Welcome to

ERKNet/ESPN/ERA Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

**Mendelian and non-mendelian inheritance**

**Speaker:** Kalman Tory (Budapest, Hungary)

**Moderator:** Elena Levtchenko (Leuven, Belgium)
May I ask your specialty?

- clinical genetics
- pediatric nephrology
- adult nephrology
- research, molecular biology
- other
Mendel's Principles of Heredity

**Mendel's Principles of Heredity**

Seven *binary* characters of pea plant

20/07/1822 – 1884

'chronic nephritis'

characters are unitary: *not a blend*, and corresponds to one of the parental character: *the dominant*

the 'recessive' characters *reappear unlinked* in the second generation in 25% of the offspring

P

\[ \times \]

F1

\[ \times \]

F2
Mendel's Principles of Heredity

Seven *binary* characters of pea plant

- **P**
  - characters are unitary: *not a blend*, and corresponds to one of the parental character: *the dominant*

- **F1**
  - alternate forms (alleles) of hereditary factors (genes) are created random and unlinked in the gametes

- **F2**
  - the *recessive* characters *reappear unlinked* in the second generation *in 25%* of the offspring

20/07/1822 – 1884

'chronic nephritis’
### Differences between Mendel’s experiments and the human monogenic disorders

<table>
<thead>
<tr>
<th>Pea Plant in Mendel’s Experiments</th>
<th>Human Monogenic Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• inbred, homogeneous population</td>
<td>• heterogeneous population</td>
</tr>
<tr>
<td>• single allele for each phenotype</td>
<td>• both the disease-causing and the benign alleles are heterogeneous</td>
</tr>
<tr>
<td>• each allele gave 50% of all, in each generation</td>
<td>• pathogenic alleles are rare</td>
</tr>
</tbody>
</table>
Mendelian genetics in clinical practice

1. the disease-causing allele is dominant and located on an autosome

<table>
<thead>
<tr>
<th>risk of inheritance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>single allele</td>
<td>50%</td>
</tr>
<tr>
<td>disease</td>
<td>50%</td>
</tr>
</tbody>
</table>
Mendelian genetics in clinical practice

2. the disease-causing allele is recessive and located on an autosome

Two affected siblings, at least one of whom is girl: AR
Oligogenic inheritance - two genes, three alleles

Risk of inheritance:
- Three alleles: $0.5^3$
- Disease: 12.5%
Monogenic disorders are clustered in families, rare multifactorial disorders are sporadic

- The higher the number ($n$) of the alleles required for a disease, the less likely is its inheritance ($0.5^n$): the less likely is familial clustering
- The more family members are affected by the same disorder, the more likely it is monogenic
Severe AD disorders cannot be transmitted, thus always result from *de novo* mutations: mendelian but no familial clustering
# Monogenic vs. non-mendelian diseases

<table>
<thead>
<tr>
<th><strong>Monogenic / Mendelian</strong></th>
<th><strong>Non-Mendelian</strong></th>
</tr>
</thead>
</table>
| 1. determined by a *single* gene  
  - completely penetrant  
  - possibility of presymptomatic / prenatal diagnosis  
  2. familial clustering is possible  
  - in some families they show typical transmission pattern / clustering  
  - most are still sporadic  | 1. determined by several genes / environmental factors  
  - ‘incompletely penetrant’  
  - only a risk might be estimated  
  2. sporadic in general  
  - *no familial clustering*  
  - unless a relatively frequent disorder (diabetic nephropathy) |
Mendelian disorders are frequent in childhood ESRD

Etiology of end-stage renal disease

**Childhood**
- CAKUT of unknown origin: 25%
- Alport: 7%
- Monogenic nephrosis: 10%
- Monogenic CAKUT: 4%
- Glomerulonephritis: 15%
- ARPKD: 4%
- Nephronophthisis: 10%
- Ischemic renal failure: 2%
- Miscellaneous: 7%
- Unknown: 7%
- HUS: 6%

**Adulthood**
- Hypertension: 25%
- Diabetes: 40%
- Unknown/other: 17%
- Cystic kidney: 5%
- Glomerulonephritis: 13%

ERA/EDTA registry

Do you ask the parents about their potential consanguinity when you consult a child with a nephropathy of unknown etiology?

1. most of the time

2. only if they come from populations with a high degree of CS

3. I prefer not, it can be insulting

4. I am an adult nephrologist...
Risk of having an affected child in consanguineous families in function of the prevalence of autosomal recessive diseases

- **Well known disorders**
- **Disorders known by experts**
- **Extremely rare disorders**

The graph shows the relative risk (compared to the general population) on the y-axis and the prevalence (1/...) on the x-axis. The risk increases significantly with higher prevalence for both first-degree and second-degree cousins.
Monogenic nephropathies
with an unexpected transmission pattern
This is the phenotype that is transmitted in a dominant or a recessive fashion.

The variant may be dominant or recessive, but always transmitted with a 50% risk.

X-linked dominant

X-linked recessive
The transmission pattern reflects the underlying pathophysiology

1. 50% function loss (haploinsufficiency)
2. dominant negative effect
3. gain of function
4. second hit

(A) Autosomal recessive
\[ n \sim 3400 \text{ disorders} \]

(B) Autosomal dominant
\[ n \sim 2900 \text{ disorders} \]

A protein may be dysfunctional through different mechanisms

The transmission pattern related to the same gene may vary
**PKD1**-related polycystic kidney disease may occasionally be transmitted in an AR fashion

null mutation of **PKD1**: ADPKD

hypomorphic mutations of **PKD1**: autosomal recessive transmission

Vujic M et al., JASN, 2010
**NPHS2-associated podocytopathy exceptionally transmitted in an AD fashion**

*NPHS2, encoding podocin - AR SRNS*

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**de novo NPHS2 mutation (L330Vfs*15), AD FSGS**

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Boute et al, Nat Genet, 2000

**NPHS2** R229Q: a benign variant that is dominant over most pathogenic variants but recessive with others.

Tory et al., Nat Gen, 2014
For genetic counseling we need to know which variants are pathogenic in trans with R229Q

1. The variant affects an evolutionary conserved amino acid,
2. located in the region of oligomerization (residues 270–351)
3. The substitution results in change of size, polarity, or hydrogen bonding capacity, but
4. does not disrupt the oligomerization!

Mikó et al, Hum Mut, 2018
Incomplete penetrance and oligogenism in nephropathies
How many families have you ever seen with an incompletely penetrant genetic nephropathy?

• 0

• 1-5

• 6-10

• >10
PLCE1-associated nephrotic syndrome is incompletely penetrant

'Autosomal recessive' diseases with *homozygous loss-of-function mutations* may be incompletely penetrant

Gilbert et al, Kidney Int, 2009

c.1303_1306delAGGA, hom, p.R434*

Boyer et al, J Med Genet, 2010

c.6448C>T, hom, p.R2150*

Hinkes et al, Nat Genet, 2006

c.1477C>T, hom, p.R493*
Digenic inheritance in Alport syndrome

Mencarelli et al, J Med Genet, 2014
Digenic inheritance in Bartter IVb

Biallelic loss-of-function mutations in both the \textit{CLCNKA} and \textit{CLCNKB} genes

- Paternal: Q260X
- Maternal: Deletion

\textbf{CLCNKA} (9727 bp)
- mild diabetes insipidus

\textbf{CLCNKB}
- classic Bartter (type III)
- severe Bartter (polyhydramnios) + deafness (type IVb)

Extra-renal involvement associated to \textit{NPHP1} may be the consequence of second-locus variants.

Frequency of \textit{AHI1} het. R830W in patients with \textit{NPHP1} mutations:
- Isolated nephronophthisis: n=76
  - 3 (4%)
  - p=0.0014
- Nephronophthisis and Joubert syndrome: n=13
  - 5 (38%)

Isolated nephronophthisis: n=137
- 5 (4%)
  - p<0.0001
- Nephronophthisis and retinitis pigmentosa: n=16
  - 8 (50%)

\textit{NPHP1} biallelic damaging variants:
- \textit{NPHP6}, \textit{AHI1} variants (in 7/13 families).

Louie et al., Nat Gen, 2010

‘Triallelic inheritance’ in Bardet-Biedl syndrome

Katsanis et al., Science, 2001
Ciliopathies are nevertheless mendelian disorders

<table>
<thead>
<tr>
<th></th>
<th>Ciliopathy group</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaheen et al, Genome Biol, 2016</td>
<td>n = 31</td>
<td>n = 64</td>
<td></td>
</tr>
<tr>
<td>additional variants in second ciliopathy genes (n=98) with a MAF&lt;1%</td>
<td>7.0 / sample</td>
<td>6.98 / sample</td>
<td>0.91</td>
</tr>
<tr>
<td>MAF&lt;1% + CADD &gt; 20</td>
<td>1.13 / sample</td>
<td>1.19 / sample</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phelps et al, Genet Med, 2018</td>
<td>n = 386</td>
<td>n = 1082</td>
<td></td>
</tr>
<tr>
<td>single heterozygous rare deleterious variants (MAF &lt; 0.2% + CADD &gt; 15) in at least two JBTS genes</td>
<td>19 (4.9%)</td>
<td>53 (4.9%)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

No difference in the mutational load between patients with ciliopathy and healthy individuals.
Reasons potentially explaining the oligogenism theories in ciliopathies

- There is a wide variation in expressivity
- During the 1st decade of this century, it was challenging to assess the pathogenicity of rare variants: many were falsely considered pathogenic
- Ciliopathies are genetically highly heterogeneous: the higher the number of the causal genes, the more frequent are heterozygous carriers in the general population

![Graph showing the relationship between the number of causal genes and the prevalence of heterozygous individuals in the general population.](image)

- Prevalence: 1:50,000 (nephronophthisis)
- Prevalence: 1:100,000 (BBS)

assuming that the genes are mutated with a similar frequency and the variants are all completely penetrant.
Identification of incompletely penetrant (non-mendelian) variants in AR disorders
Calculation of the penetrance in AR disorders

Pathogenic CFTR alleles in the European general and in the patient population

Allele count in populations

<table>
<thead>
<tr>
<th></th>
<th>general</th>
<th>patient</th>
<th>penetrance</th>
</tr>
</thead>
<tbody>
<tr>
<td>R117H</td>
<td>311</td>
<td>89</td>
<td>20.7%</td>
</tr>
<tr>
<td>LOF</td>
<td>353</td>
<td>481</td>
<td>p=9.07E-34</td>
</tr>
</tbody>
</table>

\[
P \approx \frac{AC_{pt}^{\nu}/AC_{pt}^{LOF}}{AC_{gnomAD}^{\nu}/AC_{gnomAD}^{LOF}}
\]

Mikó et al, Hum Mutat, 2021
Incompletely penetrant variants can be identified by a population-genetic approach.
**IP variants in NPHS2 and PKHD1**

<table>
<thead>
<tr>
<th>gene</th>
<th>variant</th>
<th>AF in Europe</th>
<th>LOF&lt;sub&gt;pt&lt;/sub&gt;/LOF&lt;sub&gt;gnomAD&lt;/sub&gt; (AC in Europe)</th>
<th>enrichment pt vs. gen pop (p)</th>
<th>penetrance (p)</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>patient population</td>
<td>gnomAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NPHS2</strong></td>
<td>c.686G&gt;A</td>
<td>R229Q</td>
<td>81/434 (18.66%) 4537/126346 (3.59%)</td>
<td>72/67 5.2x (1.16x10&lt;sup&gt;-33&lt;/sup&gt;)</td>
<td>1.66% (1.37x10&lt;sup&gt;-76&lt;/sup&gt;)</td>
<td>USA, AUS, CZE, FRA, ENG, DEU, TUR, GRC, HUN, ITA, POL, PRT, SVN, ESP</td>
</tr>
<tr>
<td></td>
<td>c.4870C&gt;T</td>
<td>R1624W</td>
<td>5/580 (0.86%) 28/126656 (0.02%)</td>
<td>39x (4.13x10&lt;sup&gt;-7&lt;/sup&gt;)</td>
<td>16.96% (4.39x10&lt;sup&gt;-05&lt;/sup&gt;)</td>
<td>FRA, NLD, USA</td>
</tr>
<tr>
<td></td>
<td>c.5498C&gt;T</td>
<td>S1833L</td>
<td>2/580 (0.34%) 37/126386 (0.003%)</td>
<td>11.78x (0.0138)</td>
<td>5.14% (3.15x10&lt;sup&gt;-9&lt;/sup&gt;)</td>
<td>ESP, USA</td>
</tr>
<tr>
<td></td>
<td>c.6992T&gt;A</td>
<td>I2331K</td>
<td>8/580 (1.38%) 47/126480 (0.04%)</td>
<td>37.12x (1.81x10&lt;sup&gt;-10&lt;/sup&gt;)</td>
<td>16.17% (1.05x10&lt;sup&gt;-7&lt;/sup&gt;)</td>
<td>DNK, DEU, USA</td>
</tr>
<tr>
<td></td>
<td>c.7264T&gt;G</td>
<td>C2422G</td>
<td>3/580 (0.52%) 78/126580 (0.06%)</td>
<td>8.39x (0.00619)</td>
<td>3.65% (2.43x10&lt;sup&gt;-18&lt;/sup&gt;)</td>
<td>AUT, DEU</td>
</tr>
</tbody>
</table>

Mikó et al, Hum Mutat, 2021
For the proper description of the transmission: the phenotype, the gene and the variant are all needed

- The *NPHS2* p.R138Q-related nephrotic syncrome is AR.
- The *NPHS2* p.L330Vfs*15*-related FSGS is AD.

- The *PKD1* p.Q2158*-related polycystic kidney disease is AD.
- The *PKD1* p.R220W-related polycystic kidney disease is AR.

- The *PKHD1* p.T36M-related polycystic kidney disease is AR.
- The *PKHD1* p.I2331K-related polycystic kidney disease is incompletely penetrant.

- The *NPHP1* homozygous deletion-related NPH is AR.
- The *NPHP1* homozygous deletion-related retinitis pigmentosa is multifactorial.
A multifactorial nephropathy
End-stage renal disease is 2-3x more frequent in the African American population than in the others.
## APOL1 G1 and G2 alleles: protection and risk

<table>
<thead>
<tr>
<th></th>
<th>African American FSGS, n=205</th>
<th>African American control n=180</th>
<th>p</th>
<th>African general pop n=5181</th>
<th>European general pop n=33307</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (S342G and I384M)</td>
<td>52%</td>
<td>23%</td>
<td>$1.07 \times 10^{-23}$</td>
<td>23%</td>
<td>0.01%</td>
</tr>
<tr>
<td>G2 (N388_Y389del)</td>
<td>23%</td>
<td>15%</td>
<td>$4.38 \times 10^{-7}$</td>
<td>14%</td>
<td>0.006%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>wt/wt</th>
<th>G1/G2 + wt</th>
<th>G1/G2 + G1/G2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trypanosoma b. brucei</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>Trypanosoma b. rhodesiense</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>Trypanosoma b. gambiense</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
</tr>
<tr>
<td>hypertensive nephropathy</td>
<td>1</td>
<td>1.26x (95% CI: 1.01-1.56)</td>
<td>7.3x (95% CI: 5.6 to 9.5)</td>
</tr>
<tr>
<td>FSGS</td>
<td>1</td>
<td>NS</td>
<td>10x (95% CI:6-18.4)</td>
</tr>
<tr>
<td>HIV-associated nephropathy</td>
<td>1</td>
<td>NS</td>
<td>29x (95% CI: 13 to 68)</td>
</tr>
</tbody>
</table>

Conclusions

- Nephropathies are typically either mendelian or multifactorial.
- Oligogenic inheritance is rare, but variants at second loci may modify the phenotype.
- It seems worth describing the transmission pattern in function of the causal variant and the organ involvement.
- Incompletely penetrant variants can be detected by a population-genetic approach in AR disorders and are more frequent than expected.
NEXT WEBINARS

05/04/22

**Fabry disease**
Olivier Lidove & Wladimir Mauhin (Paris, France)

19/04/22

**Methylmalonic acidemia**
Anais Brassier & Manuel Schiff (Paris, France)

03/05/22

**Collagenopathies**
Roser Torra (Barcelona, Spain)

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