Genetic testing in renal disease

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Genetic testing: why?

• If a patient is referred to you in ESKD: who cares about genetics?
objectives

• Define role of genetics in clinical nephrology
• Provide examples
• Outline a vision
Genetic testing: that’s why

- Establish a molecular diagnosis (ideally before ESKD)
- Inform prognosis
- Identify relatives at risk
- Learn about the disease
- Precision medicine
Genetic testing: how?

- Single mutation testing
- Single gene testing
- Panel testing
- Exome sequencing
- Genome sequencing
Single gene/mutation testing

- Humans have approximately 23,000 genes
- There is an estimated 6000 “monogenic” disorders
- Including a few hundred in renal disorders
Single gene/mutation testing: when?

- Traditionally, the only available test
- Still performed, if there is strong clinical suspicion for a specific monogenic disorder
Single gene/mutation testing: how?
A patient
audiogram
Biochemistry

plasma

- Na \(139 \text{ mmol/l}\)
- K \(2.9 \text{ mmol/l}\)
- Cl \(97 \text{ mmol/l}\)
- HCO_3^- \(30 \text{ mmol/l}\)
- Ca \(2.46 \text{ mmol/l} = 10.1 \text{ mg/dl}\)
- Mg \(0.5 \text{ mmol/l} = 1.25 \text{ mg/dl}\)
- Creatinine \(28 \mu\text{mol/l} = 0.3 \text{ mg/dl}\)

urine

- FEK \(59\%\)
- FEMg \(8\%\)
- Ca/Crea \(< 0.05 \text{ mmol/mmol} = <0.02 \text{ mg/mg}\)
What is the diagnosis

1. Bartter syndrome
2. Gitelman syndrome
3. EAST syndrome
4. Mitochondrial cytopathy
5. SeSAME syndrome
6. I have no clue
Sequencing of KCNJ10

WT

R65P
Genome of individual re-sequenced by aligning short reads against the reference genome.

Individual is homozygous ‘T’ at this A/T polymorphism.

Individual is heterozygous at this G/A polymorphism.
Panel testing: when?

• Phenotype with several underlying genes (e.g. hypokalaemic alkalosis, familial renal dysplasia)
Another patient

- A 13-y old is referred to the tubular clinic after moving to the UK and presenting to local hospital with carpopedal spasm
- Mg: 0.11 mmol/l, Ca: 1.33 mmol/l
- Presented initially at 4 months of age with seizures and low Mg.
- On Mg supplementation ever since, but could not get usual supplements in the UK
What is the diagnosis?

1. Familial Hypomagnesaemia with hypercalciuria and nephrocalcinosis
2. Gitelman syndrome
3. EAST syndrome
4. Familial Hypomagnesaemia with secondary Hypocalcaemia
5. HNF1B-associated hypomagnesaemia
6. I have no clue
Tubulopathy panel

- Panel testing of 37 tubulopathy genes
- In our experience (125 children): in ~80% a genetic cause is identified
Exome sequencing

“If something like 98% of the genome is junk, then the best strategy would be to find the important 2%, and sequence it first”

– Sydney Brenner, 1990
Exome sequencing

- Concentrates on the “coding regions” of the genome
- Sequencing of (almost) all genes
- When you don’t know which gene it may be
- However: the more you sequence, the more you find.
Dimensions

- Sanger Sequencing: 1-10 variants
- Exome Sequencing: 40,000 variants
Data analysis: the critical step

- Many variants not annotated yet
- “Variants of unknown significance-VUS”
- Many published “Disease-causing mutations” revealed to be polymorphisms
- Ethnic controls needed
- Functional studies
- Clinical correlation!
Genome sequencing

June, 2000 Announcement
Genome sequencing

- 1\textsuperscript{st} genome: 13 years and \sim $3bn
- Now: \sim $1000 and < week
- Clearly the future
- But: a lot of data!
Analyzing data
Dimensions

- Sanger Sequencing: 1-10 variants
- Exome Sequencing: 40,000 variants
- Genome Sequencing: 3,000,000 variants
A “typical” human genome

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein truncating</td>
<td>149 - 182</td>
</tr>
<tr>
<td>Peptide altering</td>
<td>10,000 - 12,000</td>
</tr>
<tr>
<td>Regulatory (UTR, TBS, promoter, etc.)</td>
<td>459,000 - 565,000</td>
</tr>
<tr>
<td>Associated with complex trait</td>
<td>~2,000</td>
</tr>
<tr>
<td>ClinVar disease causing</td>
<td>24 - 30</td>
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The future
Take a look at the bright side

- In 10 years, every newborn (in the developed world) will have their genome sequenced
- There is increasing knowledge of the clinical role of variants
- Allowing disease prevention and precision medicine (beyond monogenetic diseases)
The downside?
Conclusions

• Genetic testing is becoming cheaper and easier
• The trend is towards larger gene panels
  => exome => genome
• Analyzing the data is the key step and requires clinical and genetic insight
• Genetics will help personalise treatments
Questions?