Diagnostic approach to genetic diseases of the nephron

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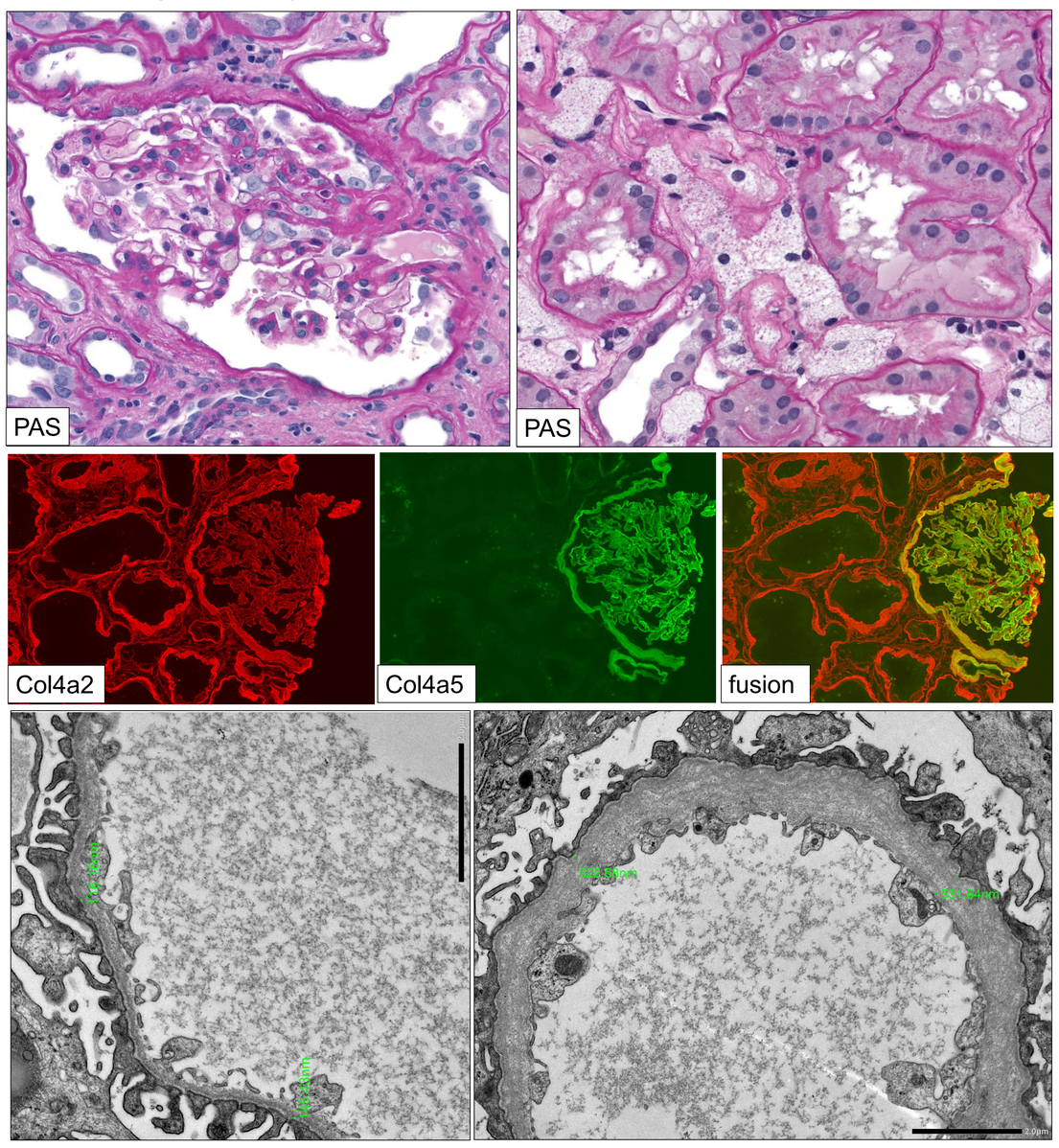
Aim

As much as 30% of CKD patients are characterized by a posivite family history. Moreover, in around 15% of ESRD cases, the etiology remains unknown. It is indicated that genetic investigation may identify the cause of ESRD of unknown etiology in a great number of such patients. A subset of glomerular diseases is determined by genetic abnormalities affecting the podocytes or the glomerular basement membrane (GBM). The usual histological pattern is focal segmental glomerulosclerosis (FSGS). In the daily practice, the diagnosis of genetic FSGS is often challenging. We present some general and practical considerations for interpreting renal biopsy findings in genetic diseases of the nephron.

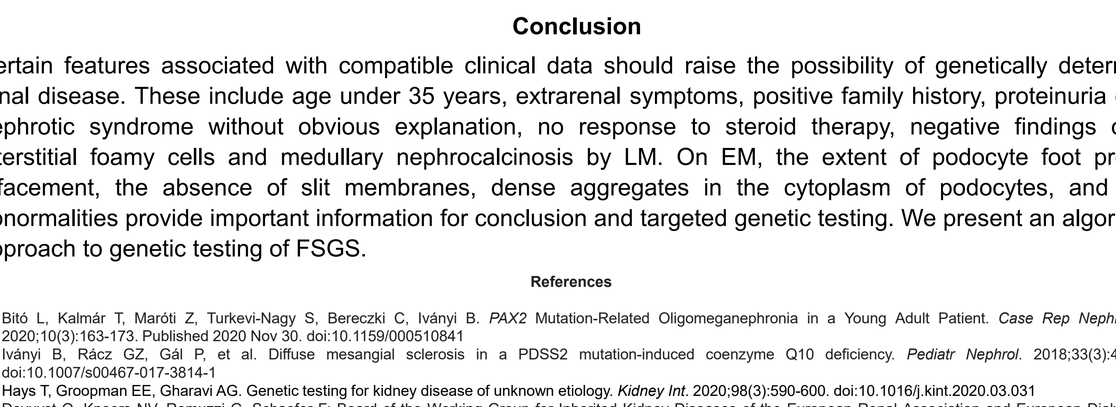
Methods

Five cases are presented from the archives of the Department of Pathology, University of Szeged, evaluated originally via light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). Based on the clinical data and the biopsy findings, genetic testing of targeted genes was performed, which confirmed genetic kidney disease.



Case 1. 43 year-old male. Chronically declining renal function, serum creatinine 205 μmol/l, eGFR 33 ml/min, proteinuria (2,73 g/d), microhematuria. LM: focal-segmental glomerulosclerosis (6%), foamy cells. IF: preserved, mild Col4a5 positivity. No ICs. EM: Thin basement membranes in 2 glomeruli; typical XLAS lesions in 1. Genetic investigation revealed a 17-bp deletion in *COL4A5*, present in the patient and his daughter.

Diagnosis: adult-onset X-linked Alport nephropathy.



Case 2. 23 year-old female. CKD for 2 years, family history: negative. Serum creatinine 145 μmol/l, eGFR 43 ml/min, proteinuria for 7 years (2,5 g/d). IF: negative.LM: Glomerulomegaly. Perihilar FSGS, probably secondary etiology. Low mean glomerular density (0.68/mm^2) → Oligomeganephronia. EM: Segmental foot process effacement.

Diagnosis: *PAX2* mutation-related oligomeganephronia with adaptive FSGS.

Results

The age of the patients ranged from 7 months to 43 years at biopsy. Each of them was admitted because of heavy proteinuria, with our without hematuria, and impaired kidney function. IF was negative for immune complexes or monoclonal immunoglobulins. The primary diagnosis was FSGS in each case, which was refined following EM analysis. EM revealed either podocytic or GBM abnormalities suspicious for genetic conditions. Genetic investigation identified pathogenic mutations in the genes *ACTN4, COL4A5, PAX2, PDSS2* or *CLCN5.*

Conclusion

Certain features associated with compatible clinical data should raise the possibility of genetically determined renal disease. These include age under 35 years, extrarenal symptoms, positive family history, proteinuria or the nephrotic syndrome without obvious explanation, no response to steroid therapy, negative findings on IF, interstitial foamy cells and medullary nephrocalcinosis by LM. On EM, the extent of podocyte foot process effacement, the absence of slit membranes, dense aggregates in the cytoplasm of podocytes, and GBM abnormalities provide important information for conclusion and targeted genetic testing. We present an algorithmic approach to genetic testing of FSGS.

References

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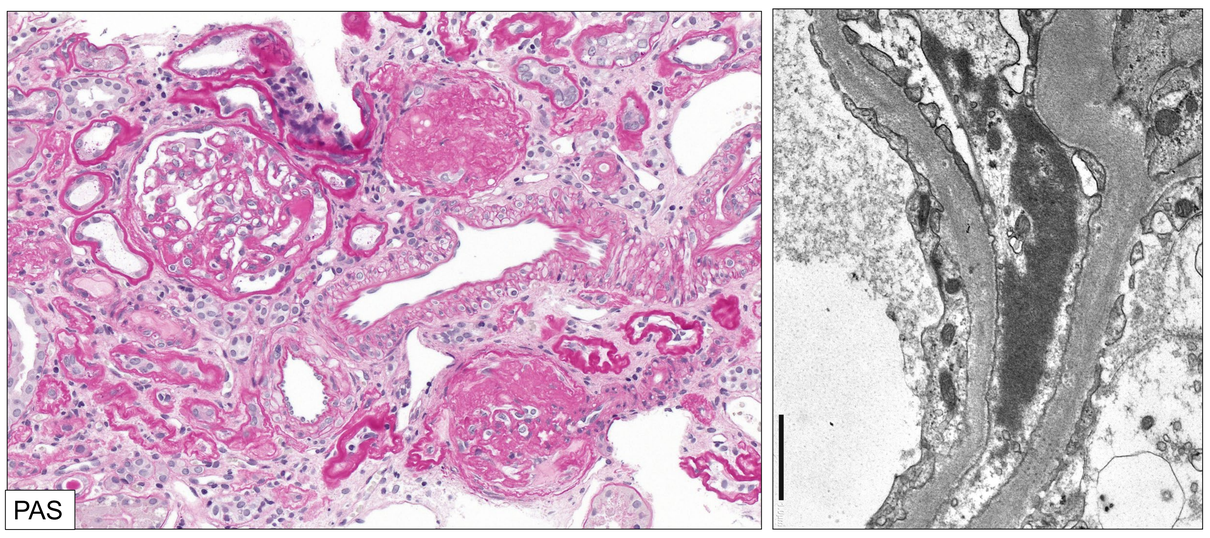
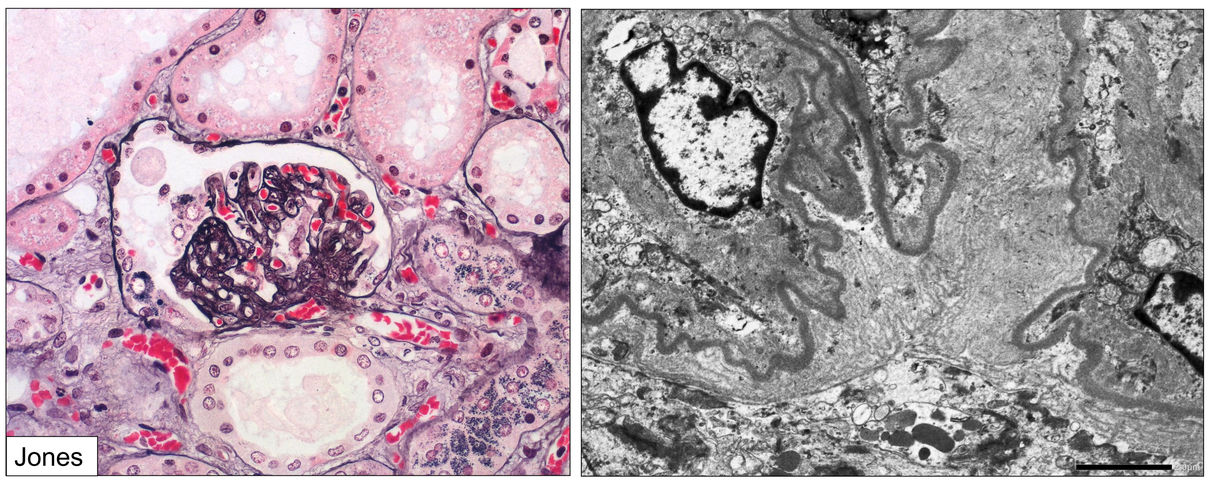


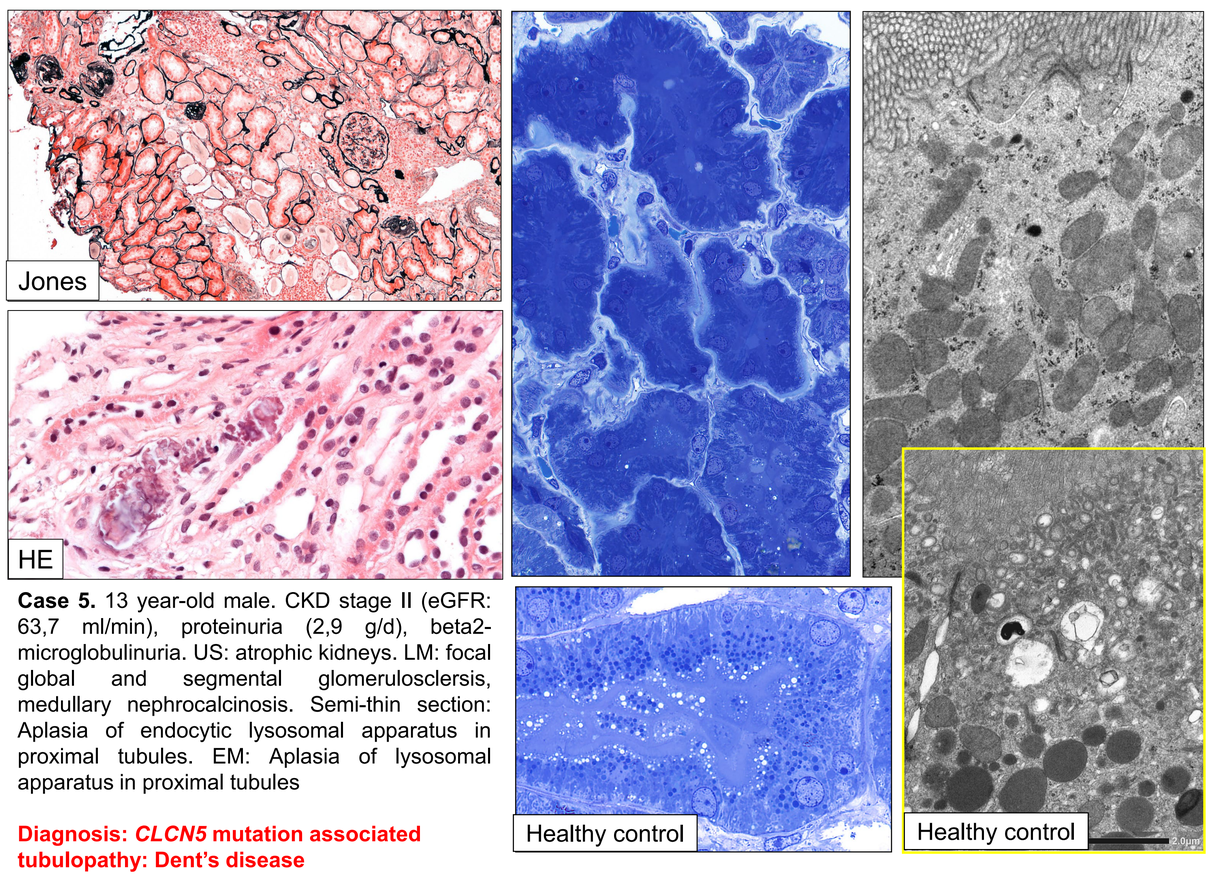
Case 3. 31 year-old male CKD for 7 years Father: ESRD. Serum creatinine 190 μmol/l, eGFR 39 ml/min Proteinuria (3 g/d) Microhematuria LM: Sclerosing glomerulopathy, 61% global sclerosis, 6% segmental sclerosis. IF: Negative. EM Dense aggregates in podocyes.

Diagnosis: *ACTN4* mutation related FSGS



Case 4. 7-month-old male infant, healthy parents. Nephrotic syndrome, encephalomyopathy, hypertrophic cardiomyopathy, deafness, retinitis pigmentosa → suspicious for CoQ_{10} deficiency.
Despite treatment, he passed away in 1 month. LM: mesangial expansion, segmental closure of capillary loops. IF: negative. EM: 70% foot process effacement, basement membrane material in capillary walls, mesangial expansion.

Diagnosis: Diffuse mesangial sclerosis (*PDSS2* mutation-induced CoQ10 deficiency)



Case 5. 13 year-old male. CKD stage II (eGFR: 63,7 ml/min), proteinuria (2,9 g/d), beta2-microglobulinuria. US: atrophic kidneys. LM: focal global and segmental glomerulosclersis, medullary nephrocalcinosis. Semi-thin section: Aplasia of endocytic lysosomal apparatus in proximal tubules. EM: Aplasia of lysosomal apparatus in proximal tubules

Diagnosis: *CLCN5* mutation associated tubulopathy: Dent's disease

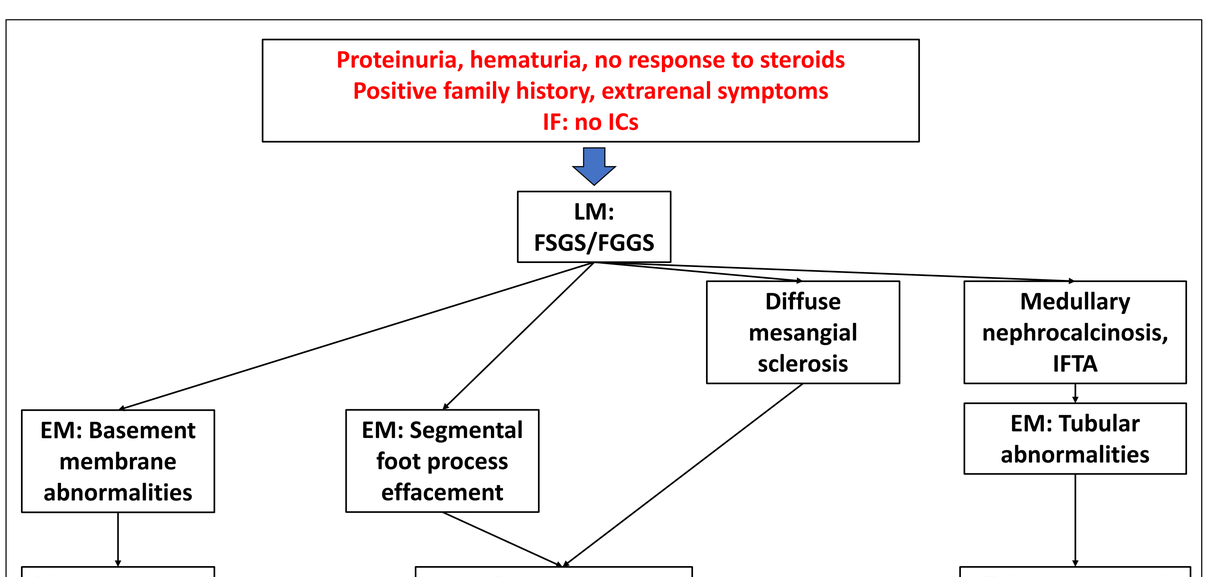


Figure 1. Algorithm for diagnosing genetically determined renal diseases.