Autosomal Dominant Tubulo-Interstitial Kidney Disease (ADTKD)

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Autosomal Dominant Tubulo-Interstitial Kidney Disease

- Medullary cystic kidney disease
- Medullary cystic kidney disease/nephronophthisis
- Familial juvenile hyperuricemic nephropathy
- Uromodulin kidney disease
Medullary Cystic Kidney Disease

- Forget about this term

- Medullary cysts are occasionally found in individuals with these conditions
  - Only seen in very advanced disease.
  - Usually not seen on ultrasound/MRI/CT
  - Sometimes seen in kidney biopsy
Tubulo-Interstitial Kidney Disease

• Not a glomerular disease
• No proteinuria
• No hematuria
• Renal ultrasound: unremarkable or small kidneys if late in the disease
• Kidney biopsy
  – Secondary glomerular changes
  – Tubular atrophy
  – No tubulointerstitial inflammation
Inherited Tubulo-Interstitial Kidney Disease

**Autosomal Recessive**
- Nephronophthisis
  - Childhood with ESRD < 20
  - CKD
  - Ciliopathies
  - Salt wasting, anemia

**Autosomal Dominant**
- UMOD
  - MCKD2
    - Gout (women, teens)
    - CKD in 3rd to 7th decade
- RENIN
  - Anemia, hyperkalemia, mild hypotension in childhood
  - CKD in 3rd to 7th decade
- MUC1
  - MCKD1
    - CKD in 3rd to 9th decade
    - No other symptoms
- Other
A 15 year old presents with anemia and decreased vision

- Serum creatinine 400 mmol/l
- Urine: dipstick negative for blood, trace protein.
- Renal ultrasound small kidneys
- Neither parent with kidney disease
- A brother with kidney disease
Family 11 Pedigree

Note characteristics of autosomal dominant inheritance
Inherited Interstitial Kidney Disease

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Nephronophthisis

Childhood CKD Ciliopathies Salt wasting, anemia

Autosomal Dominant

UMOD

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RENIN

Anemia, hyperkalemia, mild hypotension in childhood CKD in 3rd to 7th decade

MUC1

MCKD1 CKD in 3rd to 9th decade No other symptoms

Other
Nephronophthisis

• Caused by mutations in genes expressed in the renal tubular cilia

• Slowly progressive kidney disease

• Associated with: blindness, situs inversus
Greetings from NORTH CAROLINA
First Case  4/18/96

- 41 year old white male
  - Serum Creatinine 300 mmol/l

- Urinalysis:
  - Dipstick negative for blood
  - Dipstick negative for protein

- Renal ultrasound unremarkable
Family Tree

Family 1

A

I

II

A1 B3

I

II

III

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

B

I

II

III

IV

C

I

II

III

1 2 3 4

D

I

II

III

1 2 3 4 5 6

1 2 3 4

1 2 3 4
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First Case  4/18/96

• 41 year old white male
  – Gout in late teens
  – Noncompliant with allopurinol
  – Development of tophi
  – Many, but not all, family members had suffered from gout
    • Women in their 30’s and 40’s
    • Young men in their teens
  – Gout occurred prior to onset of kidney dysfunction.
• Parents watched closely for the presence of gout, which determined the fate of their child.
• Working with Thomas Hart, DDS, over the next six years we collected numerous samples and were able to identify mutations in the *UMOD* gene encoding uromodulin as the cause of this condition.
What is Uromodulin?

• “Tamm Horsfall Glycoprotein”

• The most common urinary protein

• Synthesized only in the thick ascending limb of Henle’s loop
Uromodulin

• The most cysteine residues of any known human protein

• Extensive cross-linking in the endoplasmic reticulum
Possible Uromodulin Functions

• Prevents urinary tract infection

• Prevents kidney stone formation

• Prevents inflammation in the kidney

• New data suggests that these are not the current functions of uromodulin in humans.
Uromodulin

• Regulates movement of bumetanide – sensitive Na K 2 CI (NKCC2) transporter

• Patients who produce less uromodulin excrete more sodium, have lower blood pressures, and have less interstitial fibrosis.

Renigunta A et al., J Biol Chem 2011
Mutig K et al. J biol Chem 2011
THP Production

- Uromodulin has more cysteines than any other proteins in the body.
- These cysteines allow uromodulin to cross-link.
- It is critical that the correct cysteines cross-link for the function of the molecule.
• About 75% of mutations in UKD involve a cysteine.

• Almost all are predicted to affect structure

• No mutations resulting in truncation of the protein

• The abnormal uromodulin cannot form its normal structure. It precipitates in the cell and builds up.
Mutations that Cause Uromodulin Kidney Disease

Color-coding key:
- Green: Cysteine
- Yellow: Cysteine mutation - substitution
- Red: Mutation - substitution
- Orange: Mutation - substitution & deletion
- Light blue: Mutation - deletion
- Green: Mutation - inversion
- Magenta: Likely clinically silent mutation
How does the uromodulin mutation cause gout?
Sodium Reabsorption

Reabsorption depends on volume status, diuretics
Sodium Reabsorption in UMOD mutation

Reabsorption depends on volume status, diuretics.

Decreased UMOD decreases NKCC2. More sodium in the urine.
Increased urine sodium causes volume depletion and increased proximal sodium uptake.

Reabsorption depends on volume status, diuretics.
Urate follows proximal Na reabsorption. As more Na is reabsorbed, more urate is reabsorbed.

Reabsorption depends on volume status, diuretics.
• Hyperuricemia and gout.

• More sodium is reabsorbed proximally.
• More urate is reabsorbed proximally.
• Hypouricosuric hyperuricemia
Diagnosis

• Suspect disease based on cardinal manifestations
• Send sample for UMOD genetic analysis
• We can aid in the diagnosis of new cases.
Treatment

• Allopurinol is effective in the treatment of gout and MAY slow progression of kidney disease.
• Otherwise treatment is supportive.
• Patient should undergo pre-emptive kidney transplantation.
<table>
<thead>
<tr>
<th>Mutation</th>
<th>UMOD</th>
<th>REN</th>
<th>MUC-1</th>
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<tbody>
<tr>
<td>Loss of normal gene function</td>
<td>Urate</td>
<td>Gout</td>
<td></td>
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<tr>
<td>Tx of loss of fxn</td>
<td>Allopurinol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knockout mouse</td>
<td>No effect</td>
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<tr>
<td>Abnormal production</td>
<td>Intracellular deposition, Kidney failure</td>
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</table>
• 8 year old girl
• Anemia at 1 year testing
• Mild hypotension
• Serum potassium mildly elevated
• Acute kidney injury when given a non-steroidal medication for a febrile illness.
• Father and granfather also with anemia in childhood and kidney failure
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Other
• Decreased production of normal renin
• Deposition of abnormal renin intracellularly
Effects of Low Renin

- Low BP
- High normal potassium
- Anemia
- Predisposition to acute kidney injury
Anemia

- Low erythropoietin levels
- Due to decreased renin production
  - Similar to ACE inhibitor in ESRD
  - Polycythemia in kidney transplantation

- Present by 1 year of age
- Found in all affected individuals
- Hgb from 8 to 10 g/dl.
- Responds to erythropoietin
- Resolves by adolescence due to sex steroid production
Normal BP

Low BP

Renin causes vasoconstriction
8 year old child with fever, nausea, headache – given ibuprofen
This constellation will lead to AKI
We want to decrease production via the promoter, but this will result in decreased production of both alleles.
<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal Renin</th>
</tr>
</thead>
</table>

Renin

Fludrocortisone

Negative feedback

Negative feedback
Fludrocortisone Treatment

• Treats aldosterone deficiency
  – Corrects mild hyperkalemia
  – Decreases risk from volume depletion

• Removes “bad” renin
  – Prevents tubulo-interstitial fibrosis
## Fludrocortisone Treatment

<table>
<thead>
<tr>
<th>Time</th>
<th>BP</th>
<th>Wt</th>
<th>K</th>
<th>Cr</th>
<th>Uvol</th>
</tr>
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<tbody>
<tr>
<td>-11wk</td>
<td>87/50</td>
<td></td>
<td>5.0</td>
<td>114</td>
<td>1825</td>
</tr>
<tr>
<td>-1wk</td>
<td></td>
<td>39.8</td>
<td>5.6</td>
<td>140</td>
<td>2275</td>
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<tr>
<td>1wk</td>
<td>106/69</td>
<td>40.9</td>
<td>4.2</td>
<td>96</td>
<td>2450</td>
</tr>
<tr>
<td>6wks</td>
<td>112/67</td>
<td>4.3</td>
<td>88</td>
<td>2675</td>
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</tbody>
</table>
Figure 2. Estimated Glomerular Filtration Rate vs. Age (Years)

Fludrocortisone started.
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Case Description

• 35 year old white female presents for evaluation of serum creatinine 200 mmol/l

• The patient developed HTN (140/90) at age 34 which has been easily treated with enalapril, 20 mg po q d.

• There is no history of anemia, hyperkalemia, or gout

• PE: Unremarkable
Case Description

- Urinalysis: Bland without blood or protein
- Renal ultrasound: Normal sized kidneys, no cysts
Family L1

<table>
<thead>
<tr>
<th>Affected with ESRD age</th>
<th>* Historically Affected</th>
</tr>
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<tbody>
<tr>
<td>Affected without ESRD age</td>
<td></td>
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<tr>
<td>Unknown genotype</td>
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<tr>
<td>Unaffected</td>
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</tbody>
</table>

Affected with ESRD age:
- I: 42.5*
- II: 42.5*
- III: 60
- III: 32
- IV: 34
- V: 29
- VI: 25
- VII: 25

* Historically Affected:
- II: 35*
- III: 63*
- V: 42.5*
- VI: 38*
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Other
Pathology
Medullary Cystic Kidney Disease Type 1

- Autosomal dominant
- Slowly progressive chronic kidney disease
Linkage

• First performed by Otto, Hildebrandt in 2001
• Subsequently performed by other groups
• Consistent linkage to Chromosome 1
• 37 genes evaluated with mutational analysis
MCKD1 genetics team

**Linkage, sequence analysis**
- Andrew Kirby
- Christine Stevens
- Kiran Garimella
- Mark dePristo
- Jim Robinson

**Bioinformatics Analysis**
- Jimmie Ye
- Nathalie Pochet
- Aviv Regev
- Lizzy Rossin

**MUC1, targeted sequence & assembly**
- Andi Gnirke
- Dave Jaffe
- Chad Nusbaum

**DNA sequencing**
- Jen Baldwin
- Jane Wilkinson
- Lauren Ambrogio
- Snaevar Sigurdsson
- Kerstin Lindblad-Toh

**Clinical Phenotyping & Functional Insights**
- Tony Bleyer
- Suzanne Hart
MUC1

- MUC1 is a membrane-anchored mucoprotein.
- Expressed in secretory epithelium of the lungs, kidneys, breasts, GI tract.
- Contains a VNTR unit for glycosylation.
Amino terminus
**Extra C in Patient OK #563 Causes Frameshift**

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MUC1 Mutation

- Results in addition of a cytosine to 7 cytosines
- Creation of a new repetitive unit that repeats a unique number of times for each family
- Self termination
- Cytosolic unit is not created
Mutant MUC1 protein
Theoretical Affect of MUC1 insertion

- Mutation is in the VNTR unit
- Causes a frameshift, resulting in VNTR truncation and creation of a neopeptide
- Neopeptide appears to be improperly processed in the cytoplasm
- Leads to apoptosis and slow, progressive tubular cell death
Dr. Stan Kmoch, Charles Medical School,
Normal and Mutant MUC1 Immunostaining

- TALH
- CD
- PT
Mutant MUC1 and Breast Tissue

control

patient
Skin Tissue
MUC1 Knockout Mouse

• No clinical disease

• Many mucoproteins
  – Some functions may be interchangeable
MUC1

- Mutant seen in many tissues
- Only causes kidney disease

- In the knockout mouse, MUC1 does not have an essential function.

- All patients have a mutation producing the same mutant peptide.
Hypothesis

- There are many mucoproteins, and their function overlaps.
- The absence of MUC1 is not important.
- There is some property of renal tubular cells that make them very sensitive to the abnormal MUC1, leading to slowly progressive cell death.
Clinical Characterization

• 35 imaging studies (70 kidneys)
  – Normal or small kidneys
  – 49/70 kidneys no cysts
  – 13/70 had one cyst
  – No medullary cysts
  – MCKD not suspected on any ultrasound
  – CKD was most common diagnosis
Clinical Characterization

• 34 renal biopsies reviewed:
  – All showed tubulo-interstitial kidney disease
  – 4 microcystic dilation of the tubules
    • 2 suggested medullary cystic kidney disease
    • 1 suggested polycystic kidney disease
    • 1 suggested tubular toxic injury
ESRD According to Family

![Graph showing the distribution of ESRD according to family.](image-url)
Development of Genotyping Assay

- 21 additional potential families identified
  - 18 families had the insertion
- All 24 families to date have the same type of mutation
- We have subsequently identified another 20 families with the same type of mutation
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eGFR of MCKD1 Affected and Unaffected Individuals
eGFR Decline in 12 MCKD1 Individuals

eGFR change ≥ 50 ml/min \( .99 \pm 6 \text{ ml/in/year} \)
eGFR change < 50 ml/min \( -6.7 \pm 4 \text{ ml/in/year} \)

\( p < 0.001 \)
Treatment

• Supportive
• Follow eGFR closely when <50 ml/min
• Do not allow kidney donation without genetic testing for the mutation
Issues to Reconcile

• How does mutant MUC1 contribute to pathology

• Why is pathology found only in the kidney?

• Why is there a variable rate of expression?
Identifying Families

- 450 families to date have contacted us
- 90 are positive for \textit{UMOD} mutation
- 6 are positive for \textit{REN} mutation
- 24 families with \textit{MUC1} mutation
Challenges

- Uncommon disorders
- Confusing terminology
- Predominant interest in glomerular disease
- Kidney biopsies are not diagnostic
Genetic Testing

- Available in a research setting
- Remains extremely difficult to do
- Contact me (ableyer@wakehealth.edu) for information
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  - Ciliopathies
  - Salt wasting, anemia

Autosomal Dominant

- UMOD
  - MCKD2
    - Gout (women, teens)
    - CKD in 3rd to 7th decade
- RENIN
  - Anemia, hyperkalemia, mild hypotension in childhood
  - CKD in 3rd to 7th decade
- MUC1
  - MCKD1
    - CKD in 3rd to 9th decade
    - No other symptoms
- Other
<table>
<thead>
<tr>
<th>Mutation</th>
<th>UMOD</th>
<th>REN</th>
<th>MUC 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of normal gene function</td>
<td>↑Urate</td>
<td>↓BP, Hgb</td>
<td>No other symptoms</td>
</tr>
<tr>
<td></td>
<td>Gout</td>
<td>↑K, Urate</td>
<td></td>
</tr>
<tr>
<td>Tx of loss of fxn</td>
<td>Allopurinol</td>
<td>Fludrocortisone</td>
<td>Supportive</td>
</tr>
<tr>
<td>Knockout mouse</td>
<td>No effect</td>
<td>Death in utero</td>
<td>No effect</td>
</tr>
<tr>
<td>Gene deletion or truncation</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Abnormal production</td>
<td>Intracellular deposition, Kidney failure</td>
<td>Intracellular deposition, Kidney failure</td>
<td>Intracellular deposition, Kidney failure</td>
</tr>
</tbody>
</table>
Wake Forest Medical School
Uromodulin

- A ZP domain protein
- Carboxy terminal membrane domain
- Filaments are cross linked
- Heavily glycosylated
Uromodulin

- 75,000 kD protein
- Monomers come together to form polymer that is heavily glycated
- VERY insoluble
THP Production

- Conversion of precursor (84 kD) to mature form (97 kD) depends on processing of glycans in the Golgi apparatus

Figure 2. Tamm Horsfall Protein Excretion According to Creatinine Clearance

- **Creatinine clearance (ml/min)**
- **Tamm Horsfall protein 24 hour urinary excretion (mg/d)**

Legend:
- **unaffected**
- **mutation**
## Clinical Presentation

<table>
<thead>
<tr>
<th>Nephronophthisis</th>
<th>ADTKD (UMOD and MUC1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Salt-wasting, fatigue</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>Median ESRD 13 years</td>
<td>Median ESRD  40</td>
</tr>
<tr>
<td>Bland urinary sediment</td>
<td>Bland urinary sediment</td>
</tr>
<tr>
<td>Bx: tubulo-interstitial scarring</td>
<td>Bx: tubulo-interstitial scarring</td>
</tr>
</tbody>
</table>

Conditions would not be difficult to distinguish, except for confusing terminology, early misunderstanding, and their rarity.