I have my cysts with a bit of sugar, please

Detlef Bockenhauer
A patient

- A 1-day old neonate is admitted to the renal ward because of impaired kidney function and hypertension
- 1st child of unrelated parents, no family HX of kidney disease
- Pregnancy complicated by polyhydramnios with 33-wk scan showing cystic kidneys.
- Noted to be hypoglycaemic immediately after birth
- Unremarkable examination, kidneys not palpated
- Weight: 4200g, length: 51 cm, BP: up to 138 mmHg systolic
Investigations

• Blood: creatinine 109 mcmol/l, glucose: 1.7 mmol/l with insulin of 11.3 mU/l
Diagnosis?

• Suspected ARPKD
• Hyperinsulinaemic hypoglycaemia

• Treatment:
  • HI: Diazoxide, Chlorothiazide
  • PKD: Amlodipine, Propranolol

• 'unlucky coincidence of 2 rare diseases in one patient
Further course

- Evidence of portal hypertension on endoscopy
- Progressive CKD age with nephromegaly
MRI kidneys
Liver imaging
Nephrectomies at time of transplant
More patients with “HIPKD”? 

• Parents identify through social media another patient with HI and PKD in the US
• A RaDaR ARPKD patient day is attended by a family with 2 siblings, both affected by HI and PKD
• A review of clinical features of patients followed at the GOSH HI service identifies another 9 patients with associated renal cysts
• A Spanish doctor presents a poster at an endocrine meeting describing a consanguineous family with 4 affected siblings
Liver biopsy in a 2-year old girl
Where’s the problem?

• No bi-allelic coding mutations in the linked region
• However: all patients share a non-coding mutation c.-167G>T in the promoter of *PMM2*
• Promoter mutation is either homozygous (consanguineous family) or *in trans* with *PMM2* coding mutation
Who’s PMM2

• Phosphomannomutase 2
• Key enzyme on protein glycosylation ("post translational modification")
• Recessive coding mutations cause CDG1A, which occurs in 2 forms:
  • Mild form with neurological involvement only (ataxia, cerebellar hypoplasia)
  • Severe, multivisceral form with dysmorphic features (abnormal fat pads, inverted nipples) and severe neurological problems. 20% die in infancy
• Essentially any organ system can be involved, including: renal cysts and HI
## CDG1A vs HIPKD

<table>
<thead>
<tr>
<th>CDG1A</th>
<th>HIPKD</th>
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<tbody>
<tr>
<td>• Renal cysts and HI occasionally seen</td>
<td>• HI, Renal cysts +/- liver involvement only</td>
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<tr>
<td>• only in conjunction with severe neurology and dysmorphic features</td>
<td>• No apparent neurological problems</td>
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<tr>
<td>• Abnormal transferrin mobility</td>
<td>• Normal transferrin mobility</td>
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PMM2 pleiotropy

- HIPKD = organ specific PMM2 dysfunction
- CDG1A = generalised PMM2 dysfunction

?organ specific effect of the promoter mutation?
Trying to make sense

Bidirectional PMM2 promoter

Mutation in consensus sequence of bidirectional PMM2 promoter

modified from Anno et al. 2010, Nucleic Acids Res.
→ Human Epithelial Kidney Cells

![Graph showing luminescence levels with annotations](image)
→ Compound heterozygous patient cells (c.-167G>T/c.422G>A)
→ Compound heterozygous patient cells (c.-167G>T/c.422G>A)

→ Expression level mutant allele 1/3 reduced in patient cells.
Protein-DNA interaction: EMSA

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<td>ZNF143</td>
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<td>Wild type unlabelled probe</td>
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Bar graph showing density (%) comparison between wild-type and mutant samples.
Yet: how does this cause organ-specificity?

• PMM2 is ubiquitously expressed
• why does the promoter mutation only affect pancreas, kidney and liver?
Between a chicken and a grape plant

- Chicken: 17,000 genes
- Humans: 22,000 genes
- Grape plant: 30,000 genes
I’s not the size that matters...
What does ZNF143 do?
A hypothesis

A

Wildtype Promoter
Mutant Promoter
ZNF143 CTCF HNF4A sites

B
Conclusions

• HIPKD: a newly recognised disorder consisting of HI and PKD +/- liver involvement
• Currently 18 patients identified
• Spectrum of severity (3 reached ESKD in childhood)
• Promoter mutation affects PMM2 transcription in an organ-specific manner
• Provides insights into gene regulation
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Transferrin isoelectric focusing