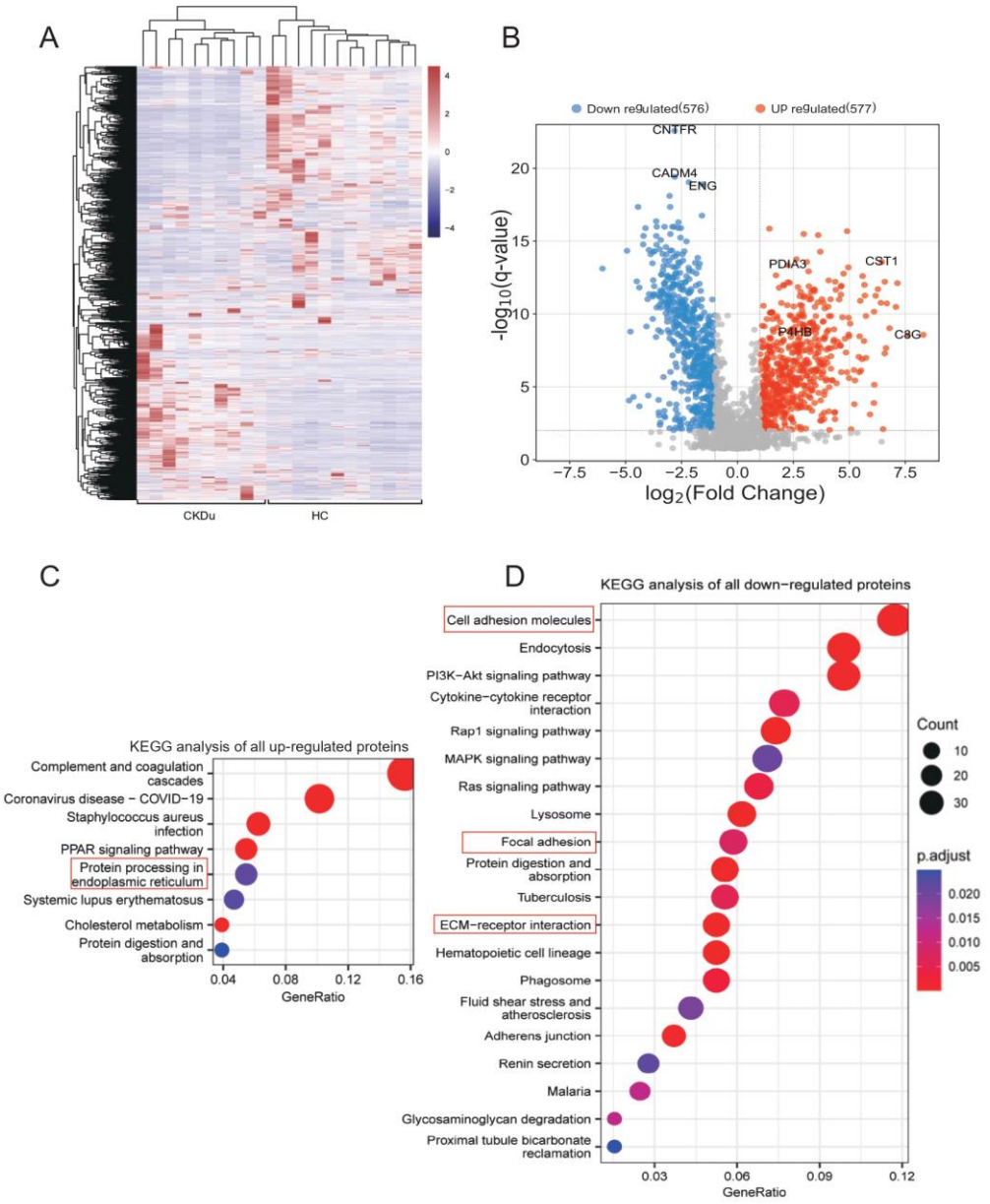
Figure1.jpg


A
CKDu
HC
B
Down regulated(576)
UP regulated(577)
CNTFR
CADM4
ENG
PDIA3
CST1
P4HB
C8G
-log10(q-value)
log2(Fold Change)
C
KEGG analysis of all up-regulated proteins
Complement and coagulation cascades
Coronavirus disease - COVID-19
Staphylococcus aureus infection
PPAR signaling pathway
Protein processing in endoplasmic reticulum
Systemic lupus erythematosus
Cholesterol metabolism
Protein digestion and absorption
GeneRatio
D
KEGG analysis of all down-regulated proteins
Cell adhesion molecules
Endocytosis
PI3K-Akt signaling pathway
Cytokine-cytokine receptor interaction
Rap1 signaling pathway
MAPK signaling pathway
Ras signaling pathway
Lysosome
Focal adhesion
Protein digestion and absorption
Tuberculosis
ECM-receptor interaction
Hematopoietic cell lineage
Phagosome
Fluid shear stress and atherosclerosis
Adherens junction
Renin secretion
Malaria
Glycosaminoglycan degradation
Proximal tubule bicarbonate reclamation
GeneRatio
Count
p.adjust