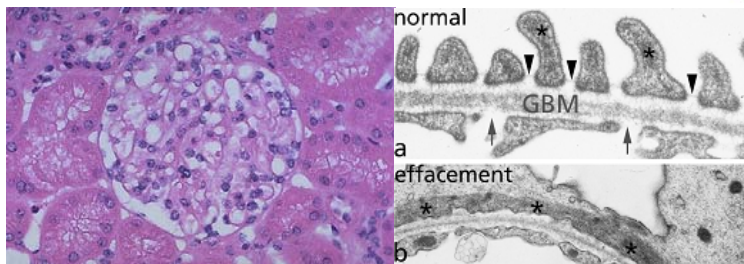


# URINARY LIPIDOMICS IN NEPHROTIC SYNDROME

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## Why urine?



Endothelial cells: There are small gaps in the endothelial cell cytoplasm that allow most proteins to penetrate

Glomerular basement membrane: composed of collagen and matrix proteins

Slit-diaphragms: connect adjacent foot processes extending from the podocytes and offer a final barrier



## Lipids and GN

- Glomerular disease (GN) is the number one cause of end-stage renal disease during adolescence.
- Adolescents on dialysis are expected to live only 16 years with a ten-year mortality rate as high as twenty percent.
- Focal segmental glomerulosclerosis (FSGS) is the most common cause of progressive glomerular disease and its treatment remains as one of the most difficult challenges in pediatric nephrology.



## Lipids and GN

- Altered lipid metabolism was implicated in progression of glomerular disease particularly in diabetic glomerulopathy in adults however the impact of accumulated lipid metabolites on the course of glomerular diseases in children has not yet been explored
- We reported mitochondrial associated, caspase-9 mediated apoptosis in FSGS

Elif Erkan, Prasad Devarajan, George Schwartz. Mitochondria are the major targets in albumin induced apoptosis in proximal tubule cells. J Am Soc Nephrol. 2007 Apr; 18(4): 1199-208



## Lipids and GN

- We hypothesize that altered lipid metabolism contributes to cellular apoptosis and the progressive nature of FSGS
- We examined urinary lipid profile of children with FSGS, minimal change disease (MCD) and healthy controls by lipidomic analysis

Erkan E et al. Distinct urinary lipid profile in children with focal segmental glomerulosclerosis. *Pediatr Nephrol.* 2016 Apr;31(4):581-8



## Lipids and GN

- *Patient population:* Patients were enrolled from Cincinnati Children's Hospital Nephrology Clinic. Random urine samples from ten patients with MCD, eight patients with FSGS and ten age-matched healthy controls were analyzed
- Patient urines were obtained at the time of nephrotic range proteinuria and relapse for patients with MCD. Glomerular filtration rate (GFR) was estimated by modified Schwartz formula

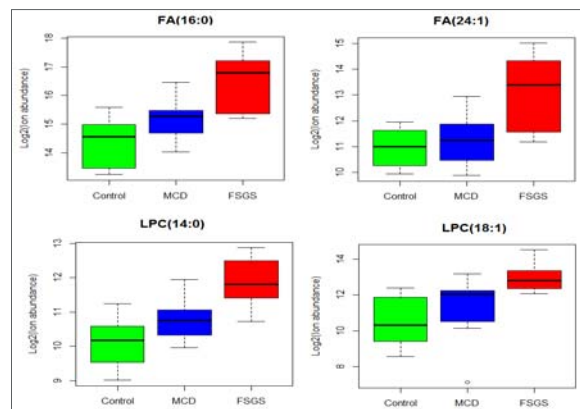


## Lipids and GN

- Non-targeted metabolomics screening of patient urines was performed at the UC Davis Metabolomic Core.
- UPLC-QTOF mass spectrometry



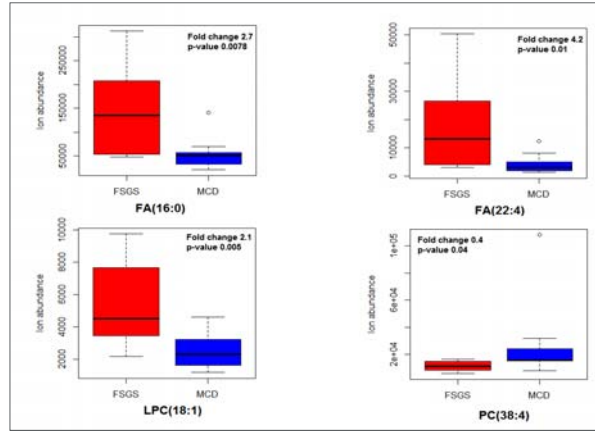
## RESULTS



**Box-and-whisker plot of representative putative biomarkers (4 metabolites) of healthy controls, FSGS, MCD (a) and FSGS and MCD (b).** Lipidomic analysis of the urine samples displayed an increase in urinary FA (16:00), FA (22:4), lysophosphatidylcholine (LPC) (18:1) and a decrease in urinary phosphatidylcholine (PC) (38:4) level in FSGS.



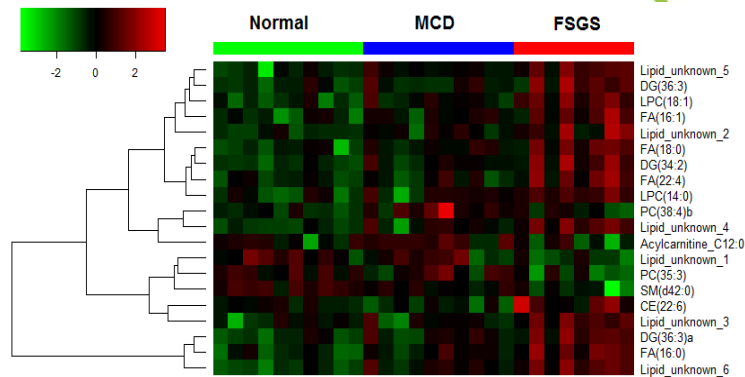
## RESULTS



Urinary FA and LPC levels are higher and PC level is lower in FSGS

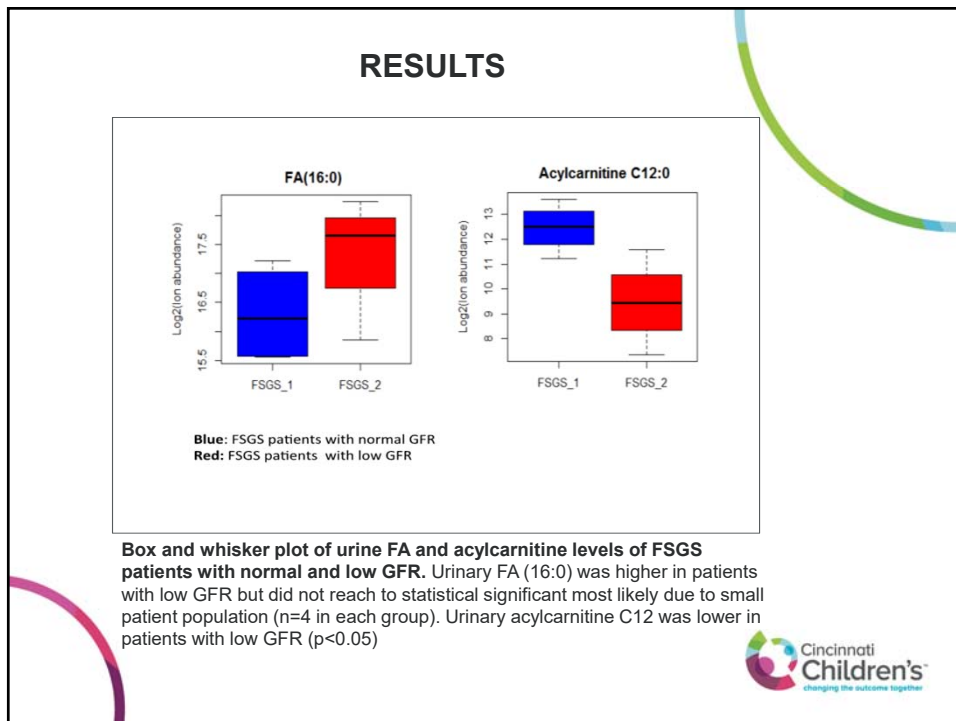
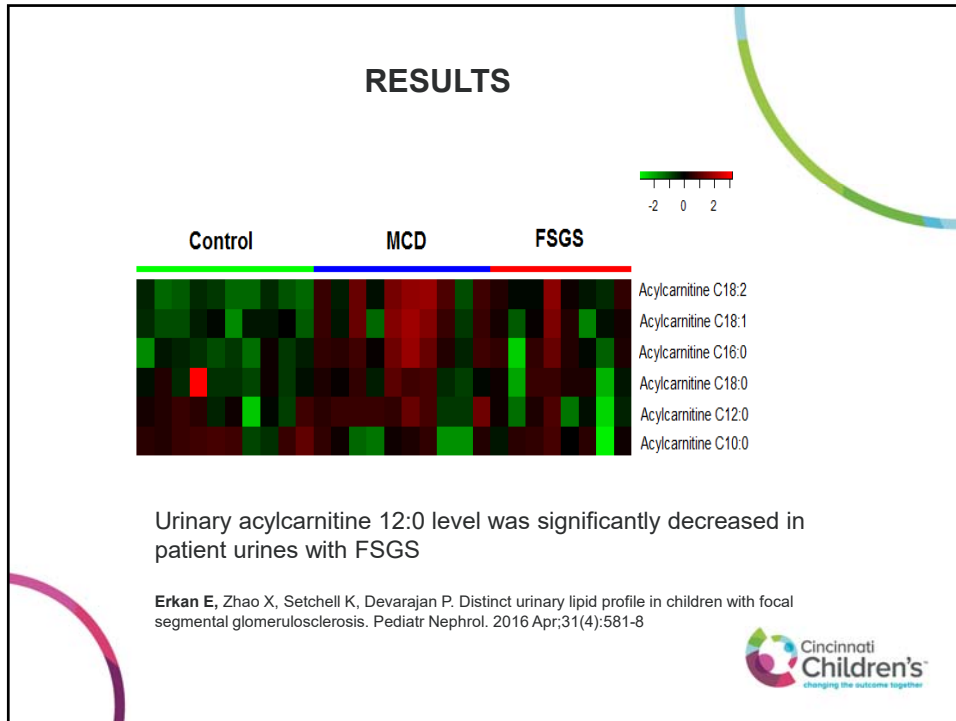


## RESULTS

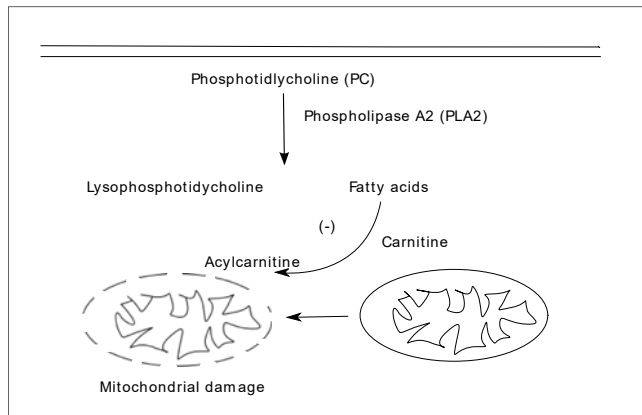


Heatmap displaying abundances in major lipid classes in patient groups and healthy controls. A heatmap displaying hierarchical clustered Pearson correlations between samples and (sum) abundances of major lipid classes is shown. 20 lipid metabolite features differentiated in were shown in the figure.





## RESULTS



**Proposed pathway for cellular damage caused by disarranged lipid metabolism in FSGS:** Increased intracellular PLA2 activity results in release of LPC and FA. These mediators cause cellular toxicity and cell damage by increasing production mitochondrial damage and ATP depletion.