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Differentiating primary and secondary FSGS using non-invasive urine biomarkers

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TRAVERE THERAPEUTICS

DISCLOSURES

- **BH, IP, MW:** Employees, Travere Therapeutics, Inc.
- **JS:** Employee of Mosaiques Diagnostics GmbH
- **HM:** Founder and co-owner of Mosaiques Diagnostics GmbH
- **RW, JB, LC, HR:** Nothing to disclose

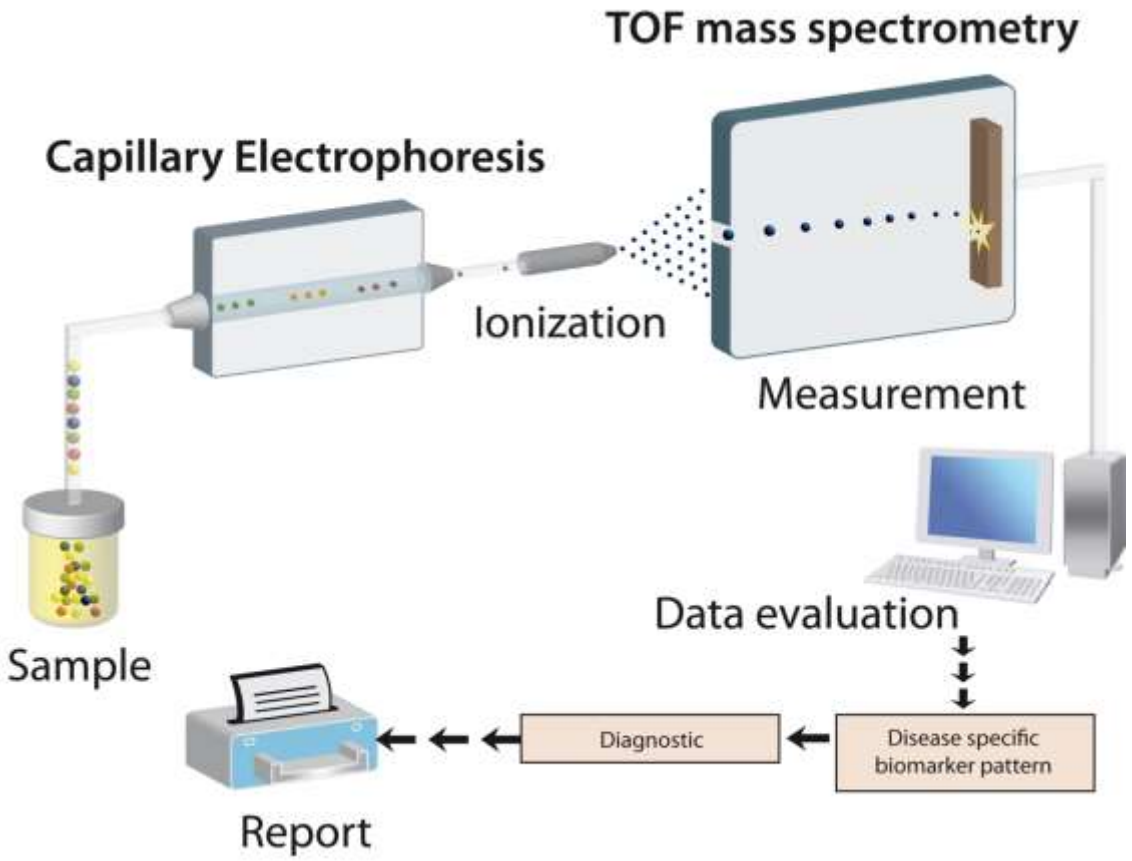
- FSGS is a descriptive renal histologic lesion with diverse causes and pathogenicities
- FSGS includes primary and secondary forms
- The subclasses differ in management and prognosis with differentiation often being challenging
- We aimed to identify specific urine proteins/peptides significantly associated with pFSGS, distinguishing it from sFSGS, other CKD etiologies, and normal controls, and combining these using machine learning algorithm into a classifier

CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; pFSGS, primary focal segmental glomerulosclerosis; sFSGS, secondary focal segmental glomerulosclerosis.

METHODS

- Urine samples were collected in two different centers in Germany from CKD patients at the time of biopsy
- Among these, 19 pFSGS and 44 sFSGS were identified based on biopsy assessment and clinical presentation
- The urine samples were analyzed using CE-MS (**Figure 1**)

Figure 1. Schematic depiction of CE-MS



CE-MS, capillary electrophoresis coupled to mass spectrometry; CKD, chronic kidney disease; pFSGS, primary focal segmental glomerulosclerosis; sFSGS, secondary focal segmental glomerulosclerosis; TOF, time-of-flight.

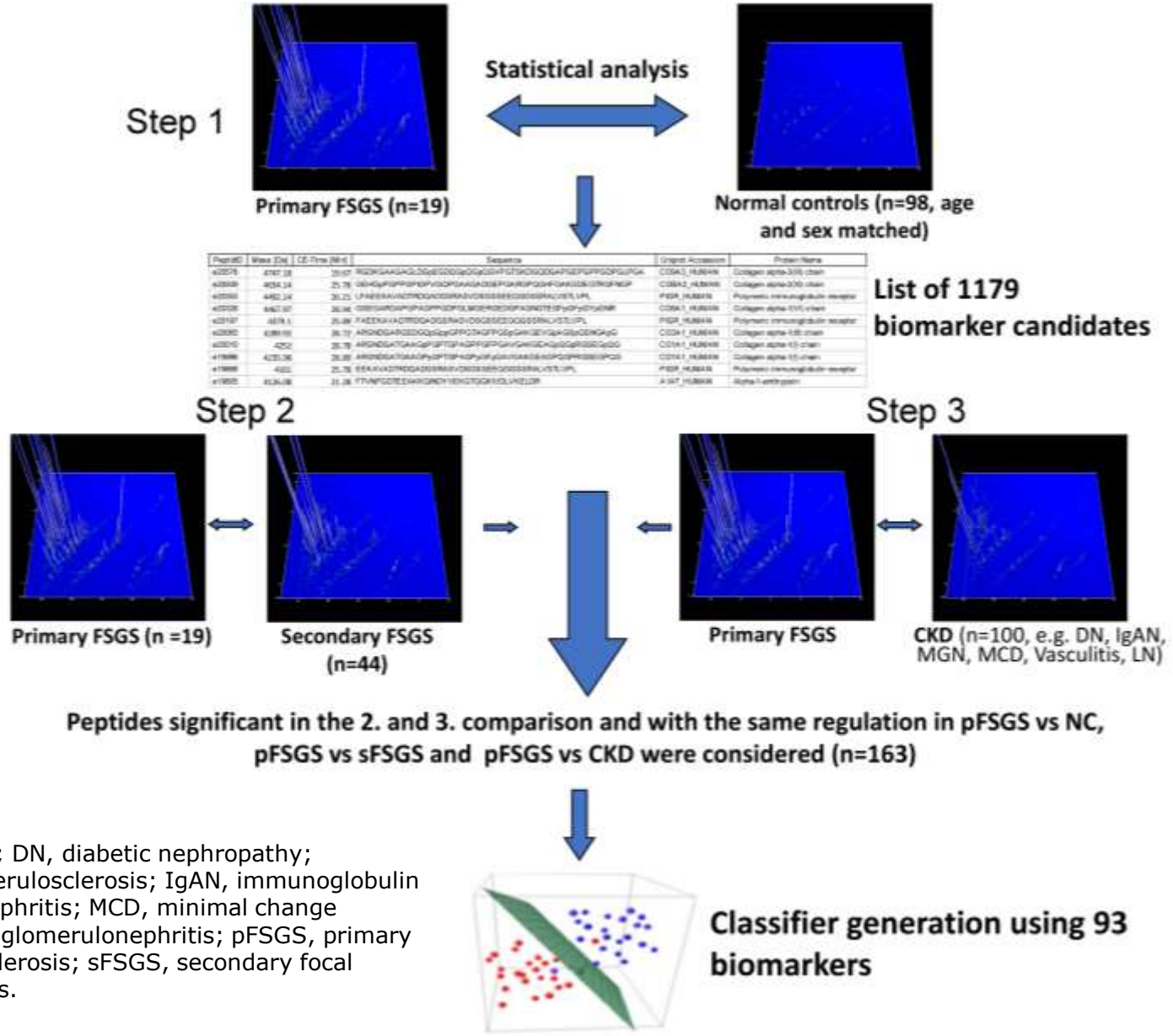
METHODS

Table 1. Characteristics of patients used for biomarker definition

	Primary FSGS	Secondary FSGS	p-value	Normal Control	p-value	CKD	p-value
	n=19	n=44		n=98		n=100	
Sex, n male (%)	13 (68.4)	30 (68.2)	0.7824	73 (74.5)	0.7913	73 (73.0)	0.8972
Age (years)	47. [33.1-30.3]	57.5 [50.0-69.9]	0.044	45 [42.3-49.2]	0.6735	46.1 [42.3-49.4]	0.8052
BMI (kg/m^2)	31.0 [27.2-33.3]	28.7 [27.1-30.4]	0.1493	na	na	na	na
BP syst. (mmHg)	140 [134-145]	140 [128-144]	0.7549	na	na	na	na
BP diast. (mmHg)	85 [78-90]	50 [75-85]	0.6499	na	na	na	na
eGFR (CKD-EPI) ml/min/1.73m²	56.0 [40.1-89.9]	31.1 [23.8-37.0]	0.0008	88.7 [77.5-107.4]	0.0054	40.7 [34.1-49.3]	0.0414
Uprot g/g Crea	8.03 [6.00-10.28]	2.56 [1.63-3.30]	<0.0001	0.012 [0.009-0.015]	<0.0001	2.00 [1.37-2.88]	<0.0001
IFTA (%)	7.5 [4.5-21.1]	21.3 [17.6-35.0]	0.0007	na	na	10.0 [5.0-15.0]	0.9469
No. Antihypertensives	3 [1-4]	3 [2-3]	0.5597	na	na	na	na
Diabetes, n yes (%)	4 (21)	9 (20)	0.7754	24 (24)	0.978	15 (15)	0.75

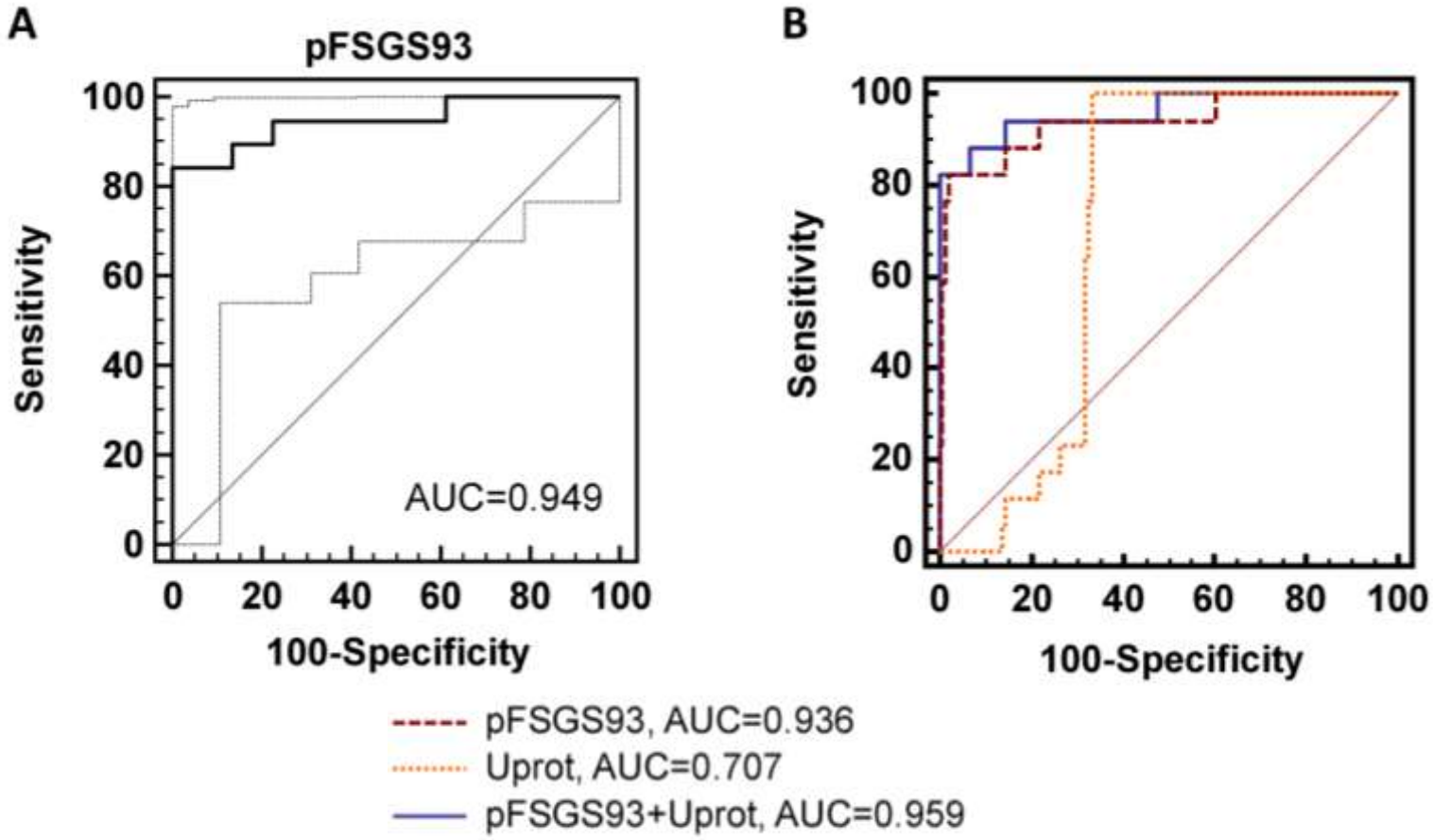
BMI, body mass index; BP, blood pressure; CKD-EPI, chronic kidney disease epidemiology collaboration; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IFTA, interstitial fibrosis and tubular atrophy.

Figure 2. Biomarker definition and generation of the classifier



CKD, chronic kidney disease; DN, diabetic nephropathy; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; LN, lupus nephritis; MCD, minimal change disease; MGN, membranous glomerulonephritis; pFSGS, primary focal segmental glomerulosclerosis; sFSGS, secondary focal segmental glomerulosclerosis.

Figure 3. ROC-analysis of the cross validated training data (pFSGS vs. sFSGS)



pFSGS, primary focal segmental glomerulosclerosis; ROC, receiver operating characteristic; sFSGS, secondary focal segmental glomerulosclerosis.

Specificity analysis in independent cohort

- Independent specificity assessment was performed in additional data of NC (n=110) and CKD (n=170)
- For this purpose, data were extracted from the human urinary database[1]
- Using the before defined cut-off of -0.001 only nine of the patients with other CKD etiologies (spec. 94.7%) and one of the NC (spec. 99.1%) were not correctly classified as no pFSGS

CKD, chronic kidney disease; NC, normal control; pFSGS, primary focal segmental glomerulosclerosis.

1. Latosinska A, et al, *Electrophoresis*. 2019;40(18-19):2294-2308.

CONCLUSIONS

- A urine peptide-based classifier that selectively detects pFSGS could be developed
- Specificity of 95%-99% could be assessed in independent samples
- The data indicate that differentiation of pFSGS can be facilitated by urinary peptide analysis and our classifier can provide helpful information for therapeutic decisions where biopsy findings and clinical presentation are inconclusive

pFSGS, primary focal segmental glomerulosclerosis.