Genes, Chromosomes, and Disorders of Sex Development: An Update

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Abstract

Disorders of sex development (DSD) comprise a group of conditions in which genotypes do not correlate with the typical male and female phenotypes. Numerical and structural abnormalities involving both autosomes and sex chromosomes have been observed in DSD. Specifically, deletions, duplications, and translocations involving specific genes as well as point mutations and less common aberrations have been implicated in the pathogenesis of these conditions. Finally, recent advances in analytical tools, namely chromosomal microarrays and sequencing methods, have greatly enhanced the precision with which DSD are genetically characterized and phenotypically correlated. Herein, we review the genes and loci involved in the pathogenesis of disorders of sex development based on recent findings and illustrate the importance of cytogenetics and molecular genetics in the clinical management of these conditions.

Key Words: disorders of sex development (DSD), *SRY*, cytogenetics, FISH

Introduction

Disorders of sexual development (DSD) is an umbrella term that encompasses an array of developmental disorders in which phenotypes do not correlate with classical male (XY) and female (XX) genotypes. DSD are characterized by the presence of intermediate or atypical combinations of both genotypic and phenotypic features that usually distinguish a male from a female, including chromosomal, gonadal, anatomical, and behavioral aspects of sex. DSD are generally classified based on chromosomal and gonadal constitution and then correlate the cytogenetic, molecular genetic, and phenotypic findings to analyze the etiology of the DSD. The two primary forms of DSD are 46,XY DSD and 46,XX DSD. Mosaicism and chimerism are not uncommon phenomena observed in DSD. The former is caused by mitotic nondisjunction of a single cell of an embryo resulting in two different clonal populations and the latter is caused by the fusion of two embryos. The resulting state is a mixture of cells of equal or unequal proportions with different genetic makeups.

Phenotypic effects of DSD are numerous and varied. A common phenotypic occurrence in DSD is gonadal dysgenesis, which is characterized by abnormal embryonic development of gonadal tissue resulting in underdeveloped and dysfunctional gonads (Nieschlag et al., 2009). In addition, ambiguous external genitalia, amenorrhea, mental retardation, and so on, are also observed in patients presenting with disorders of sexual development (Ostrer, 2008). Cytogenetic and molecular genetic studies are critical in the proper management of individuals presenting with such conditions and due to the emergence of novel analytical techniques, the understanding of the molecular basis of DSD has been significantly advanced.

Sex Chromosomes

The X chromosome in humans spans more than 153 million base pairs and approximately 1529 genes. The Y chromosome has approximately 59 million base pairs and around 50-60 genes. One of the most important genes on the X chromosome is the inactive X (Xi)-specific transcript (XIST) at the X inactivation center on Xq13.2, which is in charge of X inactivation in embryogenesis (Li, 2011). This gene is transcriptionally silent on the active X in both males and female cells (Nussbaum et al., 2007).

Xq deletions involving Xq13 to Xq26 are associated with amenorrhea and ovarian failure (Gardner et al., 2012). 1.1 Mb microdeletions on the X chromosome at Xq22.1 have been associated with severe retardation in daughters of mildly retarded mothers presenting delXq (Gardner et al., 2012). Neurocognitive loci are located on the proximal Xp so deletion of Xp21 has been associated with intellectual disability (Gardner et al., 2012).

Interstitial deletions of the Yq involving *AZFa*, *AZFb*, and *AZFc* have been associated with 10% of cases of nonobstructive azoospermia and 6% of cases of oligospermia. The *AZFc* deletion includes deletion of the *DAZ* genes (deleted in azoospermia), which arise in 1/4,000 males and are mediated by recombination between long repeated sequences. *AZFa* and *AZFb* deletions are less common but also involve recombination. De novo point mutations of the *USP9Y* on the long arm of the Y chromosome have been suggested to be associated with male infertility. Deletions of the *SRY* gene on the short arm of the Y chromosome have been associated with an XY female phenotype (Nussbaum et al., 2007) (see Figure 1).

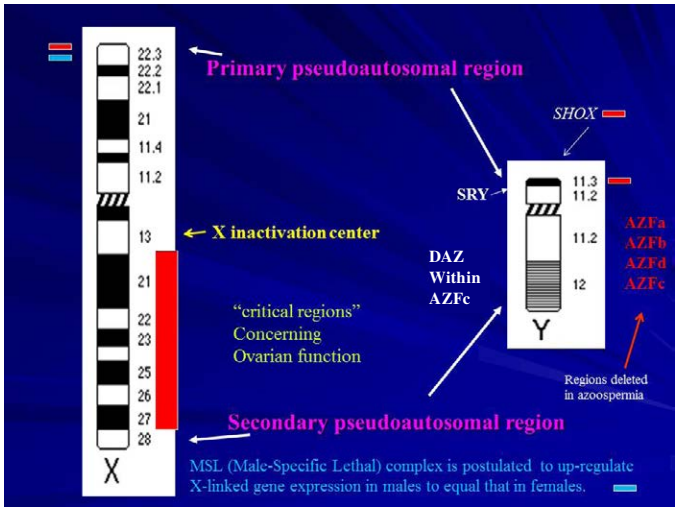

Figure 1. Ideograms of the sex chromosomes with relevant genes and loci labeled (Adapted from Nussbaum et al., 2007; http://ghr.nlm.nih.gov/chromosome/X).

Aneuploidies of Sex Chromosomes

In males, the majority of gonosomal aneuploidies result in **Klinefelter syndrome**. Males with Klinefelter syndrome bear abnormal karyotypes such as 47,XXY (1/1,000 male live births), 48,XXXY (1/25,000 male live births), and other variants (1/10,000 male live births). Phenotypically, males with Klinefelter syndrome present with infertility, hypogonadism (that is often noticed after the onset of puberty), and deficits in behavior and intelligence. The condition is observed in approximately 3% of infertile males, and in approximately 5% to 10% of males with azoospermia and oligospermia. In 15% of cases, Klinefelter syndrome exists in a mosaic state, most commonly as 46,XY/47,XXY. However, Klinefelter variants in which additional X chromosomes are present in the abnormal karyotype (48,XXXY and 49,XXXXY) tend to have a more adverse phenotypic effect than those with a lower number of X chromosomes (Nussbaum et al., 2007).

XYY syndrome is observed in approximately 1 in 1,000 male live births, but poses no consistent phenotypic effects on sex development or differentiation despite an abnormal gonosomal constitution.

Turner syndrome is observed in 1 in 4,000 live female births and about half of the females with the condition bear the 45,X karyotype; however, a number of variants including 46,X,i(Xq) (15% of cases), 45,X/46,XX mosaic (15% of cases), 45,X/46,X,i(Xq) mosaic (5% of cases) as well as other, less common ones have been documented. Females with this condition are generally shorter than average, are infertile, have streak gonads due to some degree of gonadal dysgenesis as well as certain anatomical malformations, and occasionally have deficits in intelligence and behavior.

Trisomy X (47,XXX) is also observed in approximately 1 in 1,000 female live births, but poses no phenotypic effects on female sexual development. Females with trisomy X are generally taller than average, and may have deficits in intelligence and behavior. However, the gain of additional X chromosomes in variants such as tetrasomy X (48,XXXX) and pentasomy X (49,XXXXX) has been associated with more detrimental phenotypic effects on mental and physical aspects of development (Nussbaum et al., 2007).

46,XY Disorders of Sexual Development

Individuals bearing the typical 46,XY male karyotype that present with a disorder of sexual development phenotypically present with external genital ambiguity, variable gonadal dysgenesis, hypospadias, oligospermia/azoospermia, and Müllerian structures that progress to varying degrees of development. Furthermore, in 46,XY complete gonadal dysgenesis (CGD, also known as Swyer syndrome), affected individuals present with streak gonads, azoospermia, and the presence of normal female external genitalia and Müllerian structures (Ostrer, 2008). Finally, in androgen insensitivity syndrome (AIS), affected individuals are karyotypically male, but phenotypically present with variable (generally severe) feminization of external genitalia.

A number of genes have been implicated in both 46,XY DSD and 46,XY CGD (see Table 2 and Figure 2). Abnormalities involving *SRY* (Yp11.31) have been shown to result in 46,XY DSD (1% of cases) and CGD (15% of cases) due to its integral role in male sex determination. Most often, a deletion of *SRY*, usually detected by fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR), is observed in such cases. However, sequence variants and deletions of variable sizes have been observed in both conditions (Ostrer, 2008).

NR5A1 (previously known as *SF1*), located on chromosome 9q33.3, has also been implicated in approximately 13% of cases of 46,XY DSD (Ostrer, 2008). Abnormalities involving *DHH* (12q13.12) have also been identified in individuals presenting with 46,XY DSD (20% of cases) and CGD (50% of cases) (Ostrer, 2008). *DHH* has been implicated in complete gonadal dysgenesis in a homozygous mutation state and mixed gonadal dysgenesis (46,XY DSD) in a heterozygous mutation state (Gardner et al, 2012).

Duplications of *NR0B1* (previously known as *DAX1*), located on chromosome Xp21.2, although relatively rare, have also been observed in both conditions. White et al. (2011) described an individual with 46,XY CGD bearing 708 kb duplication including the Xp21.2 locus described as dup(X)(p21.2). Furthermore, overexpression of the *WNT4* gene (1p35), most often caused by duplication (dup(1p31-p35)), can result in female phenotype characteristics (DSD and CGD) in karyotypic males (Ostrer, 2008).

46,XY DSD and CGD have also been observed in conditions caused by abnormalities of genes involved in sex development and differentiation. In cases of camptomelic dysplasia, which is caused by mutations of *SOX9* on the long arm of chromosome 17 and results in an array of skeletal malformations in affected individuals, 75% of individuals bearing the 46,XY karyotype express a female phenotype. The *SOX9* gene is located on 17q24 and

Table 1. Selected numerical and structural abnormalities of the sex chromosomes associated with disorder of sexual development adapted from Li, 2011.

Karyotype (Numerical Abnormalities)	Phenotype
47,XXY	Klinefelter Syndrome
45,X	Turner Syndrome
Karyotype (Structural Abnormalities)	**Phenotype**
del(Yp)	46,XY DSD, 46,XY CGD, infertility
r(Y)	46,XY DSD, 46,XY CGD, infertility
mar(Y)	46,XY DSD, 46,XY CGD, infertility
iY(p10)	46,XY, DSD (testicular developmental deficit), infertility
46,XX,del(Xq)	46,XX DSD (ovarian developmental deficits)
46,XY,dup(Xq21)	46,XY CGD (sex reversal)
r(X)	Turner syndrome
mar(X)	Turner syndrome

is regulated by the testis-determining factor produced by the *SRY* region of the Y-chromosome. The gene plays a pivotal role in the normal gonadal development of males. In conjunction with other key genes, *SOX9* promotes development of male sex organs through regulatory loops with proteins *FGF9* and *PDG2* (De Santa Barbara et al., 1998; Moniot et al., 2009) and it has been observed that in individuals bearing a deletion of a single copy of the *SOX9* gene, solely ovarian formation occurs, resulting in a phenotypically female 46,XY individual. Conversely, overexpression of the *SOX9* gene, most often caused by duplication, has been observed to lead to sex reversal in individuals bearing a 46,XX karyotype, suggesting an integral role of SOX9 in male gonadal development independent of *SRY*. White et al. (2011) described an individual with 46,XY CGD bearing a 1.2 Mb deletion 300 kb upstream of the *SOX9* locus. Patients affected by Denys-Drash syndrome and Frasier syndrome, both of which involve mutations of the *WT1* gene, exhibit some degree of gonadal dysgenesis. *WT1* has a regulatory role in the formation and development of testis, and can result in ambiguous external genitalia or complete gonadal dysgenesis (CGD) in the aforementioned conditions, respectively. Hersmus et al. (2012) described a female with 46,XY DSD bearing a single nucleotide *WT1* mutation in conjunction with an *SRY* gene missense mutation at position 383 (A to G). Dai et al. (2011) also characterized a completely sex-reversed 46,XY individual (phenotypically female) bearing a de novo insertion in the first exon of the *WT1* gene resulting in a shortened *WT1* gene product caused by the formation of a stop codon as a result of the insertion.

Other cytogenetic abnormalities that have been observed in patients affected by 46,XY DSD and CGD resulting in a karyotypic male (46,XY) with variable female phenotypic features that involve the long arms of chromosomes 2 and 10 and the short arms of chromosomes 9 and 20. Igarashi et al. (2013) describe three individuals with 46,XY DSD bearing cryptic cytogenetic abnormalities identified via array comparative genomic hybridization (aCGH). The first individual presented with feminized external genitalia as well as mental retardation and was found to have a deletion of 9p24.1-24.3. The second patient presented with ambiguous external genitalia and was found to have a deletion at 20p13. Finally, the third patient also presented with ambiguous external genitalia among other abnormalities and was found to have a deletion at 2q31.1-2q32. In a study conducted by Bagheri-Fam et al. (2008), knockout mice bearing an XY gonosomal constitution, but lacking the *FGFR2* gene (located at chromosome 10q26) were found to exhibit varying degrees of sex reversal, suggesting a deletion involving the 10q26 locus is a relevant cytogenetic abnormality in 46,XY DSD.

Androgen insensitivity syndrome (AIS), which occurs in approximately 1 in 20,000 live births, can also result in 46,XY disorders of sexual development. In this condition, the testes of the affected individual secrete androgens, but due to a lack of receptors on target cells, the target organs are unresponsive to the effects of androgens. Often, deficiency of **5-alpha-reductase**, which catalyzes the conversion of testosterone to active dihydrotestosterone, is the cause of deficits in sexual development. Phenotypes of affected individuals are based on the degree of androgen insensitivity, and can range from ambiguous external genitalia to apparently normal external phenotypic features (Nussbaum et al., 2007). Structural abnormalities and mutations of the androgen receptor (AR) gene located at Xq11-q12 have

Table 2. Loci and genes implicated in 46,XY DSD and 46,XY CGD adapted from Ono and Harley (2013) (also see Figure 2).

Locus	Gene Implicated	Abnormality	Phenotype
1p35	*WNT4*	Duplication	DSD and CGD
2q31.1-32	*HOXD*	Deletion	DSD
5q11.2	*MAP3K1*	Point mutation	DSD and CGD
8p23.1-p22	*GATA4*	Point mutation	DSD and congenital heart disease
9p24.3	*DMRT1*	Deletion	DSD
9q33.3	*NRFA1/SF1*	Point mutation	DSD
10q26	*FGFR2*	Deletion	DSD
11p13	*WT1*	Point mutation	DSD and CGD
12q13.12	*DHH*	Point mutation	DSD and CGD
16q23.3-q24.1	*WWOX*	Deletion	DSD and CGD
17q24-q25	*SOX9*	Deletion	DSD, CGD, and campomelic dysplasia
17q25	*CBX2*	Point mutation, Sequence variant	CGD
20p13	?	Deletion	DSD
Xp21.2	*NR0B1/DAX1*	Duplication	DSD and CGD
Xp22.13	*ARX*	Deletion	DSD and CGD
Xq11-q12	*AR*	Point mutation	DSD
Xq28	*MAMLD1*	Point mutation	DSD
Yp11.31	*SRY*	Point mutation	DSD and CGD

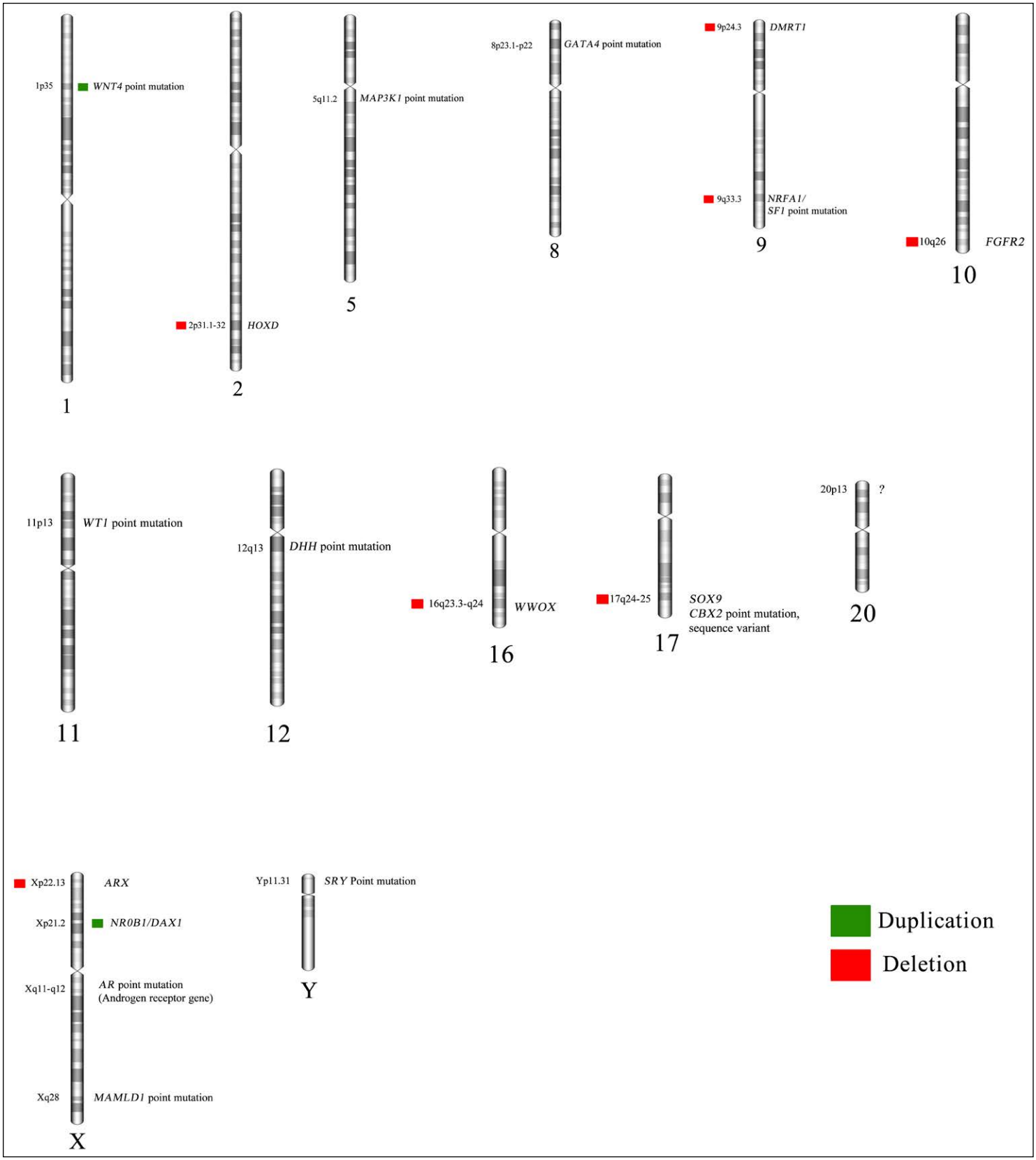

Figure 2. Main loci and genes implicated in 46,XY DSD and 46,XY CGD.

Table 3. Loci and genes implicated in 46,XX DSD and 45,X DSD adapted from Ono and Harley (2013) (also see Figure 3)

Locus	Gene Implicated	Abnormality	Phenotype
1p34.3	*RSPO1*	Point mutation	(ovotesticular) DSD
1p35	*WNT4*	Point mutation	DSD
3q23	*FOXL2*	Point mutation, sequence variant	DSD
9q33	*NR5A1/SF1*	Deletion	DSD, ovarian failure
17q24	*SOX9*	Duplication	DSD, complete sex reversal
Xq27.1	*SOX3*	Duplication	DSD, complete sex reversal
Xq28	*MAMLD1*	Point mutation	DSD
Yp11.3	*SRY*	X-Y/X-autosome translocation	DSD

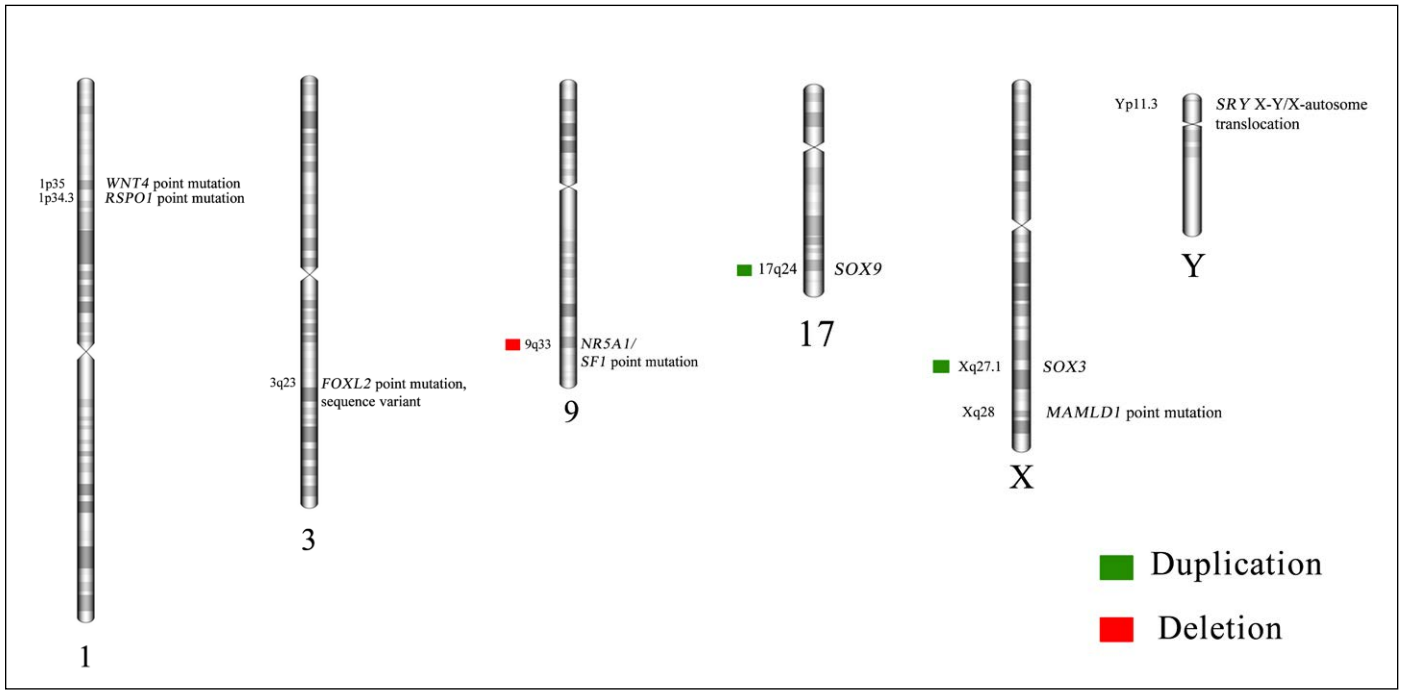

Figure 3. Ideogram showing the main genes implicated in 46,XX DSD and 45,X DSD.

been closely correlated with the development of AIS. An example of such an abnormality detectable by conventional cytogenetics is a case described by Li (2011), bearing the karyotype 46,Y,inv(X)(q11.2q27), although abnormalities vary as do their phenotypic effects (Li et al., 2011; Gardner et al, 2012). Yamaguchi et al. (2013) also reported three cases of AIS in which maternally inherited point mutations and deletions of exons 1 (nonsense, deletion), 3 (deletion) and 7 (missense) of the Xq11-q12 region were detected by DNA sequencing.

46,XX Disorders of Sexual Development

A number of genetic abnormalities have also been implicated in 46,XX DSD (see Table 3 and Figure 3). About 75% of 46,XX males are *SRY*-positive, generally as a result of abnormal paternal crossing over and translocation between the X and Y chromosomes resulting in a portion of Yp on one or both of the X chromosomes during meiosis I; more rarely, a translocation can occur between an autosome and the Y chromosome, although very few cases are reported. A single case reported by Li (2011) observed a cryptic translocation involving the short arms of the Y chromosome and chromosome 18 (Li, 2011). Although usually not visible cytogenetically, translocation involving a number of Y breakpoints and the Xp22.3 locus described as 46,X,der(X)t(X;Y)(p22.3;p11.2) have been observed (Gardner et al., 2012). The phenotype of the *SRY*-positive 46,XX males is similar to that observed in individuals with Klinefelter syndrome, although patients with *SRY*-positive 46,XX DSD generally do not have deficits in height or intelligence (Gardner et al., 2012). Cases of *SRY*-negative 46,XX individuals with complete or partial male phenotypes have also been observed. As previously stated, overexpression of *SOX9*, most often caused by duplication of the long arm of chromosome 17, can result in testis formation and complete XX sex reversal (karyotypic female, phenotypic male). Xiao et al. (2013) described a 46,XX male lacking *SRY* in

his chromosomal constitution, but bearing a 74kb duplication upstream of the *SOX9* locus. Furthermore, mutations of *FOXL2* (3q23) can result in ovarian dysgenesis and premature ovarian failure (POF), among other ovarian embryonic developmental deficits. In addition to abnormalities of *FOXL2*, premature ovarian failure can also result from cytogenetic abnormalities of Xq, which is evidence for the claim that females need two functional X chromosomes to properly complete egg production.

Karyotypically related to 46,XX DSD, ovotesticular DSD (formerly known as true hermaphroditism) occurs when testicular and ovarian gonadal components are present in a single individual. Approximately 60% of cases of ovotesticular DSD present with a 46,XX chromosomal constitution, known as 46,XX ovotesticular DSD. The majority of these cases are SRY-negative, and are likely caused by aberrant activation of embryonic gonadal development pathways. Other explanations for 46,XX ovotesticular DSD include gonadal cryptic mosaicism bearing Y chromosomal material (potentially including *SRY*) as well as cryptic cytogenetic abnormalities such as X;Y translocations. An intact Y chromosome is present in a considerably smaller number of cases of ovotesticular DSD. Approximately one-third of cases present with a mosaic karyotype, such as 46,XX/46,XY or 46,XX/47,XXY or 45,X/46,XY, and some even bear the 46,XY karyotype. Finally, abnormalities of the *RSPO1* gene (1p34.3) have been observed in clinically apparent ovotesticular DSD, although its precise role is unknown (Sutherland et al., 2004; Tomaselli et al., 2008).

45,X Disorders of Sexual Development

In addition to 46,XX/46,XY DSD, males bearing the 45,X karyotype (karyotypically female) are also observed. Most 45, males result from translocations of the *SRY* to an autosome or to the X chromosome, although a small proportion are mosaic bearing 45,X/46,XY chromosomal constitution.

Discussion

Despite the discovery of several sex-determining genes and genotype-phenotype correlation of observed abnormalities, many cases of disorders of sexual development remain genetically unexplained. Conventional cytogenetic and molecular genetic studies offer earlier and more phenotype-specific diagnoses for physicians. Standard fluorescence in situ hybridization (FISH) can assay for common structural and numerical abnormalities, such as deletions of 9p, 2q, or 10q or duplications of 1p (*WNT4*) or of Xp21 (*NR0B1*). Array comparative genomic hybridization (aCGH) gives physicians a high throughput approach to diagnosis that involve complex regulatory pathways and leads to more precise genetic characterization and genotype-phenotype correlation. Furthermore, sequence analysis can be used to detect presence of single base-pair mutations, duplications, small deletions, and insertions of the coding regions for the *SRY*, *NR5A1*, and *DHH* implicated in 46,XY disorders of sex development (Ostrer et al., 2008).

In the case of 46,XY DSD and 46,XY CGD, genotype-phenotype correlations have been established for some commonly implicated genes. Abnormalities of *SRY* that cause complete loss of function have been shown to result in 46,XY CGD as opposed to 46,XY DSD. However, mutations that do not cause complete loss of function of the gene have been observed to result in either of the two conditions. Heterozygous mutations of the *DHH* gene have been shown to correlate with 46,XY DSD while homozygous ones have been shown to correlate with 46,XY CGD. Despite these advances, distinct genotype-phenotype correlations have not been established for a number of relevant genes, such as *NR0B1* and *WNT4*, which would be beneficial in the proper management of patients presenting with clinical manifestations of DSD (Ostrer et al., 2008).

In patients presenting with Turner syndrome, an increased risk of gonadoblastoma may be correlated with the presence of material of the Y chromosome, which can be detectable cytogenetically by FISH or by polymerase chain reaction, although this is not typically performed in most laboratories. The risk may be even greater if Y chromosome material is present on the X chromosome and the patient presents with dysgenetic gonads in conjunction with this cytogenetic abnormality. An increased risk of gonadoblastoma may also be present in karyotypically female patients presenting with a derivative X chromosome resulting from partial monosomy of the short arm of the X chromosome and gain of material from the short arm of the Y chromosome, described as: 46,X,der(X) t(Xp;Yq) (Li, 2011).

It is also important to mention that many laboratories in the United States monitor the following genes by sequencing assays in patients with clinical presentation of DSD: ***AFP*** (4q13.3), ***AKR1C2*** (10p15-p14), ***AKR1C4*** (10p15.1), ***AMH*** (19p13.3), ***AMHR2*** (12q13.3), ***AR*** (Xq12), ***ARL6*** (3q11.2), ***ARX*** (Xp21.3), ***ATRX*** (Xq21.1), ***BBS1*** (11q13), ***BBS10*** (12q21.2), ***BBS12*** (4q27), ***BBS2*** (16q21), ***BBS4*** (15q22.3-q23), ***BBS5*** (2q31.1), ***BBS7*** (4q27), ***BBS9*** (7p14), ***BMPR1A*** (10q22.3), ***CBX2*** (17q25.3), ***CD96*** (13q13.13), ***CEP41*** (7q32), ***CHD7*** (8q12.2), ***CYB5A*** (18q23), ***CYP11A1*** (15q23-q24), ***CYP11B1*** (8q21-q22), ***CYP17A1*** (10q24.3), ***CYP19A1*** (15q21), ***CYP21A2*** (6p21.3), ***NR0B1*** (Xp21.3), ***DHCR7*** (11q13.4), ***DHH*** (12q13.1), ***DMRT1*** (9p24.3), ***DMRT2*** (9p24.3), ***DVL1*** (1p36), ***ERCC3*** (2q21), ***ESR2*** (14q21-q23), ***FGF8*** (10q24-q26), ***FGF9*** (13q11-q12), ***FGFR1*** (8p12), ***FGFR2*** (10q26), ***FOXL2*** (3q23), ***FREM2*** (13q13.3), ***GATA4*** (8p23.1), ***GNRH1*** (8p21), ***GNRHR*** (4q21), ***GPC3*** (Xq26), ***H2AFB*** (Xq28), ***HBA2*** (16p13.3), ***HESX1*** (3p14.3), ***HFE*** (6p21.3), ***HSD17B3*** (9q22), ***HSD3B2*** (1p12), ***IGFALS*** (16p13.3), ***IKBKG*** (Xq28), ***INSL3*** (19p13), ***KAL1*** (Xp22), ***KISS1R*** (19p13.3), ***LEP*** (7q31), ***LEPR*** (1p31), ***LHB*** (19q13.3), ***LHCGR*** (2p21), ***LHX3*** (9q34.3), ***LHX9*** (1q31), ***MAMLD1*** (Xq28), ***MAP3K1*** (5q11.2), ***MAP3K4*** (6q26), ***MC4R*** (18q22), ***MECP2*** (Xq28), ***MKKS*** (20p12), ***MNX1*** (7q36), ***MTMR1*** (Xq28), ***NR0B1*** (Xp21), ***NR3C1*** (5q31), ***NR4A1*** (12q13), ***NR5A1*** (9q33), ***NSDHL*** (Xq28), ***OCA2*** (15q), ***OPHN1*** (Xq12), ***PCSK1*** (5q15), ***PDZD7*** (10q24), ***POR*** (7q11), ***PROK2*** (3p13), ***PROKR2*** (20p12.3), ***PROP1*** (5q35.3), ***RQCD1*** (2q35), ***RSPO1*** (1p34.3), ***SHOX*** (Xp22.33;Yp11.3), ***SMTNL1*** (11q12.1), ***SOX10*** (22q13.1), ***SOX3*** (Xq27), ***SOX9*** (17q23), ***SRD5A2*** (2p23.1), ***SRY*** (Yp11.3), ***STAR*** (8p11.2), ***STAT5B*** (17q11.2), TAC3 (12q13), ***TACR3*** (4q25), ***TCF21*** (6q23), ***TP63*** (3q28), ***TRIM32*** (9q33), ***TSPYL1*** (6q22.1), ***TTC8*** (14q31.3), ***TWIST1*** (7p21), ***VNN1*** (6q23), ***WNT4*** (1p36), ***WT1*** (11p13), ***WWOX*** (16q23), ***XIC*** (Xq12-q13), ***ZFPM2*** (8q23), ZFX (Xp22).

In addition to genetic studies, clinical studies performed by the physician offer a viable front line assessment. A routine family

history should be established through carrier testing in relatives for prior sex chromosome abnormalities. Physical examinations should look for phallic size and appearance, labial scrotal folds, introitus, appearance of gonads, all in relation to gender and age. Laboratory testing can offer a second opinion that confirms the physician's initial diagnosis. Endocrine studies are particularly useful assays, including measurements of levels of LH, FSH, serum testosterone, human chorionic gonadotropin, and so on. Visualization options, including sonography, MRI, or laparoscopy, are a simpler and a more reliable, however, late term option. Histological approaches, although invasive and late stage, are able to offer a definitive diagnosis of the patient in question. Biopsies should demonstrate signs of undeveloped streak glands, as well as other phenotypic aspects of DSD. Treatment options for DSD individuals include surgical repair of the external genitalia, removal of gonadoblastoma-forming streak and dysgenetic gonads, hormone therapy, and so on.

As we can see, treatment for DSD and CGD cases emphasizes open communication between patient and clinician, along with a withholding of gender assignment in newborns presenting with ambiguous genitalia or other symptoms of DSD prior to expert evaluation. Initial contact and communication with the parents of child suspected to have DSD or CGD is vital as these encounters often leave persisting impressions that may or may not be detrimental to the overall psychological development of the patient later on. Cytogenetic and molecular genetic analyses are powerful tools that continue to further the understanding of the molecular basis of the group of conditions, and are critical to the accurate diagnosis and proper management of disorders of sexual development.

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Acknowledgements

To Rolando Garcia, MS for his technical help with the ideogram figures present in this manuscript as well as Paul A. Delgado and Victor Chen for their suggestions.

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