Novel associations in disorders of sex development: findings from the I-DSD Registry

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Context: The focus of care in disorders of sex development (DSD) is often directed on issues related to sex and gender development. In addition, the molecular etiology remains unclear in the majority of cases.

Objective: To report the range of associated conditions identified in the I-DSD Registry.

Design, Setting & Patients: Anonymized data were extracted from the I-DSD Registry for diagnosis, karyotype, sex of rearing, genetic investigations and associated anomalies. If necessary, clarification was sought from the reporting clinician.

Results: Of 649 accessible cases, associated conditions occurred in 168 (26%); 103 (61%) cases had one condition, 31 (18%) two, 20 (12%) three and 14 (8%) four or more. Karyotypes with most frequently reported associations included 45,X with 6/8 affected cases (75%), 45,X/46,XY with 19/42 cases (45%), 46,XY with 112/460 cases (24%) and 46,XX with 27/121 cases (22%). In the 112 cases of 46,XY DSD, commonest conditions included small for gestational age (SGA) in 26 (23%), cardiac anomalies in 22 (20%) and CNS disorders in 22 (20%), while in the 27 cases of 46,XX DSD, skeletal and renal anomalies were commonest at 12 (44%) and 8 (30%), respectively. Of 170 cases of suspected Androgen Insensitivity Syndrome (AIS), 19 (11%) had reported anomalies and 9 of these 19 had confirmed androgen receptor mutations.

Conclusions: Over a quarter of cases in the I-DSD Registry have an additional condition. These associations can direct investigators towards novel genetic etiology and also highlight the need for more holistic care of the affected person.

Disorders of sex development (DSD) are a group of rare conditions that usually present in early infancy with an abnormality of the external and/or internal reproductive organs, and commonly arise because of a disorder of gonadal, adrenal or hormonal function. Although the overall birth prevalence of conditions associated with

Abbreviations:
DSD may be as high as 1 in 300 (1), individual patho-
physiological conditions are much rarer, limiting the study
of their etiology and prognosis.

While enormous advances in our knowledge have been
achieved over the last decade, the genetic etiology in most
cases of DSD remains unclear (2, 3). Furthermore, our
understanding of the basis of the genetic modifiers of
monogenic DSD remains in its infancy. Mammalian sex
development, which is already known to be closely linked
to the development of the urological system (4), occurs at
critical stages of embryonic and fetal development. These
windows may also be important for the development of
other organs as illustrated by a number of known condi-
tions associated with DSD (5–7). High-throughput gene
sequencing technology has the potential to identify a num-
ber of attributable genetic variations but understanding
the link between these variations and the clinical condition
may prove to be a challenge. An improved knowledge of
the range of associated conditions that exist in people with
DSD will not only help with interpreting the results of the
genetic analyses, but will also aid with the management of
the affected patient.

Although a link between DSD and associated anom-
alies is recognized (1), it is generally felt that conditions such
as hypospadias are rarely associated with abnormalities
beyond the genitourinary (GU) system (8). Given the rarity
of DSD, it has been difficult to ascertain the frequency and
nature of associated anomalies in these cases. The Con-
sensus Guidelines on DSD published in 2006 stressed the
need for the creation and maintenance of a database in
centers of expertise (9). Such databases do exist in many
regional and national centers and have provided valuable
insights into many aspects of DSD, including epidemi-
ology (1), etiology (10, 11), variation of disease expression
(12), initial adjustment of parents to their affected child’s
condition (13), and long-term outcome (14). However, as
these databases and registries lacked uniformity, an inter-
national DSD registry that collects information on cases
with a range of conditions has now been in operation to
overcome these issues (15). We have used this model of
international collaboration to report on the largest cohort
of cases of DSD that has been studied for associated
anomalies.

**Patients and Methods**

Details of the I-DSD Registry, including its development and
current operation have been previously reported (15, 16) and are
also available from its website (www.i-dsd.org). Briefly, all cli-
nicians belonging to recognized professional medical and scient-
ific societies are eligible to register and report cases. This infor-
mation is required when the clinician first registers as a user of the
Registry. Users are then approved by the steering committee of
the Registry before they can submit any cases. There are no re-
strictions on the age requirement of the case, with the Registry
serving both adult and pediatric populations, and there is no time
limit between initial presentation or diagnosis and entry into the
Registry. Patient and/or parental consent must be obtained prior
to case registration, with the level of consent tiered according to
the extent to which the information may be shared (own center,
own country, EU member states, international). The I-DSD Reg-
istry is approved by the National Research Ethics Service of the
United Kingdom.

The terminology used within the Registry is based on the
nomenclature initially developed at the Chicago consensus meet-
ing and which has continued to evolve subsequently (9, 15). In
addition to details of diagnosis, the I-DSD Registry collects sim-
ple information on physical conditions which affect systems
other than the reproductive system, as well as the occurrence of
conditions such as small-for-gestational-age, and short stature.
See supplementary Table S1 – S4 for details of the data fields in
the Registry.

At the time of the study in September 2012, there were 1050
cases submitted by registered clinicians from 20 centers in 14
different countries. Reporting clinicians for cases represented a
range of specialties including pediatric endocrinology, adult en-
docrinology, clinical genetics and biochemistry and their coun-
tries of origin are outlined in supplementary Table S5. On ana-
lyzing the extracted data, 649 (62%) cases had a sufficient level
of consent to allow sharing of suitable information. Anonymized
data were obtained from the Registry regarding diagnosis,
karyotype, sex of rearing, clinical center, genetic investigations
and any associated anomalies. Until September 2012, the field
which captures ‘associated conditions’ was labeled as ‘associated
malformations’. The field does not seek any further information
on whether the associated condition is early onset, late onset or
acquired. Short stature in congenital adrenal hyperplasia was
excluded from the analysis as this is a condition that is acquired
as a consequence of the management of the disorder. Further-
more, the data were subanalyzed with exclusion of cases where
the condition was known to be associated with specific anom-
alies, namely P450 Oxidoreductase deficiency (PORD), Mülle-
rian duct aplasia, Renal dysplasia and Cervical Somite anomalies
(MURCS), Mayer-Rokitansky-Kuster-Hauser Syndrome
(MRKH), Turner Syndrome and 45,X/46,XY. Where information
was unclear or incomplete the reporting clinician was con-
tacted to obtain further information.

**Results**

**Karyotype**

Of the 649 cases analyzed, 460 (71%), were 46,XY,
121 (19%) were 46,XX, 42 (6%) were 45,X/46,XY, 8
(1%) were 45,X, 6 (1%) were 46,XX/46,XY, 2 (0.3%)
were 47,XXX, with other atypical karyotypes (such as
translocations) making up the remaining 10 cases (1%).
Of these cases with the respective karyotypes, associated
conditions were reported in 6 cases of 45,X (75%), 19
cases of 45,X/46,XY (45%), 112 cases of 46,XY DSD
(24%), 27 cases of 46,XX DSD (22%) and 4 cases with the
atypical karyotypes (22%). Disorders of gonadal development occur in patients with a variety of karyotypes, and in the current cohort, of the 63 cases of a disorder of gonadal development with an associated condition, 33 (52%) were 46,XY, 3 (5%) were 46,XX, 5 (8%) were 45,X, 19 (30%) were 45,X/46,XY, 1 (2%) was 47,XXY, and 2 (2%) had an atypical karyotype.

Multiple conditions

Of the 649 cases, associated conditions occurred in 168 (26%). Of these 168 cases, 103 (61%) cases had one condition each, 31 (18%) had two conditions, 20 (12%) had three and 14 (8%) had four or more with the maximum number being eight. Multiple conditions (more than one per case) were reported in 3 of 6 (50%) cases of 46,XX disorders of Müllerian development, 22 of 44 (50%) cases of nonspecific 46,XY DSD, 25 of 63 (40%) cases of disorders of gonadal development, 7 of 19 (37%) cases of disorders of androgen action, 3 of 11 (27%) cases of disorders of androgen excess and 2 of 18 (11%) cases of disorders of androgen synthesis. Further details of the conditions encountered are outlined in Table 1.

Range Of Conditions

The range and distribution of associated conditions differed substantially between cases of 46,XY and 46,XX DSD (Figure 1). Small-for-gestational age (SGA) was reported in 26 of 112 cases (23%) of 46,XY DSD with associated conditions; however, there were no cases of SGA in the 46,XX DSD group. CNS and cardiac conditions were next most frequent in 46,XY DSD, each reported in 22 of the 112 cases (20%) of 46,XY DSD with associated conditions.

In the 90 cases of nonspecific XY DSD without any clear diagnosis on the registry, 17 (19%) were reported to be SGA, 11 (12%) had cardiac abnormalities and 8 (9%) had involvement of the central nervous system (CNS) (Table 1). In the 153 cases of disorders of gonadal development on the registry, 19 (12%) had short stature (15 of which occurred in cases with 45,X or 45,X/46,XY karyotype, 3 in cases of 46,XY DSD and 1 case with an atypical karyotype), 17 (11%) had renal anomalies (7 of which occurred in cases with 45,X or 45,X/46,XY karyotype) and 14 (9%) had cardiac abnormalities (6 of which occurred in cases with 45,X or 45,X/46,XY karyotype) (Table 1).

Conditions affecting the skeleton were present in 12 of 27 (44%) cases of 46,XX DSD with an associated condition and these cases included 2 cases of MURCS, diagnosed clinically, 7 cases of PORD all with genetic confirmation of diagnosis, 2 unconfirmed nonclassical 3β-hydroxysteroid dehydrogenase deficiency, and 1 case of 11β-hydroxylase deficiency, with genetic confirmation. Conditions involving renal development were encountered in 8 of the 27 cases (30%) and were commonest in

Table 1

<table>
<thead>
<tr>
<th>Disorder Type</th>
<th>Number of cases with each type of anomaly</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number of cases with anomaly</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Gonadal Development (153)</strong></td>
<td>63</td>
</tr>
<tr>
<td>Androgen Synthesis (100)</td>
<td>18</td>
</tr>
<tr>
<td>Androgen Action (172)</td>
<td>19</td>
</tr>
<tr>
<td>Androgen Excess (75)</td>
<td>9</td>
</tr>
<tr>
<td>Non-specific XY DSD (90)</td>
<td>44</td>
</tr>
<tr>
<td>XX</td>
<td>6</td>
</tr>
<tr>
<td>Müllerian Defect (12)</td>
<td>1</td>
</tr>
<tr>
<td>PMDS (5)</td>
<td>1</td>
</tr>
<tr>
<td>Leydig Cell Defects (17)</td>
<td>7</td>
</tr>
<tr>
<td>Other (25)</td>
<td>7</td>
</tr>
<tr>
<td><strong>TOTAL (649)</strong></td>
<td>168</td>
</tr>
</tbody>
</table>

Table 1. Reported anomalies according to disorder classification. SGA: Small for gestational age, CNS: Central nervous system, GI: Gastrointestinal, ENT: Ear, nose and throat, PMDS: Persistent Müllerian Duct Syndrome
those with a 46,XX disorder of Müllerian development, occurring in 6 of 12 cases in the Registry (50%), and present in all such cases which had an anomaly recorded.

As associated conditions are already known to occur in some syndromes associated with DSD, 8 cases of Turner syndrome, 42 cases of 45,X/46,XY, 19 cases of PORD and 12 cases of Mullerian development anomalies were excluded from the overall 649 cases. Of the remaining 568 cases, 127 (22%) had an associated condition that did not form a recognized part of the disorder. Of these 127, 108 (85%) were 46,XY, 15 (12%) were 46,XX, 2 (2%) had a nonsex chromosome rearrangement, and there was 1 case each (1%) of 46,XX/46,XY and 47,XXX, respectively. Of these 127 cases, 75 (60%) had one condition, 22 (17%) had two, 18 (14%) had 3 and 12 (9%) had 4 or more, with the maximum number of conditions encountered in one patient being 8. Among these 127 cases there were 44 cases of non specific 46,XY DSD, 39 cases of disorders of gonadal development, 19 cases of disorders of androgen action, 10 case of disorders of androgen synthesis, 9 cases of disorders of androgen excess, 1 case each of Leydig cell defects and persistent Müllerian duct syndrome, and 6 cases classified as ‘other’ disorders. Of the 39 cases of disorders of gonadal development 10 (26%) had a renal condition, 8 (21%) had a cardiac condition, 8 (21%) had a CNS condition, 8 (21%) had a craniofacial disorder, 4 each (10%) had short stature, ENT, GI tract, respiratory or skeletal conditions, 3 (8%) had blood and lymph conditions, eye conditions, SGA or an unidentified syndrome, and 1 (3%) had an adrenal condition.

The pattern and frequency of anomalies also varied between 46,XY and 46,XX DSD after exclusion of the syndromic DSD conditions (Figure 2). Of the 451 cases of 46,XY DSD, an associated condition was reported in 108 (24%) and in 15 of 98 cases (15%) of 46,XX DSD. In 46,XY DSD, SGA was the most frequent condition in 26 cases (24%), with cardiac anomalies in 22 cases (20%) and CNS conditions in 21 cases (19%). In 46,XX DSD, there was an even spread of conditions with the most frequent condition being skeletal occurring in 3 of 15 cases (20%).

Monogenic DSD

Of 170 cases reported as Androgen Insensitivity Syndrome (AIS), 19 (11%) were recorded as having an associated condition. Of these 19 cases, 9 had a confirmed androgen receptor (AR) mutation, occurring in 6 cases of Complete AIS and 3 cases of Partial AIS. Associated conditions were reported to affect the renal system in 2 cases, skeleton in 1, skin in 1, CNS in 1, GI tract in 1, heart in 1 and an unspecified condition in 5 cases (Table 2). Associated conditions were also reported in 8 of 72 (11%) cases of 21α-hydroxylase deficiency (1 of which had confirmed CYP21A2 mutation, while the remainder were diagnosed clinically), 4 of 26 (15%) cases of 17β-hydroxysteroid dehydrogenase type 3 deficiency (all with confirmed HSD17B3 mutation), and 2 of 19 cases (10%) of 5α-reductase type 2 deficiency. In the 8 cases of 21α-hydroxylase deficiency, two had renal conditions. In the remainder, there was one case of a CNS condition, one affecting the GI tract and one case each detailed as severe autism, spastic paraplegia, polyarthritis, learning disability and one not specified.

Discussion

The results from this analysis of the I-DSD Registry reveal that associated conditions are frequent in DSD, with a rate of 27%, which is over 10 times the birth prevalence of congenital anomalies (17). This is not unexpected, given that the presence of one congenital condition is known to be associated with the presence of further anomalies as...
disrupting factors, whether environmental or genetic, are likely to affect multiple developmental processes. Furthermore, approximately 10% of the cases of DSD had more than one associated condition, highlighting the need for input from multiple specialists. When cases with DSD syndromes and chromosomal anomalies were excluded, the overall frequency of associated conditions was similar to the overall cohort. These figures are also in keeping with the findings of an epidemiological study carried out in Germany which identified a higher rate of 37.5% for associated malformations in infants with ambiguous genitalia (18).

Although the ranges of anomalies that are encountered are different, it is of interest that in the current cohort of cases in the I-DSD Registry, the reported prevalence of associated conditions in 46,XY and 46,XX DSD at 24% and 22% was similar. With the exclusion of the cases that are well known to be associated with anomalies, the prevalence of associated conditions in the other cases of 46,XY and 46,XX DSD was 24% and 15%, respectively. The type of conditions encountered in 45,X/46,XY cases bears a striking resemblance to the known phenotype in Turner syndrome, with partial or complete gonadal dysgenesis. This is reflected in the high frequency of associated conditions in all cases with gonadal dysgenesis. Our findings echo the description of the 45,X/46,XY phenotype by Tosson et al and Telvi et al (19, 20) and the cardiac phenotype refined by De Groote et al (21). These findings highlight the importance of thorough screening for associated conditions in both male and female individuals with this karyotype.

It has long been recognized that there is a strong association between SGA and DSD (1, 22), and this was reflected in our findings. It was notable that there were no reported cases of SGA in 46,XX DSD. It has been speculated that altered prenatal androgen exposure may alter in utero growth but this is debatable (23, 24). An alternative hypothesis for the origins of low birthweight in 46,XY DSD is that both are the result of early placental insufficiency (25, 26) and this requires further investigation.

<table>
<thead>
<tr>
<th>Disorder of androgen synthesis</th>
<th>Total number</th>
<th>Number cases with anomaly</th>
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<tbody>
<tr>
<td>17β hydroxysteroid dehydrogenase type 3 deficiency</td>
<td>26</td>
<td>4 1</td>
</tr>
<tr>
<td>5α reductase type 2 deficiency</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>11α hydroxysteroid dehydrogenase type 2 deficiency</td>
<td>19</td>
<td>10 1</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Disorder of Androgen Action</th>
<th>Number of cases with each anomaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Androgen Insensitivity Syndrome (AR mutation +ve)</td>
<td>77</td>
</tr>
<tr>
<td>Complete Androgen Insensitivity Syndrome (AR mutation -ve/unknown)</td>
<td>16</td>
</tr>
<tr>
<td>Partial Androgen Insensitivity Syndrome (AR mutation -ve)</td>
<td>39</td>
</tr>
<tr>
<td>Partial Androgen Insensitivity Syndrome (AR mutation -ve)</td>
<td>38</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Disorder of Androgen Excess</th>
<th>Number of cases with each anomaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>21α hydroxylase deficiency</td>
<td>72</td>
</tr>
<tr>
<td>11β hydroxysteroid dehydrogenase type 2 deficiency</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Reported anomalies in monogenic conditions. SGA: Small for gestational age, CNS: Central nervous system, GI: Gastrointestinal, ENT: Ear, nose and throat. Two cases reported as possible non-classic 3β-HSD have been included in Table 1 as androgen synthesis disorders, but due to diagnostic uncertainty have not been included in the monogenic conditions in Table 2. Two cases described as “disorders of androgen excess” have the diagnosis “other” with no confirmed diagnosis and are therefore not included in Table 2.
In 46,XX DSD, an association with skeletal and renal anomalies is recognized in conditions such as MURCS (Müllerian duct aplasia, Renal dysplasia and Cervical Somite anomalies), Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKH), and P450 oxidoreductase deficiency (PORO) (17). This was borne out by our results, in which renal conditions were common in women with 46,XX DSD and disorders of Müllerian development. Similarly, skeletal involvement was also observed in women with 46,XX DSD and PORO or MURCS. Renal disorders are also a recognized feature of 46,XY DSD due to the Denys Drash and WAGR (Wilms, Aniridia, Genitourinary anomalies, mental Retardation) syndromes. Furthermore, bone and kidney abnormalities combined with genital anomalies are a component of Smith Lemli Opitz syndrome (28). Renal tract anomalies have previously been reported as occurring in 14 of 66 females (21%) with congenital adrenal hyperplasia (29), and were also confirmed to be present in the current cohort occurring in 2 cases of 21α-hydroxylase deficiency. When recognized associations were excluded from the analysis, renal and skeletal disorders were still encountered in up to 4% of cases of 46,XX DSD and 46,XY DSD.

The unexpected presence of renal abnormalities in AIS cases with a confirmed androgen receptor mutation raises a question about the developmental role of the androgen receptor in the kidney. Previously, an association between CAIS and renal anomalies has been described in one case (30). In mice, the kidney is one of the most androgen sensitive, nonreproductive organs, with a close correlation between kidney mass and androgen levels in the male (31). In addition, several developmental genes are known to be androgen-regulated in the mouse (32). Our finding of 2 cases with renal anomalies in congenital adrenal hyperplasia (CAH) is also worthy of emphasis, as it highlights the importance of thorough investigation of the whole renal tract in such patients. Ten cases reported as AIS without a confirmed AR mutation had an associated condition. Of these, 5 cases had SGA and 4 had short stature. Given that these associations are often encountered in cases of gonadal dysgenesis, these cases of presumed AIS need a thorough investigation of gonadal function.

It is possible that some of the associations revealed by our analysis of the Registry may represent co-occurrence of anomalies by chance. Renal tract anomalies have been reported as occurring with a frequency of 25 per 1,000 in the general European population (17). This compares to a frequency in our analysis of 35/649, equivalent to 54 per 1,000. The frequency of cardiac anomalies, the second most common anomaly in our population, is reported as 8 per 1,000 in the European population (33). This compares to the occurrence of cardiac anomalies in our analysis of 32/649, equivalent to 49 per 1,000.

The I-DSD Registry is not an epidemiological registry and as it does not collect information on all cases of DSD, it may suffer from a reporting and selection bias. It is recognized that there may be a bias towards the reporting of more clinically unusual cases, which could increase the reported prevalence of anomalies. Registry users can also choose the extent of data sharing with other users for each individual case and this sharing may depend on the patient’s or clinician’s preference. Based on the access level of the investigators, only 60% of the cases in the Registry could be accessed for this study and this may have also introduced some selection bias. However, the similarities between our results and the findings of a national study suggest that the prevalence figure of 25% for associated conditions probably is representative of the true prevalence (18). In particular, cases of CAH may be under-represented in the Registry due to reporting methods, given that the incidence in the general population is estimated at around 1 in 15,000 live births (34). The incidence of AIS was described in a Danish population registry as 1 in 20,400 (35), while MRKH is estimated as occurring in 1 in 4,500 females (36). However the Registry does not necessarily represent the population prevalence of these disorders as it relies on clinician reporting rather than population screening.

All data are self-recorded by the clinician, with little recourse to source verification of entered data and it can be difficult in such a registry to be clear that all users have the same understanding of an associated condition that is congenital. It is also possible that some congenital conditions may not be manifested until a later age. Until recently, the data collection form asked investigators to enter data on ‘associated malformations’ which implies congenital conditions. More recently, the term ‘malformations’ has been replaced by the term ‘conditions’. It would be beneficial in future revisions of the Registry to provide some explanatory data to ensure that conditions that are considered to be of congenital and those considered to be acquired are captured separately and there may be additional value in assessing the age of onset of the manifestation of the condition.

However, the use of an international registry of such rare conditions in such a large group of cases has, nevertheless, pointed to some new associations in DSD and the study highlights the strength of a global effort to collect data in rare diseases which will encourage reporting of more cases of DSD with associated conditions. In conclusion, we have found that, in this cohort of cases, associated anomalies are reported in around a quarter of cases of DSD. The prevalence of associated conditions is much
greater in disorders of gonadal development and nonspecific 46,XY DSD. In 46,XY DSD, the largest group of cases in the Registry, commonest associated conditions included SGA, cardiac and CNS. In many cases of DSD the etiology remains obscure and the current findings may lead to new research targets as well as improved care of those affected by these disorders.

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