Genetic factors in hypospadias

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AGORA project

Aetiological research into Genetic and Occupational / Environmental Risk Factors for Anomalies in Children

Health Evidence
Genetics
Clinical departments

Pediatric Urology: Prof. Feitz, Dr. Kortman, Dr. De Gier, Dr. De Wall
• Small percentage:
  - genetic syndrome
  - single mutation

• Majority multifactorial
  - environmental factors
  - genetic variants
Single Nucleotide Variants (SNVs)
- SNV: nucleotide differs between people

> 1% of population: polymorphism
< 1% of population: mutation
• Single Nucleotide Variants (SNVs)
  - SNV: nucleotide differs between people

• Hypospadias: candidate gene studies
  - endocrine processes
  - early patterning
Screen gene in patients for presence of rare variants

Compare patients and controls for frequency of common variants

Replication of results important!

Mut Assoc

SOX9
NR5A1
AR
FKBP4
CYP1A1
CYP1A2
CYP1B1

Mut Assoc

CYP2B6
CYP3A4
CYP17A1
CYP19A1
HSD17B3
HSD3B2
SRD5A2

Endocrine system
Endocrine system

<table>
<thead>
<tr>
<th>Genes</th>
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<td>SRD5A2</td>
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- Mutations NR5A1, AR, HSD3B2 and SRD5A2 in several studies
### Endocrine system

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**Associations with SNVs in AR, HSD17B3 and SRD5A2 in more than one study**
### Early pattering

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- Mutations reported in only one study
Early patterning

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- Associations found in only one study - likely false-positive results
- Evidence for genes involved in early patterning is limited
• Likely:
  - other studies in Asia and Sweden → more consumption of phyto-estrogens
• Genes involved in early patterning
  - evidence limited

• Genes involved in endocrine processes
  - NR5A1, HSD3B2, HSD17B3, SRD5A2, AR likely to play a role in hypospadias development
• Genes involved in early patterning
  - evidence limited

• Genes involved in endocrine processes
  - NR5A1, HSD3B2, HSD17B3, SRD5A2, AR likely to play a role in hypospadias development

• Other candidate genes
  - Focus only on those with quite some evidence
• Genes involved in early patterning
  - evidence limited

• Genes involved in endocrine processes
  - NR5A1, HSD3B2, HSD17B3, SRD5A2, AR likely to play a role in hypospadias development

• Other candidate genes
  - ESR1 and ESR2
    - balance between androgens and estrogens
    - polymorphisms associated
    - decreased expression levels
• Genes involved in early patterning
  - evidence limited
• Genes involved in endocrine processes
  - NR5A1, HSD3B2, HSD17B3, SRD5A2, AR likely to play a role in hypospadias development
• Other candidate genes
  - ESR1 and ESR2
  - ATF3
    - estrogen responsive gene
    - upregulated in hypospadias
    - mutations found in patients
    - polymorphisms associated
Candidate genes

- Genes involved in early patterning
  - evidence limited
- Genes involved in endocrine processes
  - NR5A1, HSD3B2, HSD17B3, SRD5A2, AR likely to play a role in hypospadias development
- Other candidate genes
  - ESR1 and ESR2
  - ATF3
  - MAMLD1
    - contains NR5A1 target sequence
    - mutations found in patients
    - polymorphisms associated
- Genes involved in early patterning
  - evidence limited
- Genes involved in endocrine processes
  - NR5A1, HSD3B2, HSD17B3, SRD5A2, AR likely to play a role in hypospadias development
- Other candidate genes
  - ESR1 and ESR2
  - ATF3
  - MAMLD1
  - DGKK
    - identified with GWAS
    - polymorphisms associated
GWAS

Cases, 55%

Controls, 33%

OR = 2.5  95%CI 1.9-3.2
Recurrence risk

Mother: X X
Father: X Y
Son: X Y
Recurrence risk

Mother

\[X \quad X\]

Son

\[X \quad Y\]

13% chance hypospadias
Recurrence risk

Mother X X

Son X Y

Normal DGKK gene
8% chance hypospadias
Recurrence risk

Variation in DGKK gene
20% chance hypospadias
New hypotheses

Variation in DGKK

RNA  protein  metabolite

Hypospadias

Patients  Non-Patients
Causal model
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- Genes involved in endocrine processes
  - NR5A1
  - HSD3B2
  - HSD17B3
  - SRD5A2
  - AR

- Other candidate genes
  - ESR1
  - ESR1
  - ATF3
  - MAMLD1
  - DGKK