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Male infertility and genitourinary birth defects: there is more than meets the eye

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Abstract

Male factor infertility is a significant problem present in up to 50% of infertile couples. The relationship between male infertility and systemic disease is of significant interest, and emerging evidence suggests a relationship between male infertility and male genitourinary (GU) birth defects (cryptorchidism, hypospadias, ambiguous genitalia, and congenital anomalies of the kidney and urinary tract). Many of these birth defects are treated in isolation by busy urologists without acknowledgment that these may be related to more global syndromic conditions. Conversely, geneticists and nonurologists who treat variable systemic phenotypes may overlook GU defects, which are indeed related conditions. Many of these defects are attributed to copy number variants dosage-sensitive genes due to chromosome microdeletions or microduplications. These variants are responsible for disease phenotypes seen in the general population. The copy number variants described in this review are syndromic in some cases and responsible for both GU birth defects as well as other systemic phenotypes. This review highlights the emerging evidence between these birth defects, male infertility, and other systemic conditions.

Keywords

Genitourinary birth defects; male infertility; copy number variants

Infertility affects 12% of couples worldwide, with male factor present in 50% of cases (1, 2). Although the cause of abnormal sperm production in a large subset of these patients continues to remain unknown, the underlying relationship of male infertility to systemic disease has become an area of significant research and interest. Numerous reports highlight

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that infertile men may be harboring systemic disease, including malignancy, autoimmune disorders, and genetic conditions (3–5).

More specifically, men with congenital genitourinary (GU) defects, such as cryptorchidism, hypospadias, and male external genitalia anomalies, may have spermatogenic failure caused by the genetic defects underlying these conditions. Notably, these men may have significant associated phenotypes, including both syndromic as well as nonsyndromic conditions. Because these conditions are repaired surgically in infants, pediatric urologists treating GU anomalies may be unfamiliar with other systemic or dysmorphic characteristics; conversely, nonurologists treating systemic anomalies and syndromes may overlook GU birth defects.

Proper identification and characterization of male GU birth defects using history and physical examination, characterization of the responsible genes, and assessment of other related conditions are necessary in men presenting with male factor infertility (6–8). Many of these genetic abnormalities are secondary to an abnormal copy number variant (CNV) of a given gene region (i.e., duplications or deletions), which may impact one or multiple genes in the region (9). This review highlights the genetic defects associated with development of common GU birth defects and their implications in infertility as well as describes numerous well-implicated and future candidate genes known to cause GU birth defects.

COMMON GENITOURINARY BIRTH DEFECTS AND HOW THEY CAUSE INFERTILITY

Genitourinary birth defects in men include abnormalities of both the external (testis, scrotum, and penis) and internal (kidneys, ureter, and bladder) GU tract. These birth defects have varying embryologic origins, and, therefore, variable implications and associations with male infertility, ranging from mechanical barriers to spermatogenic failure.

Cryptorchidism

Cryptorchidism, or the failure of testicular decent into the scrotum, occurs in a single testicle in 9% of male births (10, 11). Significant risk factors include low birth weight, preterm delivery, small for gestational age, and twin pregnancies (10). Testicular descent occurs in two phases: the first phase of transabdominal descent and the second phase of inguinoscrotal descent (12). Descent of the testes from their original transabdominal location begins at the 10th week of gestation (13). The intra-abdominal gonad is suspended originally to the diaphragm by the cranial suspensory ligament (14). Descent depends on a complex interplay of numerous factors, and it begins with dissolving of the cranial suspensory ligament and shortening of the gubernaculum (13). Genetic factors, such as the protein insulin-like hormone, provide strong influence during this first phase of descent (13). The second phase of descent involves descent from the inguinal region into the scrotum, which begins at the 25th week of gestation (13). This involves evagination of the peritoneum, known as the processus vaginalis, which facilitates passage through the inguinal canal into the scrotum (12). Androgens play a key role in this phase in addition to increases in intra-abdominal pressure (13). Numerous other factors are involved in facilitating testicular descent, including a functional genitofemoral nerve, calcitonin gene-related peptide and

antimüllerian hormone (15). Given this complex process, cryptorchid testes may be found at any point along the pathway of descent or also may be found in other ectopic locations (such as superficial inguinal pouch, perineal, perihepatic, peri-splenic, and prepenile locations) (15). Cryptorchidism may be unilateral or bilateral, and is associated with increased risks of testicular malignancy (up to 4–9× greater), later spermatogenic deficiency, and infertility, regardless of whether an orchiopexy was performed (13, 16).

Infertility secondary to cryptorchidism is multifactorial and results predominantly from spermatogenic deficiency. Semen abnormalities occur in 30% of men with unilateral cryptorchidism and in 80% with bilateral cryptorchidism (17). Even after orchidopexy, which includes permanent anchoring of the testis into the scrotum, many men continue to have spermatogenic failure (18). This is thought to reflect a more systemic impact on spermatogenesis, rather than an isolated impact of increased scrotal temperature on the cryptorchid testis (18). Infertility in men with cryptorchidism also may be secondary to aneuploidy of chromosome 12, DNA mismatch repair alterations, Hiwi protein (member of piwi gene family), and Y-chromosome instability and microdeletions (*gr/gr* is associated specifically with spermatogenic failure) (19). Several of the most common dosage-sensitive gene defects causing cryptorchidism are discussed in a later section. It is noteworthy that this is a rapidly emerging field. Genecards (https://www.genecards.org) now lists 4,275 genes associated with cryptorchidism in humans. Genomic (microdeletions or microduplications) defects, the most common cause known currently, are discussed in the section on genes involved in GU birth defects.

Hypospadias

Hypospadias is a failure in the development and closure of the urethral plate in men creating a urethral meatus on the ventral penile surface. It occurs at variable rates worldwide with up to 34.2 per 10,000 births in North America (20). Hypospadias also may be associated with other GU defects, including cryptorchidism and/or micropenis, which, when present in combination, warrant a work-up for a disorder of sexual differentiation (21). Hypospadias is common and, to date, 2,433 genes are associated with this birth defect (https://www.genecards.org) and, like cryptorchidism, the cause is identified more frequently as associated with a gene-dosage alteration. Embryologically, development of male genitalia and urethral plate from the genital tubercle begins at the 8th week of gestation followed by elongation of the tubercle from weeks 11–16, with eventual fusion of the urethral folds to create the penile urethra (22). For the majority of hypospadias cases (70%), the urethral meatus is located on the glans, the coronal sulcus, or the distal penile shaft, but meatal openings also may be found more proximally on the penile shaft, the penoscrotal junction, or in the perineum (22). Depending on the extent of hypospadias and functional goals, treatment requires surgical reconstruction with the need for possible staged procedures and various grafts.

Patients with distal hypospadias may have normal spermatogenesis, but the data is limited. Men with proximal hypospadias, however, more commonly have significantly diminished semen volume, sperm count, sperm concentration, motility, and morphology (23). Physical changes and/or consequences of surgical correction, such as stricture

development, additionally may impact sexual and ejaculatory function, as well as urinary function (24). Sexual dysfunction is secondary to altered penile size and penile appearance, including persistent chordee, torsion, or cosmetic outcomes, and has been reported in up to 40% of these men, with limited concerns regarding organic erectile dysfunction from iatrogenic injury of the neurovascular bundle (24). Ejaculatory issues are seen in a third of men, including reduced ejaculatory force, spraying, or dribbling of their ejaculate, with some reports of reduced and absent ejaculate volume (24). These issues may be secondary to urethral anomalies (stricture or diverticula), reduced spongiosal tissue around the urethra, or abnormal prostate or seminal vesicle development (23). These alterations create barriers for natural conception and subsequent presentation for work-up of male infertility.

Ambiguous Genitalia

Ambiguous genitalia includes a wide range of phenotypes, such as micropenis, and occurs in 1 of 2,000–4,500 babies (25). Genitalia may favor either male or female external genital characteristics but can remain unclassified into one specific category depending on the level of virilization. Embryologically, genital differentiation begins secondary to both the *SRY* gene and müllerian-inhibiting substance. This causes the differentiation of wolffian (male) and regression of müllerian (female) structures. External genitalia formation begins at the 8th week of gestation and involves folding and elongation of cloaca and genital swelling, followed by complete formation at week 20 and in males is under the influence of testosterone and dihydrotestosterone (26).

Fertility potential of men with ambiguous genitalia is dependent on the degree of sexual differentiation permitting sexual intercourse as well as the presence of testicular tissue required for spermatogenesis. Men with micropenis are defined as those with stretch penile length <2.5 standard deviations below the mean (27). Due to anatomic restrictions of micropenis, men may be required to explore and experiment with sexual positions to permit satisfactory vaginal intercourse (28). Generally, scrotal anomalies will not affect fertility unless there are associated testicular anomalies.

Congenital Anomalies of the Kidney and Urinary Tract

Congenital anomalies of the kidney and urinary tract represent 30% of all prenatal anomalies (29). Common anomalies of the urinary tract include ureterovesical or ureteropelvic junction obstruction, vesicoureteral reflux, ureterocele, ectopic ureter, ureteral duplication, primary obstructive megaureter and posterior urethral valves, and renal anomalies such as hydronephrosis, agenesis, ectopia, dysplasia or hypoplasia, duplication, fusion, and supernumerary kidneys (29). Embryologically, development of the GU tract and kidneys begins at the 3rd week of gestation and continues until after birth (30). These developments rely on appropriate communication, interaction, and complex interplay between the embryologic metanephric blastema and ureteral bud (31).

Given the shared embryological origin, namely, the intermediate mesoderm, of common genetic abnormalities, men with external GU birth defects also may have congenital anomalies of the kidney and urinary tract. For example, improper development of the mesonephric duct may result in vasal agenesis (obstructive azoospermia) as well as

possible renal anomalies (32). There also exist reports of men with renal anomalies and spermatogenic failure due to an undescended testis (33). Fertility also is reduced in patients with significant renal anomalies because reduced sperm quality is seen in patients with renal failure and chronic kidney disease (34).

GENES ASSOCIATED WITH GENITOURINARY BIRTH DEFECTS

Genetic and chromosomal rearrangements beyond those identified in a karyotype are responsible for male GU birth defects, and subsequently may be associated with infertility for the reasons already described. Many of these genetic changes are due to chromosomal alterations that modify gene copy number, known as CNVs. One of the first such known CNVs was related to the Y chromosome, which contains a few of the genes required for testis development and spermatogenesis (35). These microdeletions are small, and, therefore, not detected with normal karyotype analysis, but rather using molecular microarray techniques, a more recently developed technology (36). These and more advanced techniques, including whole exome sequencing, permitted the discovery of additional CNVs responsible for genitourinary birth defects and male infertility. Some of these genes are dosage-sensitive and cause syndromic conditions, whereas others appear in nonsyndromic individuals and are seemingly benign. Potential gene hotspots for GU anomalies are illustrated in Table 1 (9).

MYC-Associated Zinc Finger Protein

MYC-associated zinc finger protein (MAZ) is located on locus 16p11.2 of the human genome and encodes a C2-H2 zinc finger transcription factor that is thought to compete with WT-1 to impact WNT signaling (37). Abnormalities of the *MAZ* gene occur in a dosage-sensitive manner (38). MYC-associated zinc finger protein is expressed ubiquitously through the body, based on human fetal complimentary heart, lung, brain, intrabdominal organs, and skeletal muscle DNA, but was identified to cause GU birth defects in nonsyndromic patients (38). The discovery of *MAZ* was novel because it was considered historically a simple housekeeping gene, but instead gene deletion was shown to have an important role in GU development, including bladder development, and defects, including cryptorchidism and micropenis (38). MYC-associated zinc finger protein abnormalities were detected in 6.2% of “nonsyndromic” patients with GU birth defects compared with 0% of controls, and 0.22% of the general population (39). Outside of the GU system, other abnormalities based on CNVs of *MAZ* and possible nearby genes include behavioral and intellectual disabilities, speech and language delays, facial dysmorphisms, ocular problems, obesity, seizures, cardiac and gastrointestinal problems, skin changes, dental anomalies, and hirsutism (40).

CRK Like Proto-Oncogene

CRK like proto-oncogene (*CRKL*) encodes a SH2 and SH3 homology adaptor protein involved in the mediation tyrosine kinase signaling pathways (41). As opposed to a simple housekeeping gene, such as *MAZ, CRKL* is associated with the well-known 22q11.2 deletion syndrome, known as DiGeorge syndrome. Similar to *MAZ*, the gene is expressed ubiquitously throughout the body. The role of *CRKL* involvement in the development of both the upper and lower GU tracts was a novel finding. Deletion of the gene locus is

responsible for upper urinary tract abnormalities but also a high incidence of cryptorchidism and micropenis in mouse models (41). Abnormalities of *CRKL* are demonstrated in 1.4% of nonsyndromic patients with GU defects as opposed to 0.09% of controls (39). Interestingly, however, the testicular architecture seen in animal models with abnormalities of this gene revealed testicular atresia, which did not resemble the classic spermatogenic failure expected in cryptorchid testes, supporting the novel role of the *CRKL* gene in fertility and spermatogenic function. These animals also demonstrated lower testis weight and lower sperm count (41). In keeping with phenotypic changes of DiGeorge Syndrome, *CRKL* deletion also is involved with cardiac, developmental, and craniofacial defects, as well as prematurity, endocrine problems, recurrent infections, liver dysfunction, gastrointestinal abnormalities, and hearing and ocular impairment (40).

Vesicle Associated Membrane Protein

Vesicle associated membrane protein (VAMP7) is responsible for vesicle transport from endosomes to lysosomes (42). The *VAMP7* gene is located on chromosome Xq28 and is part of the soluble N-ethylmaleimide–sensitive factor attachment protein receptor family (42). Vesicle associated membrane protein over-expression was detected in patients who had idiopathic disorders of sexual differentiation, suggesting its role in masculinization (42). In a gene-dosage specific manner, *VAMP7* over-expression altered the subcellular localization of the androgen receptor, suggesting interference of ligand-dependent shuttling of the androgen receptor into the nucleus, thereby altering androgen-responsive gene expression, and impairing masculinization (42). Furthermore, *VAMP7* positively impacted transcriptional activity of estrogen receptors, which enhanced development toward a more feminized pathway (42). These changes provided a novel impact of *VAMP7* duplication (over-expression) on masculinization of male GU tract development by altering steroid hormone action in ways never before considered. These studies provided insight into the association of gene-dosage changes on GU birth defects, including hypospadias, reduced penile length, and cryptorchidism (43). Fertility phenotypes from animal studies demonstrated diminished sperm motility and spermatogenic failure with aging (43). The frequency of *VAMP7* duplication in those with hypospadias and/or cryptorchidism is 3.6% (43). Other systemic symptoms of *VAMP7* gene-dosage changes from Database of Chromosomal Imbalance and Phenotype in Humans using Ensemble Resources (DECIPHER) include intellectual disability, facial dysmorphisms, autism, delayed speech, microcephaly, seizures, spasticity, and endocrinopathies (40).

E2F Transcription Factor 1

E2F transcription factor 1 (E2F1), located on human chromosome locus 20q11.22, encodes a transcription factor of the *E2F* family and is involved in cell cycle regulation and apoptosis, exhibiting variable and, at times, opposing functions (44, 45). Its function is highly related to the retinoblastoma tumor suppressor protein (46). Interestingly, both overexpression (microduplications) and deletion (microdeletions) of E2F1 are associated with infertility (45). Those men with over-expression exhibited less severe phenotypes, such as hypospermatogenesis or cryptozoospermia, whereas more severe spermatogenic defects, such as Sertoli-cell only, were identified in men with microdeletion of E2F1(46,48). Abnormal CNV of E2F1 also is associated with cryptorchidism (47). Therefore, E2F1

acts in a dosage-sensitive manner and has roles in both normal spermatogenesis as well as normal testicular descent (45, 47). Gene-dosage changes of E2F1 are present in 7.3% of patients with nonobstructive azoospermia and 0% of fertile controls (45). Furthermore, those with E2F1 exhibit increased susceptibility to multiple tumors (lung, liver, lymphoma, and sarcomas) (48). A DECIPHER query illustrates that E2F1 CNVs predispose patients to other systemic anomalies, including facial malformations, penile chordee, intellectual disability, hearing impairment, autism, short stature, language delay, renal anomalies, cardiac abnormalities, and digit abnormalities (40).

Orthodenticle Homeobox 1

Orthodenticle homeobox 1 (OTX1) is a transcription factor located on chromosome 2p15 and has roles in maintenance and organ regionalization, including the vertebrae brain (49). Although historically OTX1 was identified in neurodevelopmental phenotypes, little emphasis was placed on their role in male GU birth defects (49). Deletions of regions in this gene are associated with external genitalia birth defects, including micropenis and abnormal scrotum, cryptorchidism, small testis, bladder exstrophy, and epispadias, and kidney anomalies such as hydronephrosis and multicystic dysplastic kidney (49, 50). These findings may be explained by the role of *OTX* genes in sonic hedgehog signaling, which coordinates genitalia, bladder, and internal urethral development, or due to altered pituitary hormone release by *OTX1* (49). In a small series of men with GU defects affecting testes, external genitalia, and kidneys, 100% displayed defects in the *OTX1* gene. Additional clinical phenotypes of *OTX1* have a relationship to its pivotal role in brain development, including seizures, developmental delay, and autism spectrum disorder. *OTX1* also is associated with abnormal facial features, ocular changes, microcephaly, and malignancy (non-Hodgkin lymphoma, medulloblastoma, and gastrointestinal cancer) (49–54).

Y-Microdeletions and Short Stature of Homeobox

Microdeletions of the Y chromosome were among the first discovered CNVs and they have well-known implications in male infertility. Microdeletions of the long arm of the Y chromosome (AZFa, AFZb, and AZFc) are involved directly with infertility following analysis of men with idiopathic azoospermia and severe oligospermia and subsequent variable prognostic sperm retrieval rates (55). In addition to infertility, microdeletions of the AZF regions, which encode additional genes, including *DDX3Y*, *ELF1AY*, *KDM5D*, *USP9Y*, *UTY*, and *RBMY*, are involved with other systemic functions, including cardiovascular disease, stroke, malignancy, and neuropsychiatric disease (56).

In addition to these microdeletions, the Y chromosome is flanked by two pseudoautosomal regions (PAR1, on the tip of the long arm of Y chromosome, and PAR2, on the tip of the short arm) that undergo homologous recombination during meiosis with their counterpart on the X chromosome. The remainder of the male-specific region of the Y chromosome does not undergo homologous recombination with the X chromosome. PAR1 encodes numerous genes, including *PLCXD1*, *GTPBP6*, *PPP2R3B*, *CRFL2*, *CSF2RA*, *IL3RA*, *SLC25A6*, *ASMTL*, *P2RY8*, *AKAP17A*, *ASMT*, *DHRSX*, *ZBED1*, *CD99*, *XG*, and *short stature of homeobox* (*SHOX*) (35). PAR2 encodes fewer genes, including *IL9R*, *HSPRY3*, *CXYorf1*, and *VAMP7*, discussed earlier in this review (35). Within PAR1, duplication or deletion

of *SHOX* is associated with variable height and gene haploinsufficiency or duplication is associated with a spectrum of nonspecific stature and skeletal abnormalities, such as syndromic Leri-Weill dyschondrosteosis, resulting in body habitus anomalies commonly seen in Klinefelter syndrome (due to *SHOX* duplication) or Turner Syndrome (due to *SHOX* haploinsufficiency) (57).

As an extension to this, given the variable function of genes on the Y chromosome, abnormal fusion or translocation of the Y chromosome may result in additional phenotypes found in a subset of Y chromosome–microdeleted men. Isodicentric Y chromosomes represent one such change, and this results in a Y chromosome with two centromeres with associated gene duplication and/or loss depending on the regions involved (58). Therefore, numerous mosaic and phenotypic patterns may be seen in those with Y chromosome–associated conditions (i.e., microdeletions or CNVs of PAR1/PAR2 genes), including ambiguous genitalia (up to 75%), short stature, autism, language delay, dysmorphic facial features, mental disorders, and growth delay (59).

Cystic Fibrosis Transmembrane Conductance Regulator

The cystic fibrosis transmembrane conductance regulator (*CFTR*) gene is located on chromosome 7. Various mutations of this gene, most commonly at the phenylalanine position of 508, is associated with impaired protein folding, chloride channel dysfunction, and infertility (60). Various phenotypes exist in those with *CFTR* mutations, but the most severe includes cystic fibrosis, a condition that includes pancreatic insufficiency, chronic bronchiectasis, and recurrent infections (61). In addition to gene mutations, polymorphisms, such as the 5T allele, also reduce protein expression, altering RNA splicing and, therefore, protein translation and penetrance (62). Almost all men (>97%) with *CFTR* mutations display infertility secondary to congenital absence of the vas deferens (CBAVD), resulting in obstructive azoospermia (63). As the vas deferens develops from the mesonephric duct, those without *CFTR* mutations and abnormal vas deferens also can have other GU abnormalities, such as renal agenesis (32).

Although 80% of CBAVD is related to *CFTR* gene mutations described, the remaining have no clear cause (64). Whole exome sequencing of the *CFTR* gene revealed the role of the adhesion G protein-couples receptor G2 *(ADGRG2*), an X-linked gene located on chromosome p22.13, in these azoospermic men (65). Adhesion G Protein-Couples Receptor G2 belongs to a family of receptors with roles throughout the body, but is localized specifically to efferent duct tissue, illustrating an obstructive azoospermia phenotype in the subset of patients who do not have associated unilateral renal agenesis (65, 66).

Kidney Ankyrin Repeat-Containing Protein 1

Kidney ankyrin repeat-containing protein 1 (KANK1) is located on chromosome 9p23 and belongs to a family of proteins involved in cytoskeleton formation through actin polymerization regulation (67). Kidney ankyrin repeat-containing protein 1 impacts neurodevelopmental disorders and has a potential role in the development of GU birth defects (9, 68). It has been found in 1.4% of patients with GU defects. A DECIPHER query reveals an association with cryptorchidism, micropenis, hypospadias, and urethral

and scrotal development, as well as developmental abnormalities, cardiac problems, gastrointestinal issues, hypotonia, short stature, skeletal anomalies, renal abnormalities, vesicoureteral reflux, respiratory issues, and neurological abnormalities (40).

Potassium Channel Tetramerization Domain Containing 13

Potassium channel tetramerization domain containing 13 (KCTD13), located on chromosome 16p11.2, is a substrate-specific adapter of a BTB-CUL3-RBX1 (BCR) E3 ubiquitin protein ligase complex involved in transmission of synapses (69). It has high expression levels in human testes (70). Mutations in *KCTD13* are seen in 2.7% of patients with GU birth defects vs. 0% of controls and 0.22% of the general population (39). Based on a DECIPHER query, *KCTD13* has GU phenotypes of cryptorchidism, hypospadias, micropenis, and vesicoureteral reflux, as well as facial dysmorphisms, short stature, seizures, autism, speech abnormalities, respiratory anomalies, skeletal abnormalities, obesity, and visual impairment (40).

SH2B Adaptor Protein 1

SH2B adaptor protein 1 (SH2B1) is located on chromosome 16p11.2 and belongs to a family of adaptor proteins that bind to receptor tyrosine kinases (71, 72). Deletions of *SH2B1* gene are associated with renal abnormalities (agenesis and chronic kidney disease) (73). Copy number variants of *SH2B1* are seen in 0.5% of patients with GU birth defects vs. 0% of controls. A DECIPHER query demonstrates relationships to hypospadias, as well as language development, facial dysmorphisms, seizures, intellectual disability, cardiac abnormalities, altered body habitus, neurologic abnormalities, and autism (40).

ANDROGEN-DEPENDENT CONDITIONS AND DISORDERS OF SEXUAL DIFFERENTIATION

In addition to specific defects of novel genes, which are implicated in the GU birth defects described, rarer disorders affecting androgen production, metabolism, or androgen receptor function lead to ambiguous and/or altered male genitalia.

Androgen Insensitivity Syndrome

Androgen insensitivity syndrome (AIS) is an intersex condition secondary to mutations of the androgen receptor (*AR*) gene, presenting as a wide array of phenotypes (partial, mild, or complete) (74). In patients with partial AIS, a wide phenotypic spectrum is observed for external genitalia; the same *AR* variant in patients with partial AIS may produce variable phenotypes secondary to either differential expressivity or other modifiable factors (75). Genitourinary features in patients with complete AIS include complete feminization of the external genitalia and infertility (76). Those with mild AIS have undervirilized external genitalia, including micropenis, hypospadias, and cryptorchidism, and may be able to conceive depending on the degree of virilization or the ability to perform surgical sperm retrieval (76). Other systemic features of AIS include isolated infertility, altered stature, endocrinopathies, abnormal hair growth, and inguinal hernias (77, 78).

5α-Reductase Deficiency

5-α-reductase (5ARI) deficiency is a disorder of the five-alpha reductase enzyme, which plays a critical role in steroid metabolism and completes the conversion of testosterone to dihydrotestosterone (79). With a 46XY karyotype, patients with 5ARI have male internal sex structures (seminal vesicles, epididymis, ejaculatory ducts, and vas deferens) and testes, but have external ambiguous-appearing genitalia until puberty where phallic development generally occurs (80). In addition to reduced phallic length after puberty, 5ARI deficiency also is linked to hypospadias (81). In addition to GU birth defects, these men have impaired fertility potential due to low volume and viscous ejaculates secondary to deficient dihydrotestosterone and absence of liquifying serine proteases (82). These men generally do not experience male pattern baldness secondary to reduced dihydrotestosterone levels, but also have reduced facial and body hair (83).

Persistent Müllerian Duct Syndrome

Individuals with persistent müllerian duct syndrome have a 46XY karyotype along with presence of müllerian duct structures, including a cervix, uterus, fallopian tubes, and upper two thirds of the vagina (84). These individuals may exhibit cryptorchidism or testicular ectopia (either unilateral or bilateral) as well as hypospadias (84, 85). They are at an increased risk of malignancy, including teratomas, yolk sac, and embryonal tumors and often have hernias (84, 86). The majority of these patients are azoospermic and only rare cases of fertility in individuals with testis, vas deferens, and epididymis have been reported (87, 88).

Mixed Gonadal Dysgenesis

Mixed gonadal dysgenesis is a rare disorder of sexual development that may present with ambiguous genitalia. These individuals usually have a 45, XO/46, XY mosaic karyotype, and may present with hypospadias, abnormal scrotum, cryptorchidism, and micropenis (89). Interestingly, up to a third may have a normal karyotype, and those who do have a unilateral testicular gonad present are generally devoid of germ cells (3). These men also have cardio-renal malformations, increased risk of malignancy, such as germ cell tumors and gonadal blastomas, and short stature (90, 91).

Disorders of Testosterone Biosynthesis

Defects in testosterone biosynthesis result from enzymatic defects in the steroidogenesis pathway and include enzymes such as 17-ß-hydroxysteroid dehydrogenase, 3-ß-hydrosteroid dehydrogenase, and steroidogenic acute regular protein (92). Depending on the enzyme involved, these individuals may have deficient glucocorticoid (i.e., cortisol), mineralocorticoid (i.e., aldosterone), and/or sex steroid (i.e., testosterone and dihydrotestosterone) production. Therefore, various levels of virilization and ambiguity of genitalia may manifest (92).

46, XX Testicular Disorder of Sex Development

This condition, which includes a 46, XX male karyotype, is a disorder of sexual differentiation with a rare incidence of 1 in 20,000 live births. Embryologically, gonadal sex determination occurs during week 7 of gestation, as a result of expression of sex determining

region Y gene (*SRY*), which results in the differentiation of the bipotential gonad into a testis (12). In the 46, XX male, the defect generally results from the translocation of SRY onto an X chromosome (93, 94). The remainder of the Y chromosome is no longer present. These men may have micropenis, cryptorchidism, and hypospadias, but infertility and azoospermia are most characteristic, secondary to the absence of the remainder of the Y chromosome (94, 95).

SUMMARY

The association of male infertility and GU birth defects is an emerging field of research. Many GU birth defects are unrecognized as a possible constellation of other systemic phenotypes and are overlooked by busy healthcare providers. Men with mild phenotypic features may present for evaluation of male factor infertility before uncovering an appropriate underlying genetic cause. This spectrum of phenotypic anomalies requires adequate education about and understanding of the genes involved and their associated variable normal function. Ongoing translational research is needed to continue identifying additional implicated genes, their dosage-sensitivity, and associated birth defects in an effort to improve the overall health and well-being of men with infertility.

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TABLE 1

Genes that represent potential hot spots for genitourinary birth defects.

Gene	Location	Function	Associated phenotypes
PIK3R1	5q13	Encodes a phosphorylating kinase involved in molecular signaling (96)	SHORT syndrome cryptorchidism, decreased testicular size, ocular changes, respiratory anomalies, intellectual disability, seizures, and abnormal facial features (40, 97)
EYA1	8q13	Protein required for the development of the kidney, branchial arches, eye, and ear (98)	Branchio-oto-renal syndrome, hypospadias, facial dysmorphisms, intellectual disability, developmental delay, hearing impairment, short stature, cranial nerve anomalies, ocular changes, and renal agenesis (40, 98)
HNF1B	17q12	Encodes a homeodomain-containing transcription factor (99)	Renal hypoplasia, renal cysts, hydronephrosis, duplex and horseshoe kidneys, cryptorchidism, vasal agenesis, epididymal cysts, hypospadias, asthenospermia, diabetes mellitus, pancreatic problems, abnormal liver enzyme levels, neurodevelopmental issues, and psychiatric conditions (99, 100)
PAX2	10q24	Encodes a transcription factor that plays a role in embryogenesis (101)	Renal hypoplasia, renal-coloboma syndrome, papillorenal syndrome, vesicoureteral reflux, and cryptorchidism (101–104)
CREBBP	16p13	Involved in transcriptional coactivation (105)	Rubinstein-Taybi Syndrome and bilateral cryptorchidism (105, 106)
MECP2	Xq28	Protein involved in transcription modulation by binding of methylated CpG in DNA (107)	Cryptorchidism, hypospadias, hydronephrosis, urethral abnormalities, speech problems, hypotonia, recurrent infections, neurologic abnormalities, facial dysmorphisms, and brain abnormalities (108)
RBFOX2	22q12	Encodes an RNA binding protein involved in RNA splicing in numerous cell types (muscle, brain, and heart) (109)	Cardiac problems, development delay, facial dysmorphisms, renal development, hypospadias, scrotal development, finger abnormalities, and short stature (40)
DYRKA1	21q3	Protein kinase family (110)	Intellectual problems, failure to thrive, microcephaly, seizures, facial abnormalities, developmental delay, intrauterine growth restriction, feeding difficulties, micropenis, chordee, hypospadias, CAKUT (renal agenesis and hydronephrosis) (111)
FGFR2	10q26	Family of growth factors involved in numerous pathways and expressed in numerous cell types throughout the body (112)	Urethral formation, hypospadias, cryptorchidism, reduced testicular size, intellectual disability, facial abnormalities, renal hypoplasia, vesicoureteral reflux, ocular problems, microcephaly, seizures, developmental delay, dental problems, cardiac problems, altered stature, hand problems, altered chest, and small size for gestational age (40, 113, 114)
INSL3	19p13	Member of relaxin protein family and specific roles in male testicular descent (115, 116)	Bone metabolism, female infertility, developmental delay, facial abnormalities, intellectual disability, renal anomalies (multicystic kidney dysplasia, hypoplasia, agenesis, and hydronephrosis), skin changes, short stature, microcephaly, cardiac problems, and gastrointestinal abnormalities (40, 115, 117)
RXFP2	13q13	Encodes a member of a G-protein coupled transmembrane receptor and receptor for *INSL3* (118, 119)	Cryptorchidism, bone metabolism, osteoporosis, cardiovascular disease (120, 121)

Note: CAKUT = congenital anomalies of the kidney and urinary tract; *CREBBP = cAMP-response element binding protein; DYRKA1 = dual specificity tyrosine-phosphorylation-regulated kinase 1A; EYA1 = EYA transcriptional coactivator and phosphatase 1; FGFR2 = fibroblast growth factor receptor 2; HNF1B = hepatocyte nuclear factor 1β; INSL3 = insulin-like peptide3; MECP2 = methyl CpG binding protein 2; PAX2 = paired box gene 2; PIK3R1 = phosphoinositide-3-kinase regulatory subunit 1; RBFOX2 = RNA binding fox-1 homolog2; RXFP2 = relaxin family peptide receptor 2*; SHORT = short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly, and teething delay.