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BIRTH WEIGHT IN DIFFERENT ETIOLOGIES OF DISORDERS OF SEX DEVELOPMENT

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Key terms: Birth weight; Disorders of sex development; Fetal androgen action

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ABSTRACT

Background: It is well established that boys are heavier than girls at birth. Although the cause of birth weight (BW) difference is unknown, it has been proposed that it could be generated from prenatal androgen action.

Objective: To determine the BW of children with disorders of sex development (DSD) of different etiologies and evaluate the effects of androgen action on BW.

Methods: Data regarding diagnosis, BW, gestational age, karyotype and concomitant conditions were collected from the I-DSD Registry (www.i-dsd). BW-SDS was calculated according to gestational age. Cases were evaluated according to disorder classification in I-DSD (disorders of gonadal development, androgen excess, androgen synthesis, androgen action, nonspecific disorder of undermasculinisation groups and Leydig cell defect).

Results: A total of 533 cases were available; 400 (75%) cases were 46,XY and 133 (25%) cases were 46,XX. Eighty cases (15%) were born small for gestational age (SGA). Frequency of SGA was higher in the 46,XY (17.8%) than in 46,XX (6.7%) groups (p=0.001). Mean BW-SDSs of cases with androgen excess and androgen deficiency (in disorders of gonadal development, androgen synthesis, androgen excess and Leydig cell defect groups and androgen receptor (AR) mutation-positive cases in disorders of androgen action group) were similar to normal children with same karyotype. SGA birth frequency was higher in the AR mutation-negative cases in disorders of androgen action group and in nonspecific disorders of undermasculinisation group.

Conclusions: BW dimorphism is unlikely to be explained by fetal androgen action per se. 46,XY DSDs due to nonspecific disorders of undermasculinisation are more frequently associated with fetal growth restriction, SGA and concomitant conditions.
It is well known that birth weight (BW) in boys is higher than in girls in the general population. Difference in BW between sexes is reported in human as well as non-human primate species (1). Although the cause of BW difference is still unknown, it has been proposed that the Y chromosome and prenatal androgen action may play a role (2,3).

The effect of androgens on fetal growth and BW difference between sexes has been reported in some previous studies. Although some studies have shown that BW difference is dependent on fetal androgens, other studies reported that it is not generated by action of androgens (3-6).

It has been demonstrated that BW difference becomes obvious in the fetus in the first trimester (7). De Zegher et al (4) reported that BW difference is developed before the third trimester and is relatively less pronounced during the latter part of gestation.

The aim of the current study was to assess the BW of children with disorders of sex development (DSD) of different etiologies and evaluate the BW in relation to androgen action.

Patients and Methods

Data regarding diagnosis, BW, gestational age, karyotype constitution and concomitant conditions (abnormalities other than genital system) were collected from 15 centers in 9 countries [Turkey, United Kingdom (UK), Germany, The Netherlands, Italy, Czech Republic, Belgium, Sweden, and Poland] reported in the International DSD Registry (www.I-DSD.org). If data on gestational ages or BW were not available in the registry, clinicians were asked to report the missing data. Only patients with 46,XY DSD and 46,XX DSD conditions were included, cases with sex chromosome DSD were excluded. Cases were evaluated according to classification in the I-DSD registry given in Table 1 including disorders of gonadal development, androgen synthesis, androgen excess, androgen action, nonspecific disorders of undermasculinisation and Leydig cell defect. BW of cases was expressed as SDS for gestational age according to national references for each country for the same karyotype (8-16). In disorder of androgen action group, BWs of cases were expressed as SDS for gestational age for both boys and, taking into consideration the lack of effect of androgens, also for girls. Small for gestational age (SGA) was defined as BW <-2 SDS for gestational age.

In the I-DSD groups, BW-SDS was evaluated according to karyotype. In disorders of androgen action group, BW-SDS was also evaluated with respect to the presence or absence of an
androgen receptor gene (AR) mutation. We evaluated concomitant conditions in DSD cases and the relationship of SGA with other concomitant conditions. We excluded known DSD syndromic conditions and anomalies that are acquired as the consequences of the management of the disorders like short stature in congenital adrenal hyperplasia (CAH).

Statistical analysis was performed using SPSS statistical Package version 15 (SPSS Inc., Chicago, IL). Results are reported as means±SD. Mean BW-SDSs of groups were compared to population average value (BW-SDS=0) by one sample t tests. Fisher’s exact test was used to compare the proportion of SGA in the groups. Two-tailed p values were calculated. Statistical significance was accepted as p<0.05.

Results

Of 649 accessible cases in the registry, 533 cases were suitable for evaluation [Turkey (n=329), UK (n=28), Germany (n=14), The Netherlands (n=49), Italy (n=39), Czech Republic (n=35), Belgium (n=19), Sweden (n=13), Poland (n=7)]. 400 (75%) cases had a 46,XY and 133 (25%) cases had a 46,XX karyotype. SGA was detected in 80 cases (15%). Significantly more cases with 46,XY karyotype (17.8%) were born SGA than cases with 46,XX karyotype (6.7%) (p=0.001). Numbers of cases in each I-DSD diagnostic group in the study are shown in Figure 1.

The analysis according to the registry’s subgroups showed the following distribution:

- In disorders of gonadal development group: 12 cases (19.4%) were 46,XX and 50 cases (80.6%) were 46,XY (Table 2). None of 46,XX cases were born SGA, whereas 14% (n=7) of cases with 46,XY karyotype were born SGA. Mean BW-SDS of cases with 46,XX was similar to the national references for girls (p=0.87). Although not statistically significant, mean BW-SDS of fifty 46,XY cases showed a lower trend compared with the national references for boys (p=0.056). However after excluding SGA cases, mean BW-SDS of 46,XY cases was not different from national references for boys (mean BW-SDS: -0.1±0.9, p=0.31).
- Androgen synthesis disorders: Eighty cases had a disorder of androgen synthesis; 10 (12.5%) of these cases were 46,XX, and 70 (87.5%) were 46,XY. Mean BW-SDS of both 46,XX and 46,XY cases were normal for girls and boys, compared with the national
references (Table 2, p=0.93, p=0.17 respectively). Only 7 (10%) cases with 46,XY were born SGA (Table 2).

- Androgen excess disorders: In the 170 cases of disorders of androgen excess group, the mean BW-SDS of 111 cases with 46,XX were not different when compared to the national references for girls (Table 2, p=0.46). Similarly, the BW-SDS of 59 cases with 46,XY karyotype was not different either compared to the national references for boys (Table 2, p=0.37). Frequency of cases born SGA was 8.1% in 46,XX and 6.8% in 46,XY karyotype.

- Androgen action disorders: Of the 179 cases classified as having disorders of androgen action, 113 patients were screened for AR mutations (Figure 2). Results of 9 patients (1 AR mutation-positive, 8 AR mutation-negative) reported previously (5), were excluded from this study. Within remaining 104 cases, AR mutation was reported in 27 cases [10 CAIS (complete androgen insensitivity syndrome), 17 PAIS (partial androgen insensitivity syndrome)]. AR mutation was reported in 90% of clinically classified CAIS cases and in 18.3 of cases clinically classified as PAIS.

  Mean BW-SDS of cases with disorders of androgen action regardless of AR mutation was substantially lower compared to national references for boys and girls (respectively, -0.90±1.5, p=0.001 and -0.58±1.6, p=0.001). The mean BW-SDS of cases with AR mutations was higher than the mean BW-SDS of cases, who were AR mutation-negative (Table 2, p=0.009). Mean BW-SDS of AR mutation-positive cases was not different from the national references for boys and girls, however slightly higher with respect to national references for girls (respectively, -0.36±1.5, p=0.21 compared to boys and -0.01±1.6, p=0.97 compared to girls). Patients, whether CAIS or PAIS, with proven AR mutation had a BW-SDS similar to healthy boys and girls. SGA birth was significantly less frequent in cases with AR mutation-positive cases compared with AR mutation-negative cases (respectively, 14.8% and 40.3%, p=0.018).

- Leydig cell defects: Eight cases with Leydig cell defect were recorded in the registry. No significant difference in BW-SDS was found when compared to normal references for boys (Table 2). SGA birth was detected in only one case.
Nonspecific diagnosis: The group of nonspecific disorder of undermasculinisation in the I-DSD registry is heterogeneous and includes diagnostic groups summarized in Table 1. Interestingly, in this group; the frequency of SGA birth was very high and 12 out of 34 cases (35.3%) were born SGA (Table 2). Mean BW-SDS of patients in this group was significantly lower compared to normal boys (p=0.001). Isolated hypospadias was found in 11 cases of whom 5 were born SGA. Mean BW-SDS of 11 cases with isolated hypospadias was lower than the national references for boys (Table 2, p=0.024).

Concomitant conditions were reported in 108 (27.6%) cases of 46,XY DSD and in 14 (10.5%) cases of 46,XX DSD (Table 3). Concomitant conditions were more frequently recorded in cases born SGA than in patients born appropriate for gestational age (AGA) (Table 3, respectively 25%, 9.5%; p=0.0003). In the disorders of androgen action group, concomitant conditions were found in 31.8% of patients and concomitant conditions were more frequent in the group without an AR mutation than in the AR mutation-positive group (respectively 49.4% and 22.2%; p=0.02).

Discussion

The use of the I-DSD Registry has enabled to explore the relationship between the sexual dimorphism in BW and the role of prenatal androgens in a large cohort of 533 cases with different forms of DSD. Overall, our results demonstrate that the sexual dimorphism in BW cannot be explained by the effects of prenatal androgen action.

BW in both karyotypes in disorders of gonadal development, disorders of androgen synthesis, disorders of androgen excess groups and disorders of androgen action cases with a confirmed AR gene mutation was not different from healthy children with the same karyotype. The disorders of androgen excess group included mainly cases with 21-hydroxylase deficiency and 11β-hydroxylase deficiency. These cases have prolonged exposure to high levels of androgens, during fetal life, which may affect BW. However, BW in cases with androgen excess was similar compared to normal children with the same karyotype suggesting that excess androgen does not increase the BW. Similarly, cases with disorders of gonadal development and disorders of androgen synthesis, in which low fetal concentration of androgens is expected, did not show a decrease in BWs. The BWs in these cases were within the normal reference range for chromosomal sex. In our cohort, despite androgen resistance,
CAIS and PAIS patients with confirmed AR mutations had comparable BWs to unaffected boys with 46,XY karyotype. Although not significantly different from BW SDS in healthy boys, BW-SDS in both CAIS and PAIS is closer to female reference ranges. Considering the normal difference in BW SDS of two genders in normal population this seems reasonable.

The role of prenatal androgen action on BW is not fully understood. It has been reported that 46,XY children with CAIS have a BW comparable to that of girls with 46,XX karyotype and it has been suggested that the difference in BW between girls and boys is attributable to androgens (3). In contrast, another study from the UK and Sweden hypothesized that BWs of patients were independent of androgen exposure during prenatal period as CAIS patients had a BW similar to unaffected boys with 46,XY karyotype (6). In addition, the same study demonstrated no significant effect on the BW in CAH patients, with 46,XX karyotype, a finding which is also confirmed in our study. Subtype data of CAH patients were not available in the present study and we did not evaluate BW according to clinical form of CAH. In the study from UK and Sweden, BW did not vary according to the severity of CAH (6). On the other hand, Balsamo et al. (17) reported increased mean BW only in classical CAH girls born at 39.0±1.1 weeks compared with the national birth data. However, BW in salt-wasting group was lower than simple-virilizing group. In another report longer gestational age was found correlated with the severity of CAH in females which may be another factor affecting BW (18).

A frequency of AR mutation positivity in cases diagnosed as PAIS clinically is reported between 14-22% (5,19,20). Similar to the literature, in disorder of androgen action group in our cohort, AR mutation-positivity was found in 18.3% of clinically diagnosed PAIS cases.

In our total cohort, SGA was present in 15% of cases with a high prevalence of SGA in 46,XY DSD patients, especially in impaired androgen action patients with the absence of a mutation in the AR with and in patients with nonspecific disorders of undermasculinisation. The frequency of SGA birth is generally reported between 4.6-11.7% in Western European countries and 10.1 % in Turkey (8,21). The BWs of AR mutation-positive patients were similar to typical boys, whereas BW of AR mutation-negative patients were significantly lower than AR mutation-positive patients in accordance with previous publications (5,6). Furthermore, the frequency of SGA births in the AR mutation-negative group was markedly high (40.3%) compared to AR mutation-positive cases (14.8%). Similar to our
results, a higher frequency of SGA births was found in AR mutation-negative infants (37%) in comparison to AR mutation-positive infants (6%) (5).

In a recent study from I-DSD consortium, it was reported that genetically confirmed cases of PAIS are more likely to have a worse medical and surgical outcome as young men compared to cases with a similar phenotype at birth but in whom no AR mutation could be detected. Routine genetic analysis of AR in boys suspected of PAIS is recommended to guide long-term prognosis and tailor management (22). At birth, although, clinical phenotype and laboratory tests are not discriminative, BW-SDS adjusted for gestational age could be helpful for considering AR analysis i.e. AR sequencing should specifically be considered in children born AGA. Patients who have no AR mutation may represent a different diagnostic (sub)group. The BWs of AR mutation-positive patients with both CAIS and PAIS were not statistically different from typical boys or girls, whereas BW of AR mutation-negative patients were significantly lower than AR mutation-positive patients in accordance with previous publications (5,6).

Generally, in 46,XY DSD no genetic cause can be determined in around 30–40% of cases (23). Remarkably, around 30% of these cases are related with low BW (24), and about 30% of undetermined 46,XY DSD cases had BW lower than 2,500 g (25). There seems to be a substantial correlation between SGA birth and 46,XY DSD, more specifically with severe undermasculinisation in the presence of an apparently normal testicular function (and action) (2,26-29). Audi et al. (19) reported that in 52 patients without any detected mutation, 11 (21.1%) patients born prematurely and accompanied or not with intrauterine growth retardation had ambiguous genitalia. Low BW and SGA are well-established risk factors for hypospadias and the risk for cryptorchidism and hypospadias increase with decreasing BW independent of gestational age (26,29-31).

The nature of the relationship between genital abnormalities and restricted intrauterine growth is currently not known. However, numerous factors have been hypothesized to play a role including genetic, placental dysfunction and androgen deficiency in early pregnancy and more recently, environmental factors such as diethylstilbestrol, phytoestrogen, phthalates, and pesticides. (2,29-34). Currently, it remains unknown whether there is a causal association or a common pathogenic base. A dysfunctional placenta may provide insufficient nutrients and placental human chorionic gonadotropin
(hCG) to the fetus and lead to growth retardation and hypospadias because placental hCG during the first 14 weeks of gestation controls fetal testosterone synthesis and secretion (29,33,34). At the same time, the fetal masculinization programming window of reproductive tract is accepted to occur between gestational weeks 8–14 in humans (35).

Frequency of concomitant conditions in DSD cases were reported in 37.5% in a German cohort (36) and in 27% in a previous report from the I-DSD Registry (37). In our cohort, similar to the previous two studies, we found a frequency of 23.3% concomitant conditions in 46,XX and 46,XY DSD. Our results confirm that concomitant conditions are frequent in DSD, especially in 46,XY DSD and disorders of gonadal development group, AR negative disorder of androgen action group and nonspecific undermasculinisation group.

In confirming some of the findings in previous studies, the strength of this study is the large number of DSD cases analyzed by BW for gestational age. All data were cross-checked with the individual clinicians in order to minimize registration errors. Furthermore, significant numbers were analyzed across the range of major causes of DSD.

In conclusion, BW dimorphism is unlikely to be dependent on fetal androgen action. Our results agree with previous studies showing that nonspecific disorders of undermasculinisation in 46,XY DSD are associated with fetal growth restriction, SGA birth and concomitant conditions. Although AR mutation-negative cases have similar clinical phenotype and laboratory tests compared to AR mutation-positive cases, they have significantly lower BW, higher SGA birth frequency and higher prevalence of concomitant conditions frequency when compared with AR mutation-positive cases. Placental insufficiency / fetal growth restriction can result in severe undermasculinisation with normal testicular androgen production, thus mimicking PAIS. For the diagnostic clarity of classification of DSD, our results underscore that the diagnosis of PAIS should be reserved only for those cases with a proven AR mutation.
Acknowledgements:

The International Disorder of Sex Development (I-DSD) Registry is supported by a Medical Research Council partnership award G1100236 and National Institute for Health Research Cambridge Comprehensive Biomedical Research Center.
References


27. Boisen KA, Chellakooty M, Schmidt IM, Kai CM, Damgaard IN, Suomi AM, Toppari J, Skakkebaek NE, Main KM. Hypospadias in a cohort of 1072 Danish newborn boys: prevalence and relationship to placental weight, anthropometrical measurements at birth, and reproductive hormone levels at three months of age. J Clin Endocrinol Metab. 2005; 90(7):4041-4046.


### Table 1: Classification of disorders of sex development (DSD) in the International-DSD registry

<table>
<thead>
<tr>
<th>46,XY and 46,XX Disorders of Gonadal development</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complete gonadal dysgenesis,</td>
</tr>
<tr>
<td>• Partial gonadal dysgenesis</td>
</tr>
<tr>
<td>• Gonadal regression</td>
</tr>
<tr>
<td>• Ovotesticular DSD</td>
</tr>
<tr>
<td>• Testicular DSD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>46,XY and 46,XX Disorders of Androgen synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Steroidogenic Acute Regulatory Protein (STAR) deficiency</td>
</tr>
<tr>
<td>• P450 scc deficiency (CYP11A1)</td>
</tr>
<tr>
<td>• 3 beta hydroxysteroid dehydrogenase deficiency</td>
</tr>
<tr>
<td>• CYP 17 deficiency (P450 CYP17)</td>
</tr>
<tr>
<td>• Combined 17 alpha hydroxylase/17,20 lyase deficiency</td>
</tr>
<tr>
<td>• Isolated 17,20 lyase deficiency</td>
</tr>
<tr>
<td>• 17 beta hydroxysteroid dehydrogenase deficiency</td>
</tr>
<tr>
<td>• 5 alpha reductase deficiency (SRD5A2)</td>
</tr>
<tr>
<td>• P450 oxidoreductase deficiency (POR)</td>
</tr>
<tr>
<td>• Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>46,XY Disorders of Androgen action</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Partial androgen insensivity syndrome,</td>
</tr>
<tr>
<td>• Complete androgen insensivity syndrome</td>
</tr>
<tr>
<td>• Others</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>46,XY and 46,XX Disorders of Androgen Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 21 hydroxylase deficiency (CYP21A)</td>
</tr>
<tr>
<td>• 11 beta hydroxylase deficiency (CYP11B1)</td>
</tr>
<tr>
<td>• Aromatase deficiency (CYP19A1)</td>
</tr>
<tr>
<td>• P450 oxidoreductase deficiency (POR)</td>
</tr>
<tr>
<td>• Maternal androgens</td>
</tr>
<tr>
<td>• Others</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>46,XY Nonspecific Disorders of Undermasculinisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Isolated hypospadias,</td>
</tr>
<tr>
<td>• Isolated bilateral cryptorchidism,</td>
</tr>
<tr>
<td>• Isolated micropenis</td>
</tr>
<tr>
<td>• Complex genital anomalies</td>
</tr>
<tr>
<td>• External masculisation score (EMS)≥9, EMS 5-8, EMS&lt;5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>46,XY Leydig Cell Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Leydig cell hypoplasia</td>
</tr>
<tr>
<td>• Luteinising hormone deficiency</td>
</tr>
</tbody>
</table>
Table 2: Birth weight SDS and frequency of small for gestational age (SGA) birth in 46,XX and 46,XY cases according to classification in the International DSD (Disorders of Sex Development) Registry.

<table>
<thead>
<tr>
<th>Disorder type</th>
<th>46,XX (n)</th>
<th>46,XY (n)</th>
<th>Birth Weight SDS [mean±SD (95% CI)]</th>
<th>SGA(n,%)</th>
<th>46,XX</th>
<th>46,XY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonadal Development</td>
<td>12</td>
<td>50</td>
<td>-0.03±0.75 (-0.51 to 0.44)</td>
<td>0.03</td>
<td>0</td>
<td>7(14)</td>
</tr>
<tr>
<td>Androgen Synthesis</td>
<td>10</td>
<td>70</td>
<td>-0.01±0.5 (-0.37 to 0.34)</td>
<td>0.93</td>
<td>0</td>
<td>7(10)</td>
</tr>
<tr>
<td>Androgen Excess</td>
<td>111</td>
<td>59</td>
<td>-0.08±1.15 (-0.29 to 0.13)</td>
<td>0.46</td>
<td>0</td>
<td>9(8.1)</td>
</tr>
<tr>
<td>Androgen Action</td>
<td>-</td>
<td>170</td>
<td></td>
<td></td>
<td>-</td>
<td>40(22.9)</td>
</tr>
<tr>
<td>AR mutation- positive</td>
<td>27</td>
<td>77</td>
<td>-0.90±1.53 (-1.17 to 0.71)</td>
<td>0.001</td>
<td>-</td>
<td>4(14.8)****</td>
</tr>
<tr>
<td>AR mutation- negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31(40.3)****</td>
</tr>
<tr>
<td>Nonspecific Disorder of Undermasculinisation Isolated hypospadias</td>
<td>-</td>
<td>34</td>
<td>-1.31±1.45 (-1.81 to -0.80)</td>
<td>0.001</td>
<td>-</td>
<td>12(35.3)</td>
</tr>
<tr>
<td>Leydig Cell Defects</td>
<td>-</td>
<td>8</td>
<td>-0.68±1.61 (-2.02 to 0.66)</td>
<td>0.27</td>
<td>-</td>
<td>1(12.5)</td>
</tr>
</tbody>
</table>

* One sample t test: comparison mean birth weight SDS of 46,XX cases to the population average value for girls (birth weight SDS=0).
** One sample t test: comparison mean birth weight SDS of 46,XY cases to the population average value for boys (birth weight SDS=0).
*** Comparison of BW-SDS of AR mutation positive and negative groups p=0.009
**** Comparison of SGA frequency between AR mutation positive and negative groups p=0.018
Table 3. Number of concomitant conditions in I-DSD (International Disorders of Sex Development) Registry.

<table>
<thead>
<tr>
<th>Disorder Type</th>
<th>46,XX (n)</th>
<th>46,XY (n)</th>
<th>Number of Cases with Concomitant Conditions (n)</th>
<th>Number of AGA Born Cases with Concomitant Conditions (n)</th>
<th>Number of SGA Born Cases with Concomitant Conditions (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>46,XX</td>
<td>46,XY</td>
<td>46,XX</td>
<td>46,XY</td>
<td>46,XX</td>
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<tr>
<td>Gonadal Development</td>
<td>12</td>
<td>50</td>
<td>2</td>
<td>23</td>
<td>2</td>
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<tr>
<td>Androgen Synthesis</td>
<td>10</td>
<td>70</td>
<td>2</td>
<td>9</td>
<td>2</td>
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<tr>
<td>Androgen Excess</td>
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<td>59</td>
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<td>6</td>
<td>1</td>
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<tr>
<td>Androgen Action</td>
<td>-</td>
<td>170</td>
<td>-</td>
<td>54</td>
<td>-</td>
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<tr>
<td>AR mutation-positive</td>
<td>-</td>
<td>27</td>
<td>-</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>AR mutation-negative</td>
<td>-</td>
<td>77</td>
<td>-</td>
<td>38</td>
<td>-</td>
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<tr>
<td>Nonspecific Disorder of Undermasculinisation</td>
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<td>34</td>
<td>-</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>Isolated hypospadias</td>
<td>-</td>
<td>11</td>
<td>-</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Leydig Cell Defects</td>
<td>-</td>
<td>8</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

SGA: small for gestational age, AGA: appropriate for gestational age
Figure 1: Number of cases according to I-DSD (International Disorders of Sex Development) registry groups in 46,XY and 46,XX karyotype

533 cases with gestational ages

46,XX
133 cases

46,XY
400 cases

Disorders of gonadal development
50 46,XY cases
12 46, XX cases

- CGD(n=24)
- PGD(n=13)
- Gonadal regression(n=11)
- Ovotesticular DSD(n=9)
- Testicular DSD(n=5)

Disorders of androgen synthesis
70 46,XY cases
10 46,XX cases

- STAR deficiency(n=5)
- 3BHSD(n=4)
- Isolated 17,20 LD(n=1)
- 17BHSD(n=13)
- C17BHSD/17,20 LD(n=2)
- SRD5A2(n=24)
- CYP17D(n=7)
- Other(n=22)
- POR(n=2)

Disorders of androgen excess
59 46,XY cases
111 46,XX cases

- 21HD(n=147)
- 11BHD(n=23)

Disorders of androgen action
179 46,XY cases

- CAIS(n=39)
- PAIS(n=140)

Non-specific disorders of undermasculinisation
34 46,XY cases

- CGA(n=7)
- Isolated hypospadias(n=11)
- Isolated micropenis(n=2)
- Isolated bilateral cryptorchidism(n=1)
- EMS≥9 (n=3)
- EMS5-8(n=6)
- EMS<5(n=4)

Leydig cell defect
8 46,XY cases

- LCH(n=8)

3BHSD:3 beta hydroxysteroid dehydrogenase deficiency, 17BHSD:17 beta hydroxysteroid dehydrogenase deficiency, 11BHD:11 beta hydroxylase deficiency

Figure 2. The number of patients in disorders of androgen action group with respect to androgen receptor (AR) mutation.

179 cases of disorders of androgen action

170 patients birth weight SDS evaluated

Results of 9 patients reported previously (5) were excluded

66 patients were not screened for AR mutation

27 patients AR mutation-positive

77 patient AR mutation-negative

10 CAIS, 17 PAIS

1 CAIS, 76 PAIS phenotype

CAIS: Complete androgen insensitivity syndrome, PAIS: Partial androgen insensitivity syndrome