Disorders of Sex Development: Nomenclature, Pathophysiology, Diagnostics, and Ethics for Management

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www.kinderhormonzentrum-luebeck.uk-sh.de
www.eurodsd.eu
Biological Development of Sex

Parents

Prenatal Development

Postnatal Maturation
Endocrine determination of phenotype

Developmental stages

Androgens
Androgen action

Birth
Background

• Virilization deficit
  – (46,XY) gonadal dysgenesis (including 45,X/46,XY), disorders of androgen biosynthesis (with or without CAH), androgen insensitivity, unclassified hypospadias

• Virilization excess
  – (46,XX) adrenal androgen excess (CAH), aromatase deficiency, iatrogenic

• Development of both gonadal tissues
• Non-endocrine malformations (epispadias, syndromic, bladder extrophy)
Nomenclature

• Disorders of sex development (DSD)
  – Avoid terms as
    • „Intersex“
    • Pseudohermaphroditism, undervirilized males
    • Sex reversal
  – Instead use neutral terms that will allow for a biological classification even if no definitive diagnosis can be made
    • Ovotesticular DSD = true hermaphroditism
    • 46,XY DSD = male pseudohermaphroditism
    • 46,XX DSD = female pseudohermaphroditism
Classification

- Numerical chromosomal disorders
  - 45,X
  - 47,XXY
  - 45,X/46,XY etc.

- 46,XY DSD
  - Disorders of gonadal development (dysgenetic gonad)
  - Disorders of hormone synthesis and action
  - Non-classified (hypospadias, syndromic, bladder extrophy)

- 46,XX DSD
  - Disorders of gonadal development (e.g. POF, Duplication SOX9)
  - Androgen excess (CAH, aromatase deficiency)
  - Non-classified (e.g. Mayer-Rokitansky-Küster-Hauser syndrome)
Holistic view on DSD

- External Sex Phenotype depends on endocrine action.
- Prenatal development is driven by androgens
  - Lack of androgenisation = female phenotype
  - Androgenisation = male phenotype
- (Postnatal development depends on both estrogens and androgens)

- Androgen synthesis is variable and cell dependent.
- Therefore the time-dependent androgenisation potential will make up the individual composition of phenotype (regardless of karyotype) also in Disorders of Sex Development
Different androgens may elicit different androgen action.
Genomic androgen action

Testosterone

5α-Red.-II
DHT
Androgen receptor

Translation

Translation

Phenotype

HSP90
p23
C

Co CoR
Kinases
GTF

Core CoR

Activation

Transkription

HRE

P
P
P
P
Clinical grades of genital ambiguity

46,XX
Clinical grades of genital ambiguity

46,XY and others

Clinical assessment 46,XY DSD

EXTERNAL MASCULINIZATION SCORE

- n.v. 12
- Y N Nor
- Gla Scr Scr
- Pen Ing Ing
- Abd Abs Abs

INTERNAL MASCULINIZATION SCORE

- n.v. 10
- Y N Y Y N N
- uterus Fallop. tube* Epi didymis* Vas defer.*

*score right and left

## Single gene disorders in 46,XX DSD

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>OMIM</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Gonad</th>
<th>Mullerian structures</th>
<th>External genitalia</th>
<th>Associated features/variant phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRY</td>
<td>TF</td>
<td>480000</td>
<td>Yp11.3</td>
<td>Translocation</td>
<td>Testis or ovotestis</td>
<td>−</td>
<td>Male or ambiguous</td>
<td>CAH, primary adrenal failure, partial androgenisation due to ↑ DHEA</td>
</tr>
<tr>
<td>SOX9</td>
<td>TF</td>
<td>608160</td>
<td>17q24</td>
<td>dup17q24 ND</td>
<td>−</td>
<td>Male or ambiguous</td>
<td>CAH, phenotypic spectrum from severe salt losing forms associated with adrenal failure to simple virilising forms with compensated adrenal function, ↑ 17-hydroxyprogesterone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAH, hypertension due to ↑ 11-deoxy cortisol and 11-deoxy corticosterone</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency and aromatase deficiency; associated with Antley Bixler craniostenosis</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Maternal androgenisation during pregnancy, absent breast development at puberty, except in partial cases</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ ACTH, 17-hydroxyprogesterone and cortisol; failure of dexamethasone suppression (NB patient heterozygous for a mutation in CYP21)</td>
</tr>
</tbody>
</table>

**Androgen excess**

- **HSD3B2**: Enzyme 201810 1p13 AR Ovary + Clitoromegaly
- **CYP21A2**: Enzyme 201910 6p21-23 AR Ovary + Ambiguous
- **CYP11B1**: Enzyme 202010 8q21-22 AR Ovary + Ambiguous
- **POR (P450 oxidoreductase)**: CYP enzyme electron donor 124015 7q11.2 AR Ovary + Ambiguous
- **CYP19**: Enzyme 107910 15q21 AR Ovary + Ambiguous
- **Glucocorticoid receptor**: Nuclear receptor TF 138040 5q31 AR Ovary + Ambiguous
# Single gene disorders in 46,XY DSD testicular dysgenesis

## Disorders of gonadal (testicular) development: single gene disorders

<table>
<thead>
<tr>
<th>Gene</th>
<th>Type</th>
<th>Chromosome</th>
<th>Band</th>
<th>Inheritance</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT1</td>
<td>TF</td>
<td>607102</td>
<td>11p13</td>
<td>AD</td>
<td>Dysgenetic testis, Wilms tumour, renal abnormalities, gonadal tumours (WAGR, Denys-Drash, and Frasier syndromes)</td>
</tr>
<tr>
<td>SF1 (NR5A1)</td>
<td>Nuclear receptor TF</td>
<td>184757</td>
<td>9q33</td>
<td>AD/AR</td>
<td>Dysgenetic testis or ovotestis, Female or ambiguous</td>
</tr>
<tr>
<td>SRY</td>
<td>TF</td>
<td>480000</td>
<td>Yp11.3</td>
<td>Y</td>
<td>Dysgenetic testis or ovotestis, Female or ambiguous</td>
</tr>
<tr>
<td>SOX9</td>
<td>TF</td>
<td>608160</td>
<td>17q24-25</td>
<td>AD</td>
<td>Dysgenetic testis or ovotestis, Female or ambiguous</td>
</tr>
<tr>
<td>DHH</td>
<td>Signalling molecule</td>
<td>605423</td>
<td>12q13.1</td>
<td>AR</td>
<td>Dysgenetic testis, Female</td>
</tr>
<tr>
<td>ATRX</td>
<td>Helicase (?chromatin remodelling)</td>
<td>300032</td>
<td>Xq13.3</td>
<td>X</td>
<td>Dysgenetic testis, Female, ambiguous or male</td>
</tr>
<tr>
<td>ARX</td>
<td>TF</td>
<td>300382</td>
<td>Xp22.13</td>
<td>X</td>
<td>Dysgenetic testis, Female, ambiguous or male</td>
</tr>
</tbody>
</table>

## Disorders of gonadal (testicular) development: chromosomal changes involving key candidate genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Type</th>
<th>Chromosome</th>
<th>Band</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMRT1</td>
<td>TF</td>
<td>602424</td>
<td>9p24.3</td>
<td>Monosomy deletion, Dysgenetic testis, Female or ambiguous</td>
</tr>
<tr>
<td>DAX1 (NROB1)</td>
<td>Nuclear receptor TF</td>
<td>300018</td>
<td>Xp21.3</td>
<td>dupXp21</td>
</tr>
<tr>
<td>WNT4</td>
<td>Signalling molecule</td>
<td>603490</td>
<td>1p35</td>
<td>dup1p35</td>
</tr>
</tbody>
</table>

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*Note: Detailed descriptions of each disorder can be found in various medical references.*
## Single gene disorders in 46,XY DSD hormone synthesis and action

<table>
<thead>
<tr>
<th>Disorders of hormone synthesis or action</th>
<th>LHGCR</th>
<th>G protein receptor</th>
<th>152790 2p21</th>
<th>AR</th>
<th>Testis</th>
<th>--</th>
<th>Female, ambiguous or micropenis</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHC77</td>
<td>Enzyme</td>
<td>602858 11q12-13</td>
<td>AR</td>
<td>Testis</td>
<td>--</td>
<td>Female</td>
<td>Smith-Lemli-Opitz syndrome: coarse facies, second-third toe syndactyly, failure to thrive, developmental delay, cardiac and viseral abnormalities</td>
<td></td>
</tr>
<tr>
<td>STAR</td>
<td>Mitochondrial membrane protein</td>
<td>600617 8p11.2</td>
<td>AR</td>
<td>Testis</td>
<td>--</td>
<td>Female</td>
<td>Congenital lipoid adrenal hyperplasia (primary adrenal failure), pubertal failure</td>
<td></td>
</tr>
<tr>
<td>CYP11A1</td>
<td>Enzyme</td>
<td>118485 15q23-24</td>
<td>AR</td>
<td>Testis</td>
<td>--</td>
<td>Female or Ambiguous</td>
<td>Congenital adrenal hyperplasia (primary adrenal failure), pubertal failure</td>
<td></td>
</tr>
<tr>
<td>HSD3B2</td>
<td>Enzyme</td>
<td>201810 1p13.1</td>
<td>AR</td>
<td>Testis</td>
<td>--</td>
<td>Ambiguous</td>
<td>CAH, primary adrenal failure, partial androgenisation due to ↑ DHEA</td>
<td></td>
</tr>
<tr>
<td>CYP17</td>
<td>Enzyme</td>
<td>202110 10q24.3</td>
<td>AR</td>
<td>Testis</td>
<td>--</td>
<td>Female, ambiguous or micropenis</td>
<td>CAH, hypertension due to ↑ corticosterone &amp; 11-deoxycorticosterone (except in isolated 17,20-lyase deficiency)</td>
<td></td>
</tr>
<tr>
<td>POR (P450 oxido-reductase)</td>
<td>CYP enzyme electron donor</td>
<td>124015 7q11.2</td>
<td>AR</td>
<td>Testis</td>
<td>--</td>
<td>Male or ambiguous</td>
<td>Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency, and aromatase deficiency; sometimes associated with Antley Bixler craniosynostosis</td>
<td></td>
</tr>
<tr>
<td>HSD17B3</td>
<td>Enzyme</td>
<td>605573 9q22</td>
<td>AR</td>
<td>Testis</td>
<td>--</td>
<td>Female or ambiguous</td>
<td>Partial androgenisation at puberty, ↑ androstenedione/testosterone ratio</td>
<td></td>
</tr>
<tr>
<td>SRD5A2</td>
<td>Enzyme</td>
<td>607306 2p23</td>
<td>AR</td>
<td>Testis</td>
<td>--</td>
<td>Ambiguous or micropenis</td>
<td>Partial androgenisation at puberty, ↑ testosterone:DHT ratio</td>
<td></td>
</tr>
<tr>
<td>AMH</td>
<td>Signalling molecule</td>
<td>600957 19p13.3-13.2</td>
<td>AR</td>
<td>Testis</td>
<td>+</td>
<td>Normal male</td>
<td>Persistent mullerian duct syndrome (PMDS). Male external genitalia, bilateral cryptorchidism</td>
<td></td>
</tr>
<tr>
<td>AMH-Receptor</td>
<td>Serine-threonine kinase transmembrane receptor</td>
<td>600956 12q13</td>
<td>AR</td>
<td>Testis</td>
<td>+</td>
<td>Normal male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>Nuclear receptor TF</td>
<td>313700 Xq11-12</td>
<td>X</td>
<td>Testis</td>
<td>--</td>
<td>Female, ambiguous, micropenis or normal male</td>
<td>Phenotypic spectrum from complete androgen insensitivity syndrome (female external genitalia) and partial androgen insensitivity (ambiguous) to normal male genitalia/infertility</td>
<td></td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; CAH, congenital adrenal hyperplasia; TF, transcription factor; X, X chromosomal; Y, Y chromosomal.
Differential diagnosis DSD

Patients reported = 80

CAH: 32
AIS: 14
5aR: 13
Ovotest: 9
Gon Dys: 7
SLO: 2
Syndromal: 2
Undiagnosed: 1
Ambiguous Genitalia: Evaluation

- History
- Clinical Evaluation
- Diagnostic Approaches
  - Cytogenetic Analysis
  - Imaging
  - Laboratory Investigations
    - Hormonal Assessment
    - Biochemical Studies
  - Molecular Genetic Analysis
  - Surgical assessment of Gonads and internal genitalia
- Diagnosis
- Management
  - Psychosocial support
  - Sex of rearing
  - Therapeutic measures
  - Follow-up
Management

• Diagnostic work-up
• Team discussion (even in the time „in-between“:
  – Sex assignment on the basis of
    • Acceptance of parents and patient
    • Amount of procedures
    • Reproductive capacity, endocrine function
• Counselling on prognosis and genetics of patient and family
52 activities and interests investigated
N = 33 XY DSD children and 166 controls

"Androgens and Behaviour"

Jürgensen, Hiort, Holterhus, Thyen 2007, Hormones and Behavior 2007
"Gender role behavior in children with XY karyotype and disorders of sex development"
Optimal gender policy

To determine the optimal gender in terms of future functioning the following issues are considered:

– reproductive function (if attainable at all)
– sexual function
– minimal medical procedures
– an overall gender-appropriate appearance
– a stable gender identity
– appropriate gender role behaviour
Issues of Gender Assignment

- Specific Disorder
- Phenotype, associated disorders
- Magnitude of Interventions
- Gender aspects
- Fertility
- Sociocultural Background
- Parental Believes
  - Family integrity
  - Value of personality
  - Economic challenges in some societies
Strategies for management

Primary center (Pediatrician)

Secondary center (Pediatric Endocrinology)

Tertiary center (DSD Team)
Multidisciplinary Team

- Age-appropriate for the child and the family
  - Ability to answer questions regarding diagnosis, counselling, therapy, surgery
- Newborns
  - Pediatric Endocrinology, Psychology, Genetics, Neonatology, Pediatric Surgery (Pediatric Urology)
- Childhood and Adolescence
  - Pediatric Endocrinology, Psychology, Genetics, Gynecology, Pediatric Surgery (Pediatric Urology)
- Adulthood
  - Transition to Endocrinology, Psychology, Genetics, Gynecology, Urology, Sexual Medicine
- Further Members:
  - Ethics, Religious Counsel
Center of Reference

- Take-in interview
- Meeting of all team members with the parents/patient to discuss diagnostic and possible therapeutic steps.
- Counselling for the “time in between“
- Explanation of Diagnosis and prognosis from the views of different experts.
- Joint agreement of parents/patient about sex of rearing and future steps of therapy and education about DSD.

www.netzwerk-is.de
Centres of Reference

Clinical Research

Clinical & psychosocial care

Basic Research

Basic Science Facilities

Centres of Reference for Patient care & Quality assurance
Ethical conclusions

• Correction of genital status is not mandatory
• Patient and parents need to be actively involved
• The needs of the child are priority
• Openness and acceptance are important
• Therapy should always be optimal
• Avoid irreversible measures if possible
• A detailed documentation is necessary
• The child has to be informed age-appropriately
• The medical consensus has to be discussed and renewed regularly

Wiesemann C (2010) Sex Dev
Thank you very much

UNIVERSITÄT ZU LÜBECK

3rd Symposium on Disorders of Sex Development
20–22 May, 2011, Lübeck, Germany

From Gene to Gender
• what we’ve learned and what we need to learn
• New Prospects in DSD Research

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