Ethical aspects of genetic diagnosis

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I'll climb up this strand of DNA to see where life takes me.
What would you do?

HIV infection

what does my sister have?
What would you do?

Lowe syndrome (oculo-cerebro-renal S.)
X-linked recessive

* what does the son of my sister have

* what is the risk for my children?
What would you do?

Lowe syndrome
(oculo-cerebro-renal syndrome
X-linked recessive)

* 50% carrier
* Boy = 25% risk
Why disclose genetic information within a family?

- perceived need or obligation to disclose
- the fear that the relative carries a reproductive risk
- a close social relationship with the relative
- the need for support
- a feeling of responsibility toward the younger generation
- a perceived need to retrieve information about familial risk
- obtain advice about medical decisions

Reasons given for not disclosing within a family include:

- A lack of closeness
- Desire to protect family members from troubling information
- A perception that the relative has a lower risk of passing on the disorder
- Because she or he is unmarried or childless or plans to have no additional children
- Test results were uninformative or negative
- Relative's youth or immaturity
- Family disagreements
- Assumptions that information had been imparted by other family members
- An anti-abortion stance
- A lack of “openness” regarding cancer
- Happenstance (it “never came up”).
- Nondisclosure decisions also may be influenced by guilt or anxiety.
Genetic testing and the family

Confidentiality

prevention of harm
social criterion

• close relatives are not entirely outside the private sphere of the individual but rather are integral to his or her identity.

• confidentiality and privacy as embrace the family unit

=> effect of (non)disclosure on family relationships?

Patient autonomy and relatives' right to know genetic information.
Genetic mutation  \[\rightarrow\]  disease

* presymptomatic diagnosis
* carrier diagnosis
* prenatal diagnosis

* “classical” diagnostics
presymptomatic diagnosis

ADPKD

carrier testing

Nephronophthisis

2 yrs 9 months

7 yrs 5 years
WHAT WOULD YOU DO?

carrier testing

Nephronophthisis

AUTONOMY
CARRIER TESTING IN CHILDREN

Current consensus:

**no** carrier testing in children until they can make an autonomous decision.
CHALLENGES

- *Unintended carrier detection*
  prenatal testing, newborn screening

- *Many parents are in favour of carrier testing in their children*

* learning one’s carrier status may help their children adapt to the carrier status
* Reduce uncertainty about the carrier status,
* avoid resentment from children later in life
* parents have the right and the ability to make decisions regarding their children’s health.
* children become aware of their genetic risk before becoming sexually active
* child is able to chose a partner, informed of his carrier status.
* good parent should know as much as possible about their children,
* emotional benefit of the child to grow up knowing carrier status
presymptomatic diagnosis?  

carrier testing?

Carrier diagnosis: recurrence risk for children later?

Presymptomatic diagnosis: need for medical follow-up?

X-linked Alport syndrome

7 yrs  5 years
Predictive genetic testing
What would you do?

Huntington's disease

Autosomal dominant
Risk = 50%
100% penetrance
No cure, no prevention
Starting < age 5: annual ophthalmologic examination
starting at age 5:
- annual blood pressure monitoring
- annual urinary catecholamine metabolites
Starting age 16: annual abdominal ultrasound

Von Hippel Lindau

Renal cell carcinoma

Pheochromocytoma

5 yrs 9 months
TRAC variants associate with IgA nephropathy.


Department of Medical Genetics and Center for Genome Research, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, China.

The T cell receptor alpha constant gene (TRAC) encodes the constant region of the alpha chain for the T cell receptor, and the association of its gene variants with IgA nephropathy remains controversial. The authors resequenced the gene in 100 patients with IgA nephropathy and 100 controls, tested its linkage disequilibrium pattern, constructed haplotypes, and performed association and functional studies. First, the association between TRAC variants and IgA nephropathy was tested in 704 patients and 704 controls. Next, these 704 patients were divided into two independent datasets--310 with family member(s) and 394 single patients--to test the association separately. Results showed that the gene is located in a recombination hot spot, with nine linkage disequilibrium blocks within a 6.9-kb region. There is a hypervariable region with six single-nucleotide polymorphisms (SNPs) in an 85-bp stretch in intron 1. We identified multiple SNPs and two haplotypes that associate with IgA nephropathy (P = 0.0000013-0.0096 by logistic regression for SNPs; P = 0.0003 and P = 0.0398 for haplotype associations). The family-based study replicated both haplotype findings, and the 394 single-patient case-control study replicated the association with haplotype 1 (P = 0.0033). The overtransmitted/observed haplotypes demonstrated reduced transcription activity compared with the undertransmitted/observed haplotypes. In conclusion, this study suggests an association between TRAC variants and susceptibility to IgA nephropathy.
Currently: no indication for testing of asymptomatic children
Future: Depending on results from ongoing trials...
<table>
<thead>
<tr>
<th>PREDICTIVE VALUE</th>
<th>Management options (at age of diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>high high</td>
</tr>
<tr>
<td>HIGH</td>
<td>Von Hippel Lindau</td>
</tr>
<tr>
<td></td>
<td>TEST TEST</td>
</tr>
<tr>
<td>LOW</td>
<td>ADPKD ADPKD</td>
</tr>
</tbody>
</table>
first technique

then ethics
screening

resolution

karyotyping

Array-CGH

mlpa

FISH

Next generation sequencing

sequencing
High resolution genome-wide screening

Novel ethical problems
certain genetic alterations

not a known pathogenic variant
not a known variant in normal population

“unclassified variant”
DNA testing BRCA1 & 2
5 Dutch laboratories in 2001

<table>
<thead>
<tr>
<th>Mutations</th>
<th>10.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclassified variants</td>
<td>13.1%</td>
</tr>
</tbody>
</table>

How to communicate on U.V.’s?

1. Communicate to the referring physician (geneticist)?

Viewpoint of 8 laboratories

<table>
<thead>
<tr>
<th>Additional information or tests offered</th>
<th>Number of centres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report the detected UV to the requesting counselor</td>
<td>7</td>
</tr>
<tr>
<td>UV has a high probability of being pathogenic\textsuperscript{a}</td>
<td>4</td>
</tr>
<tr>
<td>UV has been detected before\textsuperscript{a}</td>
<td>4</td>
</tr>
<tr>
<td>Presymptomatic testing of UV</td>
<td>0\textsuperscript{b}</td>
</tr>
</tbody>
</table>
2. Communicate to the patient?

Viewpoint of 10 clinical geneticists

<table>
<thead>
<tr>
<th>Clinical geneticist</th>
<th>Answers received</th>
<th>Number of compliant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss the possibility of finding a UV before testing</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Inform the counselee when a UV is detected</td>
<td>10</td>
<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Feels that the counselee understands the UV-report</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Offer presymptomatic testing</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>One does this sometimes, depending on the UV. <sup>b</sup>In addition to these seven, two other counselors do this sometimes depending on family structure, and one principally does not offer segregation analysis.
3. What did the patients understand?

After 3 years – 24 patients receiving U.V. as a test result

19/24 : pathogenic

follow-up of unclassified variants

• 2007: 8 unclassified variants in 60 patients with CHD

• 2009: 5/8 now known as not pathogenic
  3 remain unclassified

⇒ Need for systematic re-evaluation of U.V.’s

• during clinical follow-up (patient still has no diagnosis!)
• local molecular (cyto)genetic database
Prenatally:

- Unilateral renal agenesis
- Contralateral renal hypoplasia
- Oligohydramnios

Postnatally:

- Renal function
- Developmental delay
  ⇒ unexplained cerebellar lesions
**Deletion** *HNF1b*  
renal cysts and diabetes syndrome  
= MODY5  
= explains renal manifestations  
= warrants follow-up for diabetes mellitus
Branchio-oto-syndrome 2

- Hearing loss
- Inner ear malformation
- Ear pit

11Mb Deletion 1q31.2q32.1
**CDC73 = HRPT2:**
hyperparathyroidism-jaw tumor syndrome (MIM: #145001)

- hyperparathyroidism (adenoma / carcinoma)
- ossifying fibromas of the mandible or maxilla
- renal cysts
“incidental findings”
1. Medically significant

= predictive testing for “late onset” disorders

for index (when inherited, also for parent & relatives)

- deletion NF2-gene = neurofibromatosis type 2
- RB gene deletion = retinoblastoma
- BRCA deletion = hereditary breast and ovarium cancer
- p53 deletion = Li-Fraumeni syndrome
- APC deletion = polyposis coli
- PTCH-deletion = Basal cell nevus syndrome
- deletion PMP22 gene = HNPP (hereditary pressure neuropathy)
- deletion HNF1B = renal hypoplasia & MODY5
- del16p11 = increased risk autism, schizophrenia
“incidental findings”

1. Medical consequences: “predictive testing”

2. Reproductive consequences:
   “carrier” detection - autosomal recessive
   - X-linked
   - autosomal dominant
   (↓ penetrance / variable expression)
Itsara et al. AJHG 2009

$N = 2493$

NPHP1 deletions : $3 = 1/800$
Deletion NPHP1 (NEPHRONOPHTHISIS)

*typically inherited from healthy parent

Risc for being a carrier of NPHP1 mutation = 1/120

1. MR/dysmorphism
2. NPHP1 : 1/480
“incidental findings”

1. Medical consequences: “predictive testing”

2. Reproductive consequences:
   “carrier” detection - autosomal recessive
   - X-linked
   - autosomal dominant
   (↓ penetrance / variable expression)

3. Other aspects of genetic testing:
   - paternity
   - adoption
   - ethnicity
   - ...
the incidentalome*

- threat of unwanted information right not to know
- potential benefit to patient right to know

• Informed consent:
  - [ ] I do not want to know this information
  - [x] I want to know all incidental findings
  - [x] I only want to know medically important findings for which therapeutic or preventive options exist
  - [ ] I wish to be informed on carrier state for hereditary disorders
  ...

* Kohane et al. JAMA 2006;296:212
Genetic diagnosis in children

**fascination**
- Etiological diagnosis
- Genetic counselling
- Prognosis & guidance
- research

**frustration**
- confidentiality
- autonomy
- Unclassified variants
- Incidental findings