Genet(h)ics in Pediatric Nephrology

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Outline: Genet(h)ics in Pediatric Nephrology

- Short look back
- Presymptomatic testing
- Prenatal diagnosis
- Own duties
Garden Pea Flowers
Short History of Genetics in Medicine

Discovery of the laws of inheritance

Versuche über Pflanzen- Hybriden.
Verhandl d Naturforsch Ver Brünn; 4, 3-47; 1865

Distributed to 120 libraries
40 personal reprints

„warmheartedly ignored“

Gregor Johann Mendel (1822-1884)
Short History of Genetics in Medicine

Description of several INBORN errors of metabolism

- albinism
- alkaptonuria
- cystinuria
- pentosuria

Inherited as *autosomal recessive* traits

Similar to that of the white color in Mendel’s garden pea flowers

Sir Archibald Garrod, early 1900s
Molecular Genetics, first gene identifications

1983 - PKU gene cloned and first mutation described

1986 - 1st gene positionally cloned
      (X-linked, granulomatous disease, cytogenetic rearrangement)

1989 - CFTR, 1st gene cloned by pure positional cloning

1990 - WT1

1990 - Alport Syndrome (X-linked, COL4A5)

1992 - Lowe Syndrome

1994 - PKD1
Human Genome   (3 x 10^9 bp)

90% anonymous genomic sequences

10% gene-encoding protein sequences (30,000 genes)

Molecular Genetics in Medicine

Human Genome   (3 x 10^9 bp)
Acceleration of Gene Cloning by the Human Genome Project

- Chromosomal localization
- Physical map
- Identification of the gene
- High resolution genetic map
- Integrated physical and genetic map of the whole genome
- EST mapping consortium: human transcript map whole genome sequence

From: Collins, Nat Genet 1995
Consequences of the Human Genome Project

Collins, Nat Genet 1995
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Locus</th>
<th>Gene</th>
</tr>
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<tr>
<td>ADPKD</td>
<td>AD</td>
<td>16p13.3</td>
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<tr>
<td></td>
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<td>4q21</td>
<td>PKD2</td>
</tr>
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<td></td>
<td>AD</td>
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<td>PKD3</td>
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<tr>
<td>ARPKD</td>
<td>AR</td>
<td>6p21</td>
<td>PKHD1</td>
</tr>
<tr>
<td>NPH</td>
<td>AR</td>
<td>2q12-13</td>
<td>NPHP1</td>
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<tr>
<td></td>
<td>AR</td>
<td>9q22-31</td>
<td>NPHP2</td>
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<td></td>
<td>AR</td>
<td>3q21-22</td>
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<td>NPH/Cogan</td>
<td>AR</td>
<td>2q12-13</td>
<td>NPHP1</td>
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<td>Senior Loeken</td>
<td>AR</td>
<td>3q21-22</td>
<td>NPHP5</td>
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<td>Tuberous sclerosis</td>
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<td>VHL</td>
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<tr>
<td>Disease</td>
<td>Inheritance</td>
<td>Locus</td>
<td>Gene</td>
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<td>--------------</td>
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<tr>
<td>Diabetes insipidus renalis</td>
<td>XR</td>
<td>Xq28</td>
<td>AVPR2</td>
</tr>
<tr>
<td></td>
<td>AR / AD</td>
<td>12q13</td>
<td>AQP2</td>
</tr>
<tr>
<td>antenatal Bartter syndr</td>
<td>AR</td>
<td>15q15-21</td>
<td>NKCC2</td>
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<td>11q24</td>
<td>ROMK</td>
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<td>NCCT</td>
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<td>AR</td>
<td>1p31</td>
<td>Barttin</td>
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<td>proximal RTA</td>
<td>AD</td>
<td>4q21</td>
<td>SLC4A3</td>
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<td>2cen-q13</td>
<td>ATB6B1</td>
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<td>AR</td>
<td>3q27</td>
<td>CLDN16</td>
</tr>
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<td>FHHNC / ocular involvem</td>
<td>AR</td>
<td>1p34.2</td>
<td>CLDN19</td>
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## Hereditary Glomerular Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Locus</th>
<th>Gene</th>
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<tbody>
<tr>
<td>Alport syndrome</td>
<td>XR</td>
<td>Xq22</td>
<td>COL4A5</td>
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<tr>
<td></td>
<td>AR</td>
<td>2q35-36</td>
<td>COL4A3/A4</td>
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<td>familial Hematuria</td>
<td>AD</td>
<td>2q35-36</td>
<td>COL4A3/A4</td>
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<tr>
<td>Congenital NS</td>
<td>AR</td>
<td>19q13.1</td>
<td>NPHS1/Nephrin</td>
</tr>
<tr>
<td>DMS</td>
<td>AR ?</td>
<td>11p13</td>
<td>WT1</td>
</tr>
<tr>
<td>Frasier syndrome</td>
<td>AD</td>
<td>11p13</td>
<td>WT1</td>
</tr>
<tr>
<td>familial FSGS</td>
<td>AR</td>
<td>1q25-32</td>
<td>NPHS2/Podocin</td>
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<tr>
<td></td>
<td>AD</td>
<td>19q13</td>
<td>ACTN4</td>
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<tr>
<td></td>
<td>AD</td>
<td>11q21-22</td>
<td>TRPC6</td>
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<tr>
<td></td>
<td>AR</td>
<td>10q23</td>
<td>PLCE1</td>
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<tr>
<td>IgA-Nephritis</td>
<td>AD incomplete</td>
<td>6q22-23</td>
<td>?</td>
</tr>
</tbody>
</table>
What does this mean for Pediatric Nephrology?

At present time, the chances and possibilities for molecular biology in medicine are almost indefinite …,

which is in sharp contrast to the limitations!

- money, sequencing capacities
- man power, time
What does this mean for Pediatric Nephrology?

At present time, the chances and possibilities for molecular biology in medicine are almost indefinite …,

which is in sharp contrast to the limitations!

- money, sequencing capacities
- man power, time
- the complexity of the human genome
Gene Cloning in Medicine

- Disease with Genetic Component
  - Map
    - Clone gene
      - Accelerated by Human Genome Project
      - Understand basic biological defect
        - Drug therapy
        - Gene therapy
      - Preventive Medicine
        - Diagnostics
          - TIME
          - Gene Cloning in Medicine

Collins, Nat Genet 1995
Outline: Genet(h)ics in Pediatric Nephrology

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Example: Chorea Huntington, presymptomatic test?

The parents wish a genetic test for their children, what would you do?
Chorea Huntington, background information

Neurodegenerative disorder, no therapeutic options

Onset around 40 yrs of age

Death after 10 – 20 yrs
Example: Chorea Huntington, presymptomatic test?

The parents wish a genetic test for their children, what would you do?
## Willingness to perform presymptomatic testing

<table>
<thead>
<tr>
<th></th>
<th>Huntington</th>
<th>Alzheimer</th>
<th>Alcoholism</th>
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<tbody>
<tr>
<td>Geneticists UK</td>
<td>2 %</td>
<td>2 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Geneticists Canada</td>
<td>12 %</td>
<td>11 %</td>
<td>26 %</td>
</tr>
<tr>
<td>Geneticists USA</td>
<td>27 %</td>
<td>25 %</td>
<td>48 %</td>
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<tr>
<td>Primary care physicians USA</td>
<td>66 %</td>
<td>58 %</td>
<td>76 %</td>
</tr>
<tr>
<td>Patients USA</td>
<td>-</td>
<td>61 %</td>
<td>-</td>
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<tr>
<td>Geneticists Germany</td>
<td>14 %</td>
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<td>27 %</td>
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<tr>
<td>Patients Germany</td>
<td>37 %</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Geneticists Greece</td>
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<td>70 %</td>
<td>70 %</td>
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<tr>
<td>Geneticists Turkey</td>
<td>68 %</td>
<td>68 %</td>
<td>91 %</td>
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<tr>
<td>Geneticists Asia</td>
<td>~75 %</td>
<td>~70 %</td>
<td>~65 %</td>
</tr>
<tr>
<td>Geneticists South America</td>
<td>~85 %</td>
<td>~80 %</td>
<td>~80 %</td>
</tr>
</tbody>
</table>
Example: The Huntington Dilemma

Grandfather is affected, grandson wants to know, but not the father…….

Grandfather

Father

Grandson

The father has the right of not knowing his gene status
Example: The dilemma in Pediatrics
Arguments against presymptomatic testing in children

- Children are getting deprived of their own decision as adults later in life.
- In general, adults often refuse testing (e.g. 15 % in Chorea Huntington).
- Respecting confidentiality is much more difficult in a family setting.
- Results may change the expectations of the parents and others.
- Disturbance of the parent-child-relationship (fear, blame).
- Results could be considered as a punishment (by the child).
- Misinterpretation by other family members.
- Issues related to health insurance, life insurance, etc.

Duncan, Clin Genet 2006
Arguments in favour of presymptomatic testing

- Young reflected people have a right of getting tested.
- Knowledge of the gene status could influence life planning.
- Not being tested could results in psychological burden.
- Early knowledge helps the parents to prepare their children.

- Parents are primarily responsible and therefore should decide...
- Prohibiting testing would be paternalistic.
- No doubt for disorders, that can be treated or avoided.

- Also for untreatable diseases predictive testing may be helpful for further life planning and cannot be prohibited completely.

- In children, testing should only be performed if disease onset is expected before adult age and therapeutic measures are available.
Example: ADPKD, presymptomatic testing

The parents are worried and ask for genetic testing . . .
Example: ADPKD, presymptomatic testing

50 yrs, 1 yr on dialysis

30 yrs, large cysts, Crea 1.3, hypertension

Who is going to protect the „right of not knowing“?
Example: ADPKD, presymptomatic testing

Who is going to protect the „right of not knowing“?
Example: The dilemma in Pediatrics
These parents are also worried and ask for a genetic test...
Probability of ESRD in 315 males and 288 females with COL4A5 mutations (X-linked ALPORT syndrome)
These parents are also worried and ask for a genetic test. . .
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Idiopathic Nephrotic Syndrome
The (steroidresistant) nephrotic syndrome, a genetic disease entity?

- In 1969, Mehl et Schärer describe, that familial occurrence of nephrotic syndrome is associated with poor prognosis, except patients with minimal change disease.

- The majority of familial forms are steroidresistant suggesting a different etiology than the sporadic cases (possibly not related to immunological factors).
In 2000, the \textit{NPHS2} gene encoding podocin was identified.

Boute et al., Nature Genetics 2000
Clinical significance

Mutation in NPHS2 (podocin) are responsible for approximately 30% of familial cases and 10% of sporadic cases with SRNS.

Patients with mutations in NPHS2 have a steroidresistant NS and do not respond to other immunosuppressive agents.

Only 3% of patients with SRNS and NPHS2 mutations develop proteinuria after renal transplantation.
Steroids

CyA

Biopsy
Steroid pulses

NS

weeks

4 6 12

Molecular Diagnostics (Podocin, WT1)?
Thank you very much!