



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/114461/>

Version: Accepted Version

---

**Article:**

Poyrazoglu, S., Darendeliler, F., Ahmed, S.F. et al. (2017) Birth weight in different etiologies of disorders of sex development. *Journal of Clinical Endocrinology and Metabolism*, 102 (3). pp. 1044-1050. ISSN: 0021-972X

<https://doi.org/10.1210/jc.2016-3460>

---

**Reuse**

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.

1                   **BIRTH WEIGHT IN DIFFERENT ETIOLOGIES OF DISORDERS OF SEX**  
2                   **DEVELOPMENT**

3           Poyrazoglu S<sup>1</sup>, Darendeliler F<sup>1</sup>, Ahmed SF<sup>2</sup>, Hughes IA<sup>3</sup>, Bryce J<sup>2</sup>, Jiang J<sup>2</sup>, Rodie M<sup>2</sup>, Hiort O<sup>4</sup>,  
4           Hannema SE<sup>5,6</sup>, Bertelloni S<sup>7</sup>, Lisa L<sup>8</sup>, Guran T<sup>9</sup>, Cools M<sup>10</sup>, Desloovere A<sup>10</sup>, Claahsen-van der  
5           Grinten HL<sup>11</sup>, Nordenstrom A<sup>12</sup>, Holterhus PM<sup>13</sup>, Köhler B<sup>14</sup>, Niedziela M<sup>15</sup>, Krone N<sup>16,17</sup>

6           <sup>1</sup>Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

7           <sup>2</sup>University of Glasgow, Glasgow, United Kingdom

8           <sup>3</sup>University of Cambridge, Cambridge, United Kingdom

9           <sup>4</sup> Division of Pediatric Endocrinology and Diabetes, University of Luebeck, Luebeck, Germany

10          <sup>5</sup> Sophia Children's Hospital, Erasmus Medical Centre, Rotterdam, The Netherlands

11          <sup>6</sup>Leiden University Medical Center, Leiden, The Netherlands

12          <sup>7</sup> Adolescent Medicine, Pediatric Division, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

13          <sup>8</sup> Institute of Endocrinology, Prague, Czech Republic

14          <sup>9</sup>Marmara University, Istanbul, Turkey

15          <sup>10</sup> University Hospital Ghent, Ghent University, Ghent, Belgium

16          <sup>11</sup> Radboudumc Amalia Children's Hospital, Radboud University Medical Center, Nijmegen, The  
17          Netherlands

18          <sup>12</sup> Karolinska University Hospital, Stockholm, Sweden

19          <sup>13</sup> University Hospital Schleswig-Holstein, Kiel, Germany

20          <sup>14</sup> University Children's Hospital, Charite, Humboldt University, Berlin, Germany

21          <sup>15</sup> Poznan University of Medical Sciences, Department of Pediatric Endocrinology and Rheumatology,  
22          Poznan, Poland

1 <sup>16</sup> Birmingham Children's Hospital, Birmingham, United Kingdom

2 <sup>17</sup> Academic Unit of Child Health, University of Sheffield, United Kingdom

3

4 **Abbreviated Title:** Birth weight in disorders of sex development

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

6 **Word count:**2611

7 **Number of figures and tables:** 5

8 **Corresponding author and person to whom reprint requests should be addressed:**

9 Feyza Darendeliler

10 İstanbul Tıp Fakültesi, Çocuk Kliniği

11 Çapa 34390 İstanbul, TURKEY

12 Tel: Work: +90 212 414 20 00

13 Fax: +90 212 533 13 83

14 E-mail: feyzad@istanbul.edu.tr

15 **Disclosure Statement:** The authors have nothing to disclose

16 **Funding information:** Funding information is not available

17

18

19

20

21

22

23

24

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27

## 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](http://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.

1 It is well known that birth weight (BW) in boys is higher than in girls in the general  
2 population. Difference in BW between sexes is reported in human as well as non-human primate  
3 species (1). Although the cause of BW difference is still unknown, it has been proposed that the Y  
4 chromosome and prenatal androgen action may play a role (2,3).

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

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

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

### 13 **Patients and Methods**

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

27 In the I-DSD groups, BW-SDS was evaluated according to karyotype. In disorders of  
28 androgen action group, BW-SDS was also evaluated with respect to the presence or absence of an

1 androgen receptor gene (*AR*) mutation. We evaluated concomitant conditions in DSD cases and the  
2 relationship of SGA with other concomitant conditions. We excluded known DSD syndromic  
3 conditions and anomalies that are acquired as the consequences of the management of the disorders  
4 like short stature in congenital adrenal hyperplasia (CAH).

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

## 10 **Results**

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

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

- 18 • In disorders of gonadal development group: 12 cases (19.4%) were 46,XX and 50 cases  
19 (80.6%) were 46,XY (Table 2). None of 46,XX cases were born SGA, whereas 14% (n=7)  
20 of cases with 46,XY karyotype were born SGA. Mean BW-SDS of cases with 46,XX was  
21 similar to the national references for girls ( $p=0.87$ ). Although not statistically significant,  
22 mean BW-SDS of fifty 46,XY cases showed a lower trend compared with the national  
23 references for boys ( $p=0.056$ ). However after excluding SGA cases, mean BW-SDS of  
24 46,XY cases was not different from national references for boys (mean BW-SDS: -  
25  $0.1 \pm 0.9$ ,  $p=0.31$ ).
- 26 • Androgen synthesis disorders: Eighty cases had a disorder of androgen synthesis; 10  
27 (12.5%) of these cases were 46,XX, and 70(87.5%) were 46,XY. Mean BW-SDS of both  
28 46,XX and 46,XY cases were normal for girls and boys, compared with the national

1 references (Table 2,  $p=0.93$ ,  $p=0.17$  respectively). Only 7 (10%) cases with 46,XY were  
2 born SGA (Table 2).

- 3 • Androgen excess disorders: In the 170 cases of disorders of androgen excess group, the  
4 mean BW-SDS of 111 cases with 46,XX were not different when compared to the national  
5 references for girls (Table 2,  $p=0.46$ ). Similarly, the BW-SDS of 59 cases with 46,XY  
6 karyotype was not different either compared to the national references for boys (Table 2,  
7  $p=0.37$ ). Frequency of cases born SGA was 8.1% in 46,XX and 6.8% in 46,XY karyotype.
- 8 • Androgen action disorders: Of the 179 cases classified as having disorders of androgen  
9 action, 113 patients were screened for *AR* mutations (Figure 2). Results of 9 patients (1 *AR*  
10 mutation-positive, 8 *AR* mutation-negative) reported previously (5), were excluded from  
11 this study. Within remaining 104 cases, *AR* mutation was reported in 27 cases [10 CAIS  
12 (complete androgen insensitivity syndrome), 17 PAIS (partial androgen insensitivity  
13 syndrome)]. *AR* mutation was reported in 90% of clinically classified CAIS cases and in  
14 18.3 of cases clinically classified as PAIS.

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

- 26 • Leydig cell defects: Eight cases with Leydig cell defect were recorded in the registry. No  
27 significant difference in BW-SDS was found when compared to normal references for  
28 boys (Table 2). SGA birth was detected in only one case.

- 1           • Nonspecific diagnosis: The group of nonspecific disorder of undermasculinisation in the I-  
2           DSD registry is heterogeneous and includes diagnostic groups summarized in Table1.  
3           Interestingly, in this group; the frequency of SGA birth was very high and 12 out of 34  
4           cases (35.3%) were born SGA (Table 2). Mean BW-SDS of patients in this group was  
5           significantly lower compared to normal boys ( $p=0.001$ ). Isolated hypospadias was found  
6           in 11 cases of whom 5 were born SGA. Mean BW-SDS of 11 cases with isolated  
7           hypospadias was lower than the national references for boys (Table 2,  $p=0.024$ ).

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

#### 14           **Discussion**

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

19          BW in both karyotypes in disorders of gonadal development, disorders of androgen synthesis,  
20          disorders of androgen excess groups and disorders of androgen action cases with a confirmed *AR* gene  
21          mutation was not different from healthy children with the same karyotype. The disorders of androgen  
22          excess group included mainly cases with 21-hydroxylase deficiency and 11 $\beta$ -hydroxylase deficiency.  
23          These cases have prolonged exposure to high levels of androgens, during fetal life, which may affect  
24          BW. However, BW in cases with androgen excess was similar compared to normal children with the  
25          same karyotype suggesting that excess androgen does not increase the BW. Similarly, cases with  
26          disorders of gonadal development and disorders of androgen synthesis, in which low fetal  
27          concentration of androgens is expected, did not show a decrease in BWs. The BWs in these cases were  
28          within the normal reference range for chromosomal sex. In our cohort, despite androgen resistance,

1 CAIS and PAIS patients with confirmed *AR* mutations had comparable BWs to unaffected boys with  
2 46,XY karyotype. Although not significantly different from BW SDS in healthy boys, BW-SDS in  
3 both CAIS and PAIS is closer to female reference ranges. Considering the normal difference in BW  
4 SDS of two genders in normal population this seems reasonable.

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

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

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

1 results, a higher frequency of SGA births was found in *AR* mutation-negative infants (37%) in  
2 comparison to *AR* mutation-positive infants (6%) (5).

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

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

23 The nature of the relationship between genital abnormalities and restricted intrauterine growth  
24 is currently not known. However, numerous factors have been hypothesized to play a role including  
25 genetic, placental dysfunction and androgen deficiency in early pregnancy and more recently,  
26 environmental factors such as diethylstilbestrol, phytoestrogen, phthalates, and pesticides. (2,29-34).  
27 Currently, it remains unknown whether there is a causal association or a common pathogenic base. A  
28 dysfunctional placenta may provide insufficient nutrients and placental human chorionic gonadotropin

1 (hCG) to the fetus and lead to growth retardation and hypospadias because placental hCG during the  
2 first 14 weeks of gestation controls fetal testosterone synthesis and secretion (29,33,34). At the same  
3 time, the fetal masculinization programming window of reproductive tract is accepted to occur  
4 between gestational weeks 8–14 in humans (35).

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

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

15 In conclusion, BW dimorphism is unlikely to be dependent on fetal androgen action. Our  
16 results agree with previous studies showing that nonspecific disorders of undermasculinisation in  
17 46,XY DSD are associated with fetal growth restriction, SGA birth and concomitant conditions.  
18 Although *AR* mutation-negative cases have similar clinical phenotype and laboratory tests compared to  
19 *AR* mutation-positive cases, they have significantly lower BW, higher SGA birth frequency and higher  
20 prevalence of concomitant conditions frequency when compared with *AR* mutation-positive cases.  
21 Placental insufficiency / fetal growth restriction can result in severe undermasculinisation with normal  
22 testicular androgen production, thus mimicking PAIS. For the diagnostic clarity of classification of  
23 DSD, our results underscore that the diagnosis of PAIS should be reserved only for those cases with a  
24 proven *AR* mutation.

25  
26  
27  
28

1 **Acknowledgements:**

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

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

## 1 **References**

- 2 1. Smith RJ, Leigh SR. Sexual dimorphism in primate neonatal body mass. *J Hum Evol.*  
3 1998;34:173–201.
- 4 2. Hughes IA, Northstone K, Golding J. the ALSPAC Study Team. Reduced birth weight in boys  
5 with hypospadias: an index of androgen dysfunction? *Arch Dis Child Fetal Neonatal Ed.*  
6 2002; 87:150–151.
- 7 3. de Zegher F, Francois I, Boehmer AL, Saggese G, Muller J, Hiort O, Sultan C, Clayton P,  
8 Brauner R, Cacciari E, Ibanez L, Van Vliet G, Tiulpakov A, Saka N, Ritzen M, Sippell WG.  
9 Androgens and fetal growth. *Horm Res.* 1998;50(4):243-244.
- 10 4. de Zegher F, Devlieger H, Eeckels R. Fetal growth: boys before girls. *Horm Res.* 1999;  
11 51:258–259.
- 12 5. Lek N, Miles H, Bunch T, Pilfold-Wilkie V, Tadokoro-Cuccaro R, Davies J, Ong KK, Hughes  
13 IA. Low frequency of androgen receptor gene mutations in 46 XY DSD, and fetal growth  
14 restriction. *Arch Dis Child.* 2014; 99(4):358-361.
- 15 6. Miles HL, Gidlof S, Nordenstrom A, Ong KK, Hughes IA. The role of androgens in fetal  
16 growth: observational study in two genetic models of disordered androgen signalling. *Arch*  
17 *Dis Child Fetal Neonatal Ed.* 2010; 95(6):435-438.
- 18 7. Bukowski R, Smith GC, Malone FD, Ball RH, Nyberg DA, Comstock CH, Hankins GD,  
19 Berkowitz RL, Gross SJ, Dugoff L, Craigo SD, Timor-Tritsch IE, Carr SR, Wolfe HM,  
20 D'Alton ME; FASTER Research Consortium. Human sexual size dimorphism in early  
21 pregnancy. *Am J Epidemiol.* 2007; 165(10):1216-1218.
- 22 8. Kurtoglu S, Hatipoglu N, Mazicioglu MM, Akin MA, Coban D, Gokoglu S, Bastug O. Body  
23 weight, length and head circumference at birth in a cohort of Turkish newborns. *J Clin Res*  
24 *Pediatr Endocrinol.* 2012; 4(3):132-139.
- 25 9. Bertino E, Spada E, Occhi L, Coscia A, Giuliani F, Gagliardi L, Gilli G, Bona G, Fabris C, De  
26 Curtis M, Milani S. Neonatal anthropometric charts: the Italian neonatal study compared with  
27 other European studies. *J Pediatr Gastroenterol Nutr.* 2010; 51(3):353-361.

- 1 10. Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA. Cross sectional stature and  
2 weight reference curves for the UK, 1990. *Arch Dis Child*. 1995; 73(1):17-24.
- 3 11. Malewski Z, Słomko Z, Klejewski A. Relacja wieku ciążowego i masy urodzeniowej  
4 noworodków z regionu Wielkopolski (Relationship between gestation age and birth weight  
5 from Poznan region). *Klin Perinat Ginek*. 1995; 12((2): 734-741.
- 6 12. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the  
7 Swedish reference standards for weight, length and head circumference at birth for given  
8 gestational age (1977-1981). *Acta Paediatr Scand*. 1991; 80(8-9):756-762.
- 9 13. Voigt M, Fusch C, Olbertz D, Schneider KT. Analysis of the Neonatal Collective in the Federal  
10 Republic of Germany 12th: Presentation of detailed percentiles for the body measurement of  
11 newborns. *Geburtsh Frauenheilk*. 2006; 66:956-970.
- 12 14. Gerver WJ, de Bruin R. *Paediatrics Morphometrics*. Wetenschappelijke uitgeverij Bunje  
13 Utrecht, The Netherlands, 1996.
- 14 15. Bocca-Tjeertes IF, van Buuren S, Bos AF, Kerstjens JM, Ten Vergert EM, Reijneveld SA.  
15 Growth of preterm and full-term children aged 0-4 years: integrating median growth and  
16 variability in growth charts. *J Pediatr*. 2012; 161(3):460-465.
- 17 16. Blaha P, Vignerova J, Riedlova J, Kobrova J, Krejcovsky L, Brabec M. The 6th National-wide  
18 Anthropological Survey 2001, Czech Republic. Basic body parameters 0-19 years, percentile  
19 charts 0-18 years, head parameters of children 0-6 years. *Szatní zdravotní ustav (National*  
20 *Institute of Health) Praha (Prague)*, 2005.
- 21 17. Balsamo A, Wasniewska M, Di Pasquale G, Salzano G, Baronio F, Bombaci S, De Luca F.  
22 Birth length and weight in congenital adrenal hyperplasia according to the different  
23 phenotypes. *Eur J Pediatr*. 2006; 165(6):380-383.
- 24 18. Gidlof S, Wedell A, Nordenstrom A. Gestational age correlates to genotype in girls with  
25 CYP21 deficiency. *J Clin Endocrinol Metab*. 2007; 92(1):246-249.
- 26 19. Audi L, Fernandez-Cancio M, Carrascosa A, Andaluz P, Toran N, Piro C, Vilaro E, Vicens-  
27 Calvet E, Gussinyé M, Albisu MA, Yeste D, Clemente M, Hernandez de la Calle I, Del  
28 Campo M, Vendrell T, Blanco A, Martinez-Mora J, Granada ML, Salinas I, Forn J, Calaf J,

- 1 Angerri O, Martínez-Sopena MJ, Del Valle J, García E, Gracia-Bouthelier R, Lapunzina P,  
2 Mayayo E, Labarta JI, Lledo G, Sanchez Del Pozo J, Arroyo J, Perez-Aytes A, Beneyto M,  
3 Segura A, Borrás V, Gabau E, Caimari M, Rodríguez A, Martínez-Aedo MJ, Carrera M,  
4 Castano L, Andrade M, Bermudez de la Vega JA; Grupo de Apoyo al Síndrome de  
5 Insensibilidad a los Andrógenos (GrApSIA). Novel (60%) and recurrent (40%) androgen  
6 receptor gene mutations in a series of 59 patients with a 46,XY disorder of sex development. *J*  
7 *Clin Endocrinol Metab.* 2010; 95(4):1876-1888.
- 8 20. Jeske YW, McGown IN, Cowley DM, Oley C, Thomsett MJ, Choong CS, Cotterill AM.  
9 Androgen receptor genotyping in a large Australasian cohort with androgen insensitivity  
10 syndrome; identification of four novel mutations. *J Pediatr Endocrinol Metab.* 2007;  
11 20(8):893-908.
- 12 21. Ruiz M, Goldblatt P, Morrison J, Kukla L, Svancara J, Riitta-Jarvelin M, Taanila A, Saurel-  
13 Cubizolles MJ, Lioret S, Bakoula C, Veltsista A, Porta D, Forastiere F, van Eijsden M,  
14 Vrijkotte TG, Eggesbo M, White RA, Barros H, Correia S, Vrijheid M, Torrent M, Rebagliato  
15 M, Larranaga I, Ludvigsson J, Olsen Faresjö A, Hryhorczuk D, Antipkin Y, Marmot M,  
16 Pikhart H. Mother's education and the risk of preterm and small for gestational age birth: a  
17 DRIVERS meta-analysis of 12 European cohorts. *J Epidemiol Community Health.* 2015;  
18 69(9):826-833.
- 19 22. Lucas-Herald A, Bertelloni S, Juul A, Bryce J, Jiang J, Rodie M, Sinnott R, Boroujerdi M,  
20 Lindhardt-Johansen M, Hiort O, Holterhus PM, Cools M, Guaragna-Filho G, Guerra-Junior G,  
21 Weintrob N, Hannema S, Drop S, Guran T, Darendeliler F, Nordenstrom A, Hughes IA,  
22 Acerini C, Tadokoro-Cuccaro R, Ahmed SF. The Long Term Outcome of Boys with Partial  
23 Androgen Insensitivity Syndrome and A Mutation In The Androgen Receptor Gene. *J Clin*  
24 *Endocrinol Metab.* 2016 12:jc20161372. [Epub ahead of print] PubMed PMID: 27403927.
- 25 23. Mendonca BB, Domenice S, Arnhold IP, Costa EM. 46,XY disorders of sex development  
26 (DSD), *Clin Endocrinol(Oxf).* 2009; 70(2): 173–187.
- 27 24. Morel Y, Rey R, Teinturier C, Nicolino M, Michel-Calemard L, Mowszowicz I, Jaubert F,  
28 Fellous M, Chaussain JL, Chatelain P, David M, Nihoul-Fekete C, Forest MG, Josso N.

- 1 Aetiological diagnosis of male sex ambiguity: a collaborative study. *Eur J Pediatr.* 2002;  
2 161(1):49-59.
- 3 25. Veiga-Junior NN, Medaets PA, Petroli RJ, Calais FL, de Mello MP, Castro CC, Guaragna-  
4 Filho G, Sewaybricker LE, Marques-de-Faria AP, Maciel-Guerra AT, Guerra-Junior G.  
5 Clinical and Laboratorial Features That May Differentiate 46,XY DSD due to Partial  
6 Androgen Insensitivity and 5 $\alpha$ -Reductase Type 2 Deficiency. *Int J Endocrinol.*  
7 2012;2012:964876. doi: 10.1155/2012/964876.
- 8 26. Hussain N, Chaghtai A, Herndon CD, Herson VC, Rosenkrantz TS, McKenna PH  
9 Hypospadias and early gestation growth restriction in infants. *Pediatrics*, 2002; 109:473–478.
- 10 27. Boisen KA, Chellakooty M, Schmidt IM, Kai CM, Damgaard IN, Suomi AM, Toppari J,  
11 Skakkebaek NE, Main KM. Hypospadias in a cohort of 1072 Danish newborn boys:  
12 prevalence and relationship to placental weight, anthropometrical measurements at birth, and  
13 reproductive hormone levels at three months of age. *J Clin Endocrinol Metab.* 2005;  
14 90(7):4041-4046.
- 15 28. Yinon Y, Kingdom JC, Proctor LK, Kelly EN, Salle JL, Wherrett D, Keating S, Nevo O,  
16 Chitayat D. Hypospadias in males with intrauterine growth restriction due to placental  
17 insufficiency: the placental role in the embryogenesis of male external genitalia. *Am J Med*  
18 *Genet A.* 2010; 152(1):75-83.
- 19 29. Fujimoto T, Suwa T, Kabe K, Adachi T, Nakabayashi M, Amamiya T. Placental insufficiency  
20 in early gestation is associated with hypospadias. *J Pediatr Surg.* 2008; 43(2):358-361.
- 21 30. Weidner IS, Moller H, Jensen TK, Skakkebaek NE. Risk factors for cryptorchidism and  
22 hypospadias. *J Urol.* 1999; 161(5):1606-1609.
- 23 31. Akre O, Lipworth L, Cnattingius S, Sparen P, Ekblom A. Risk factor patterns for  
24 cryptorchidism and hypospadias. *Epidemiology.* 1999; 10(4):364-369.
- 25 32. Brouwers MM, Feitz WF, Roelofs LA, Kiemeny LA, de Gier RP, Roeleveld N. Risk factors  
26 for hypospadias. *Eur J Pediatr.* 2007; 166(7):671-678.
- 27 33. Baskin LS. Hypospadias and urethral development. *J Urol.* 2000; 163(3):951-956.

- 1 34. Kalfa N, Philibert P, Sultan C. Is hypospadias a genetic, endocrine or environmental disease,  
2 or still an unexplained malformation? *Int J Androl.* 2009; 32(3):187-197.
- 3 35. Welsh M, Suzuki H, Yamada G. The masculinization programming window. *Endocr Dev.*  
4 2014; 27:17-27.
- 5 36. Thyen U, Lanz K, Holterhus PM, Hiort O. Epidemiology and initial management of  
6 ambiguous genitalia at birth in Germany. *Horm Res.* 2006; 66(4):195-203.
- 7 37. Cox K, Bryce J, Jiang J, Rodie M, Sinnott R, Alkhawari M, Arlt W, Audi L, Balsamo A,  
8 Bertelloni S, Cools M, Darendeliler F, Drop S, Ellaithi M, Guran T, Hiort O, Holterhus PM,  
9 Hughes I, Krone N, Lisa L, Morel Y, Soder O, Wieacker P, Ahmed SF. Novel associations in  
10 disorders of sex development: findings from the I-DSD Registry. *J Clin Endocrinol Metab.*  
11 2014; 99(2):348-355.
- 12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28

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

<p>46,XY and 46,XX Disorders of Gonadal development</p> <ul style="list-style-type: none"> <li>• Complete gonadal dysgenesis,</li> <li>• Partial gonadal dysgenesis</li> <li>• Gonadal regression</li> <li>• Ovotesticular DSD</li> <li>• Testicular DSD</li> </ul>
<p>46,XY and 46,XX Disorders of Androgen synthesis</p> <ul style="list-style-type: none"> <li>• Steroidogenic Acute Regulatory Protein (STAR) deficiency</li> <li>• P450 scc deficiency (CYP11A1)</li> <li>• 3 beta hydroxysteroid dehydrogenase deficiency</li> <li>• CYP 17 deficiency (P450 CYP17)</li> <li>• Combined 17 alpha hydroxylase/17,20 lyase deficiency</li> <li>• Isolated 17,20 lyase deficiency</li> <li>• 17 beta hydroxysteroid dehydrogenase deficiency</li> <li>• 5 alpha reductase deficiency (SRD5A2)</li> <li>• P450 oxidoreductase deficiency (POR)</li> <li>• Other</li> </ul>
<p>46,XY Disorders of Androgen action</p> <ul style="list-style-type: none"> <li>• Partial androgen insensitivity syndrome,</li> <li>• Complete androgen insensitivity syndrome</li> <li>• Others</li> </ul>
<p>46,XY and 46,XX Disorders of Androgen Excess</p> <ul style="list-style-type: none"> <li>• 21 hydroxylase deficiency (CYP21A)</li> <li>• 11 beta hydroxylase deficiency (CYP11B1)</li> <li>• Aromatase deficiency (CYP19A1)</li> <li>• P450 oxidoreductase deficiency (POR)</li> <li>• Maternal androgens</li> <li>• Others</li> </ul>
<p>46,XY Nonspecific Disorders of Undermasculinisation</p> <ul style="list-style-type: none"> <li>• Isolated hypospadias,</li> <li>• Isolated bilateral cryptorchidism,</li> <li>• Isolated micropenis</li> <li>• Complex genital anomalies</li> <li>• External masculinisation score (EMS)<math>\geq</math>9, EMS 5-8, EMS<math>&lt;</math>5</li> </ul>
<p>46,XY Leydig Cell Defects</p> <ul style="list-style-type: none"> <li>• Leydig cell hypoplasia</li> <li>• Luteinising hormone deficiency</li> </ul>

2

3

4

5

6

1

2

3

4

5

6

1

2 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  
3 DSD (Disorders of Sex Development) Registry.

Disorder type	46,XX (n)	46,XY (n)	Birth Weight SDS [mean±SD (95% CI)]				SGA(n,%)	
			46,XX	*p	46,XY	**p	46,XX	46,XY
Gonadal Development	12	50	-0.03±0.75 (-0.51 to 0.44)	0.87	-0.29±1.07 (-0.60 to 0.05)	0.056	0	7(14)
Androgen Synthesis	10	70	-0.01±0.5 (-0.37 to 0.34)	0.93	-0.16±1.0 (-0.40 to 0.07)	0.17	0	7(10)
Androgen Excess	111	59	-0.08±1.15 (-0.29 to 0.13)	0.46	-0.14±1.14 (-0.48 to 0.16)	0.37	9(8.1)	4(6.8)
Androgen Action	-	170	-	-	-0.90±1.53 (-1.17 to 0.71)	0.001	-	40(22.9)
<i>AR</i> mutation- positive		27	-	-	-0.36±1.51***	0.21	-	4(14.8)****
<i>AR</i> mutation- negative		77	-	-	-1.38±1.75***	0.001	-	31(40.3)****
Nonspecific Disorder of Undermasculinisation	-	34	-	-	-1.31±1.45 (-1.81 to -0.80)	0.001	-	12(35.3)
Isolated hypospadias		11	-	-	-1.48±1.84	0.024	-	5(45.5)
Leydig Cell Defects	-	8	-	-	-0.68±1.61 (-2.02 to 0.66)	0.27	-	1(12.5)

4

\* One sample t test:comparison mean birth weight SDS of 46,XX cases to the population average value for girls (birth weight SDS=0).

5

\*\*One sample t test:comparison mean birth weight SDS of 46,XY cases to the population average value for boys (birth weight SDS=0).

6

\*\*\* Comparison of BW-SDS of *AR* mutation positive and negative groups p=0.009

7

\*\*\*\* Comparison of SGA frequency between *AR* mutation positive and negative groups p=0.018

1  
2 Table 3. Number of concomitant conditions in I-DSD (International Disorders of Sex Development) Registry.

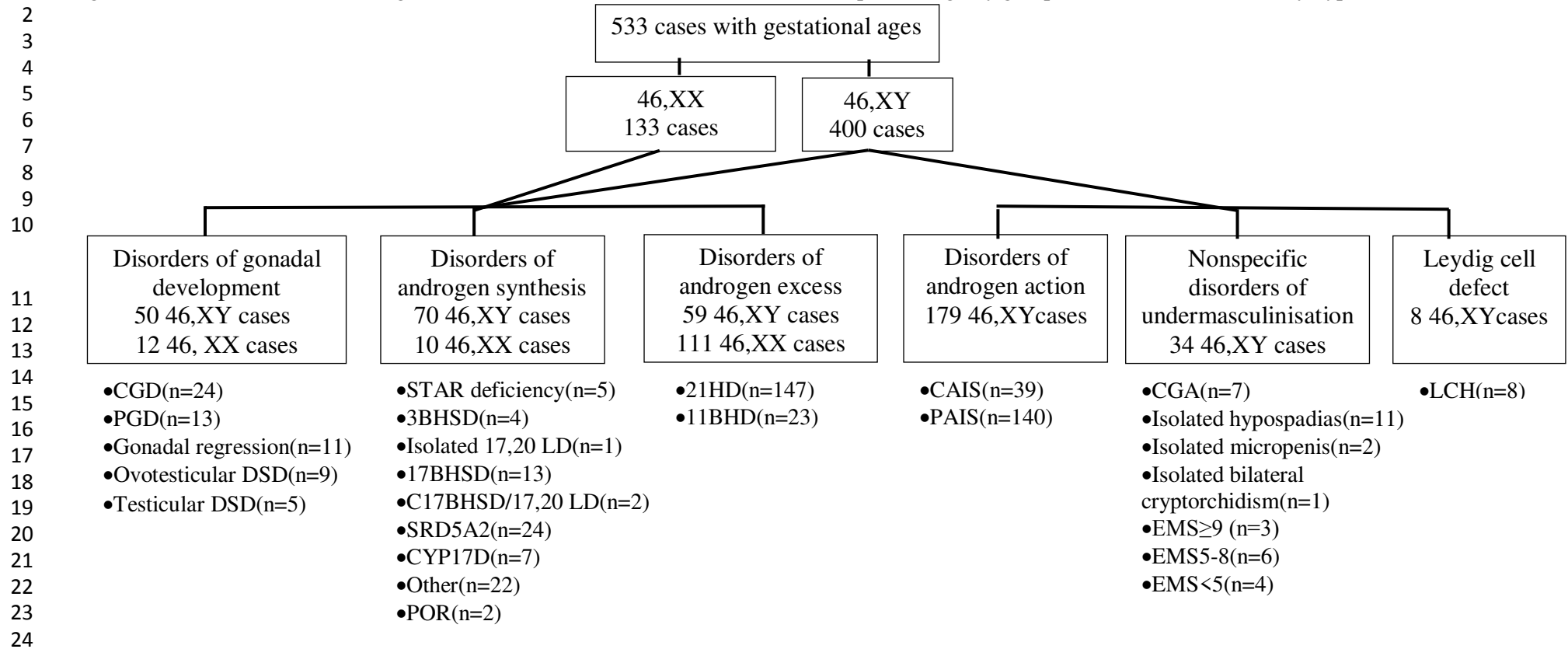
Disorder Type	46,XX (n)	46,XY (n)	Number of Cases with Concomitant Conditions (n)		Number of AGA Born Cases with Concomitant Conditions (n)		Number of SGA Born Cases with Concomitant Conditions (n)	
			46,XX	46,XY	46,XX	46,XY	46,XX	46,XY
Gonadal Development	12	50	2	23	2	16	0	6
Androgen Synthesis	10	70	2	9	2	2	0	0
Androgen Excess	111	59	10	6	1	2	0	1
Androgen Action	-	170	-	54	-	14	-	8
<i>AR</i> mutation-positive	-	27	-	6	-	2	-	1
<i>AR</i> mutation-negative	-	77	-	38	-	7	-	6
Nonspecific Disorder of Undermasculinisation	-	34	-	15	-	3	-	5
Isolated hypospadias	-	11	-	7	-	2	-	2
Leydig Cell Defects	-	8	-	1	-	-	-	-

3 SGA:small for gestational age, AGA:appropriate for gestational age

4

5

Figure 1: Number of cases according to I-DSD (International Disorders of Sex Development) registry groups in 46,XY and 46,XX karyotype



25 3BHSD:3 beta hydroxysteroid dehydrogenase deficiency, 17BHSD:17 beta hydroxysteroid dehydrogenase deficiency, 11BHD:11 beta hydroxylase deficiency

26 CAIS:Complete androgen insensitivity syndrome, C17BHSD/17,20 LD:Combined 17 alpha hydroxylase/17,20 lyase deficiency, CGD:Complete gonadal

27 dysgenesis, CYP17D:CYP 17 deficiency, CGA:Complex genital anomalies EMS:External masculinisation score, 21HD:21 hydroxylase deficiency,

28 LCH:Leydig cell hypoplasia, LD:lyase deficiency, PAIS:Partial androgen insensitivity syndrome, PGD:Partial gonadal dysgenesis, POR:P450 oxidoreductase

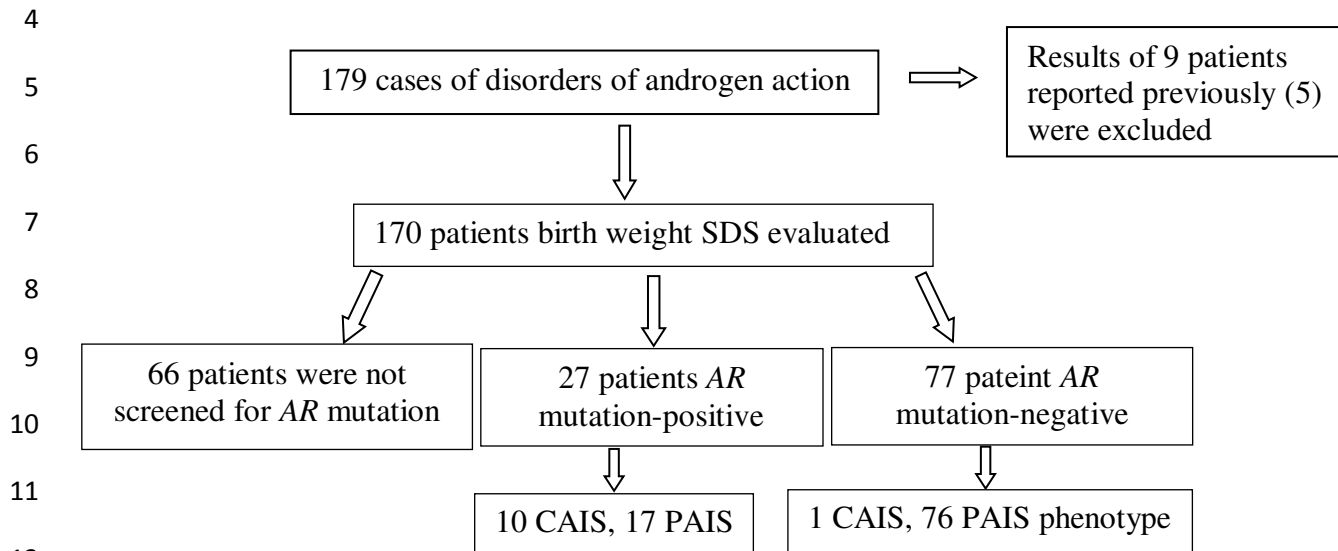
29 deficiency, STAR:Steroidogenic acute regulatory protein deficiency, SRD5A2:5 alpha reductase deficiency.

1

2

1

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



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