

THE SEX DEVELOPMENT
HANDBOOK

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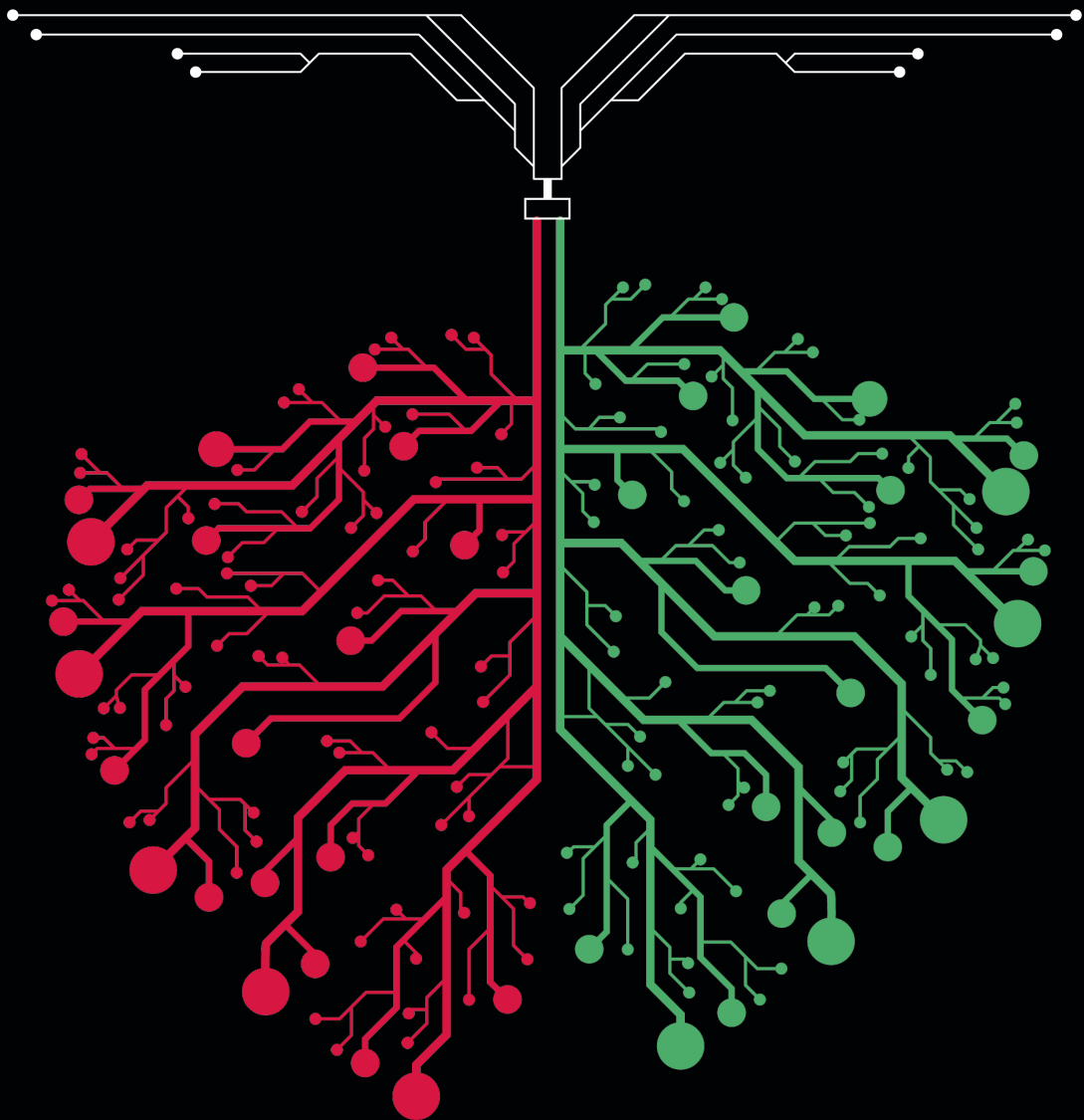
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THE SEX DEVELOPMENT **HANDBOOK**



ZACHARY A. ELLIOTT

WHY WAS THIS BOOK WRITTEN?

Sex is a near universal reality present across almost all multicellular plant and animal species, where two cells called gametes (each with half the number of chromosomes) combine to form a unique individual. There are two specialized roles for this process. One role, the male sex, provides the smaller gamete (sperm). The other role, the female sex, provides the larger gamete (the egg). This difference in gamete type is the universal difference between male and female no matter the species, and it has directly influenced the biological differences between the sexes we see today.

This binary system is produced through the process of sex development, where individual embryos develop as males or females. In most instances, this path is straightforward, producing typical males or females. But in rare instances, the sex development path can be disrupted due to a variety of causes, producing males or females with a Disorder of Sex Development (DSD). Medically complex and often misunderstood, DSDs impact biology, medicine, law, and the individual.

I wrote *The Sex Development Handbook* to provide clarity in a topic clouded by politics, obfuscation, and misinformation. My goal is to provide readers with a clear,

scientific map for how the binary system of sex develops in humans, and how, even in rare cases, a person's sex can and should be reliably traced and understood for accurate medical treatment and compassionate care.

With diagrams of development paths, accessible scientific commentary, and an informed compassion for people with these conditions, the handbook is a first of its kind tool for clinicians, educators, policymakers, and curious readers who want to understand sex differentiation and its rare disruptions, from sex chromosome disorders to enzyme deficiencies and hormone insensitivities.

Each section is structured to stand on its own, while contributing to a coherent understanding of human sex development. I've included diagrams to aid visualization of each condition's common development path, along with thorough scientific references from relevant papers and textbooks to help you learn deeper.

There are real people living with these conditions, and while this book speaks from a biological and clinical perspective, I wrote it with full respect for the personal and emotional realities that often accompany a diagnosis. Understanding sex development is important for everyone, and this handbook provides the essential foundation.

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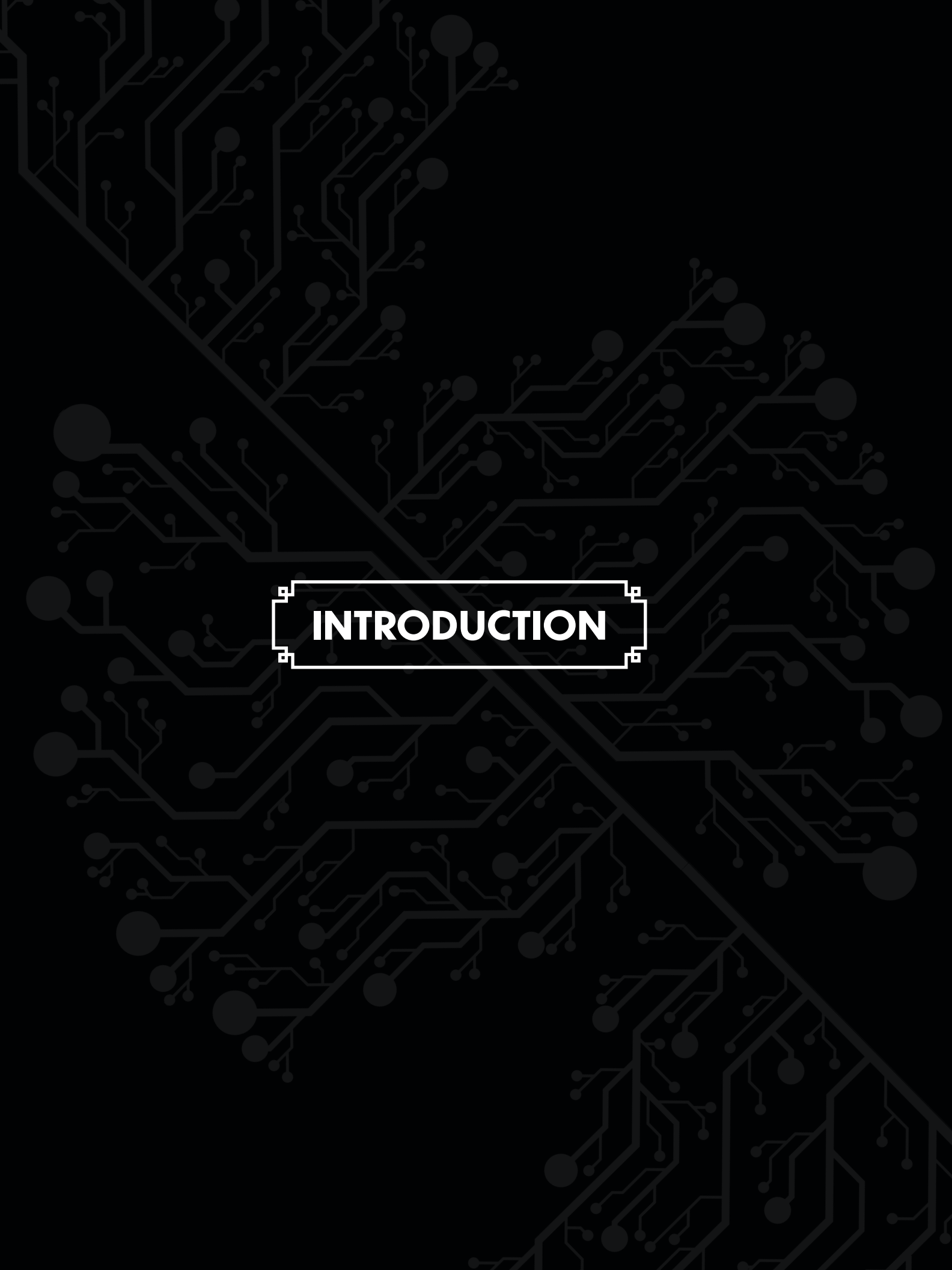
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INTRODUCTION

INTRODUCTION

Scientific background and purpose of the Sex Development Handbook

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Most people have never considered how their sex develops—how we develop as male or female after starting as a single cell. The genetic and hormonal processes that guide this journey are foundational to biology, ensuring that males and females are produced so that the species can successfully propagate into the future generations. Understanding sex development helps us understand not just ourselves, but also those whose development path differs from us.

Yet today, there is vast confusion in the culture around what sex is, how it develops, and the various disorders that impact it. This misinformation creates substantial harm not just on those who have typical sex development, but especially on those with disorders of sex development. When biological facts are obscured or misrepresented, those who are suffering from congenital conditions—who need accurate medical treatment and scientific understanding so that they can live healthy lives—often suffer the most.

This handbook is the definitive response to the cultural confusion surrounding sex development. With visual diagrams and accessible commentary, it provides educators, scientists, parents, students, and policymakers a grounded reference to understand how each of us—whether we have typical or atypical sex development—develop as male or female.

WHAT ARE MALE AND FEMALE?

Across all species with male and female sexes, the male sex is the phenotype (or body plan) that produces the smaller gametes called sperm, and the female sex is the phenotype (or body plan) that produces the larger gametes called eggs (Lehtonen & Parker 2014). This system is called *anisogamy*, and it has evolved in nearly all lineages of multicellular plants and animals. The function of these two sexes is to combine their gametes to form a unique individual—a process called sexual reproduction.

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The difference in size between sperm and egg is important because it represents an underlying functional difference. Sperm function as missiles that deliver a small genetic payload. Other than the genes they will deliver, they hold little to no cellular resources for the zygote (the fertilized egg cell resulting from the fusion of an egg and sperm). Eggs, on the other hand, function as provisioning cells. They hold all the cellular resources used in the initial development of the zygote. This difference in resource investment on the gamete level is the fundamental difference between the sexes. It is so important, in fact, that it led to the major biological differences between males and females, including the differences in reproductive anatomy to support the production and release of the two different gamete types.

It is true there is vast diversity across species in how male and female can be composed. For example, some species like slugs combine the male and female sexes into the same individual organism (known as *hermaphroditism*). Yet most animal species, including humans, separate the sexes, where individuals are either male or female for life (known as *gonochorism*). In both cases, even though there is diversity in how the sexes are composed, there are only ever two: male and female (Scharer, 2017). This is because there is no third gamete type, and therefore no third role in reproduction.

HOW IS SEX IDENTIFIED?

Now that we know how the sexes are defined, how do we identify male and female in practice, even when the production of sperm or eggs cannot be directly observed? Or when an individual is unable to currently produce sperm or eggs?

Secondary sex characteristics like fat distribution, hip width, breasts, facial hair, and voice pitch are common indicators that everyone uses day to day. These traits are usually created from the hormone environment produced by the gonads, but secondary sex characteristics are not

COMMENTARY CONTINUED

Scientific background and purpose of the Sex Development Handbook

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themselves part of the reproductive system and can vary between the sexes. Because of this, they are not defining features of sex and are not always accurate indicators.

On the other hand, a highly accurate marker for sex is chromosomes. In mammals, XY almost always indicates a male, while XX almost always indicates a female. But chromosomes are not the defining feature of sex either. Instead, chromosomes hold the genes that determine your gonad type (testes or ovaries)—the factories that produce sperm or eggs. Because the gonads are the producers of the gametes, and gamete type is the universal difference between male and female, gonad type functions as the primary marker of an organism’s sex (Eggers and Sinclair, 2012). The genitalia—the reproductive structures that transport and release gametes—are secondary indicators. They develop in response to the hormone environment produced from the gonads.

While chromosomes, genitalia, and, to a lesser extent, secondary sex characteristics are usually reliable markers of sex, they are not the universal difference. This is why it’s critical not to confuse these *markers* with the central feature of sex: the *gonad-gamete* unit. The gonad is central because it is the organizer of your sex. It produces the hormone profile that differentiates your genitalia, and it also fashions the raw material of germ cells into sperm or eggs (Rey et al., 2020).

Understanding this hierarchy—that genes determine your gonad type, and that your gonad type organizes your genitalia and gamete type—helps illuminate each person’s development path. Whether you have typical or atypical sex development, your sex has a traceable path. Sex development is not some vague process. It is an orchestrated sequence of development written into every cell.

WHAT ARE DSDs?

For around 0.2% of the population, sex development does not follow the typical path. Whether caused by failure of the chromosomes to divide properly or a single gene mutation passed onto us from our parents, these genetic issues can cause *disorders of sex development* (DSDs).

DSDs are a heterogeneous group of congenital conditions within the binary system of sex that cause atypical development of the gonads, internal genital ducts, or the external genitalia (Witchel, 2018). There are more than 40 known DSDs, each with distinct, sex-specific complications such as infertility. Most result in unambiguous males or females whose sex is clear from external observation. Only a small fraction of DSDs—around 0.01-0.02% of the population—result in “ambiguous” external genitalia or a mismatch of chromosomes and gonads (Sax, 2002). This does not mean, however, that this small portion are not male or female, as we will explore in this handbook.

The umbrella term, *disorders of sex development*, was created in 2006 to replace the outdated terms “intersex” and “hermaphrodite” (Hughes et al., 2006). These old labels were scientifically flawed and clinically unhelpful, leading to misdiagnoses and harmful practices.¹ Because of this flawed terminology and failure to understand individual conditions, ignorant clinicians and scared parents often employed cosmetic surgeries on infants with “ambiguous genitalia” to align them with cultural expectations, rather than addressing their underlying medical needs. Boys with underdeveloped external genitals were castrated and “raised as girls.” Girls with masculinized external genitalia were mutilated and “raised as boys.”

There was profound harm in focusing solely on cosmetics: the underlying internal disorder causing the

¹ The term intersex implied that people with these conditions were “between sexes,” causing public confusion and patient distress, while the term “hermaphrodite” implied people with these conditions were “both sexes,” when these conditions are sex-specific disorders that uniquely impact one sex or the other. To date, no human hermaphrodite has been found, despite the incorrect usage of the term in some medical papers to describe humans with these rare disorders (Rosenfield, 2018).

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COMMENTARY CONTINUED

Scientific background and purpose of the Sex Development Handbook

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atypical genitalia was ignored, resulting in failure of prompt treatment. Some infants died shortly after birth. Others had life-long debilitations and shortened lifespans.

Today, especially in the developed world, the medical approach has shifted. When ambiguous genitalia is identified, clinicians perform immediate screening to diagnose the underlying genetic or hormonal condition. Such atypical genitalia is often a sign of a genetic and hormonal condition that must be identified to prevent life-threatening complications (Lee et al., 2016).

Surgical interventions, when necessary, are now focused on restoring essential functions, such as ensuring a functional urinary tract to prevent complications, rather than on cosmetic conformity. The history of unnecessary cosmetic surgeries on infants with ambiguous genitalia highlights the importance of clear, scientific language and an understanding of a condition's sex development path to ensure long-term health and wellbeing. Through this, clinicians are recognizing that every infant, even those with rare disorders, have a definable sex, and that understanding their sex is critical for treatment.

Instead of hiding information from patients and performing cosmetic surgeries on them before they can consent, honest and direct communication with the parents and patient is now prioritized. Because of this, individuals with these conditions are learning about the reality of their development, empowering them to understand their bodies so they can be informed self-advocates. Our handbook aligns with these values, emphasizing a biology-first, patient-respecting position.

WHAT THIS BOOK COVERS

The Sex Development Handbook features visual diagrams and scientific commentary for 25 unique DSDs, ranging from chromosomal disorders and enzyme deficiencies to hormone insensitivities, gonadal dysgenesis, and multi-organ syndromes. Each left-hand page features a diagram mapping the condition's development

path—from chromosomes, genes, gonads, hormones, and genitalia—along with prevalence, fertility outcomes, and the sex that is affected. Color coding indicates which reproductive structures are male (green) vs female (red), providing a step-by-step visual guide.

Each right-hand page features accessible scientific commentary that provides an overview of the genetic causes, hormonal effects, clinical presentation, diagnosis, and treatment—forming a narrative companion to the diagram. Within the commentary, we also feature in-text citations from scientific journals. You'll see the author(s) name and publishing date within parentheses. To find the full-length citation, see our *References* section at the end of the book.

Together, these paired pages give readers a clear, structured understanding of each condition no matter their field of expertise or level of knowledge.

While not every known DSD is given an individual chapter, an extensive *Glossary of Conditions* near the end of this handbook provides brief descriptions of 40+ DSDs to help readers find relevant information.

WHY THIS MATTERS

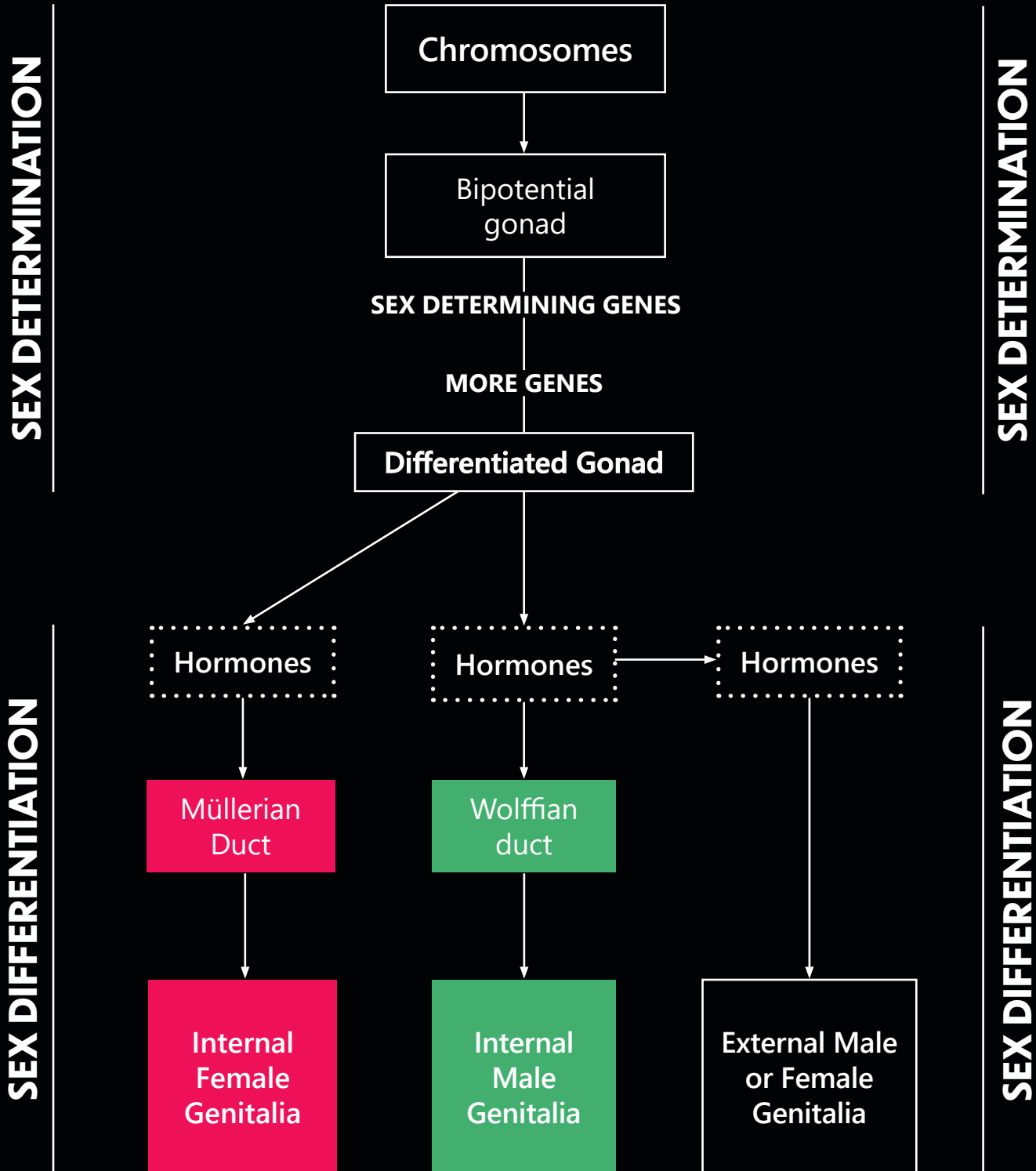
Sex development is not an obscure or ambiguous topic. It is a foundational field of biology that has transformed how congenital conditions are treated, diagnosed, and understood. Its vast impact spans across reproductive biology, medicine, and law.

Accurately mapping the paths of typical and atypical sex development helps us understand every human being, provides an evidence-based framework for sex-specific treatment, and forms the basis for protecting each person's health, well-being, and rights.

The journey of sex development—from a single cell to a fully formed male or female body—is a universal process that we all take. Follow this handbook, and you will learn how each of us becomes a male or female.

SEX DEVELOPMENT BASICS

Mapping the components of sex determination and differentiation



COMMENTARY

Scientific discussion of sex development principles

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No one begins their life by producing mature gametes; this requires a long developmental pathway. Similar to how our organs do not immediately function when they first start developing, so too our sex requires development before its role is fulfilled. In this way, sex can be thought of as a developmental pathway towards sperm or egg production.

Sex development is the process of developing males and females so that sperm and egg production can be achieved. This process involves two distinct steps: first, *sex determination*, and second, *sex differentiation*.

Sex determination is the trigger event that places an embryo on the male or female pathway by directing the gonads to differentiate into testes or ovaries (Eggers and Sinclair 2012). Before sex determination occurs, the gonad sits in a neutral state until the trigger disrupts the balance. In humans, this trigger is genetic through the sex chromosomes we inherit: XX or XY.

At conception, the sperm and egg cell each provide half the genetic material of a full cell, mixing the genomes and creating a new individual. The sperm will provide an X or Y, and the egg will provide an X. In this sense, the sex chromosome in the sperm cell will decide the sex of the baby. For the first six weeks, however, human fetuses are undifferentiated on a physical level, appearing identical externally. During this time, the primordial genital ducts (Wolffian for males and Müllerian for females) are present in each individual, waiting for the differentiation of the gonads into testes or ovaries (Jones and Lopez 2014).

Once the gonad is established thanks to sex determining genes located on the chromosomes, *sex differentiation* uses the hormone profile produced by the gonad to direct the internal and external genitalia down the male or female path. The male embryo differentiates the Wolffian duct and eliminates the Müllerian duct, while the female embryo differentiates the Müllerian duct and eliminates the Wolffian duct. Both sexes still require genetics to guide this process (Rey et al 2020). The initial differentiation

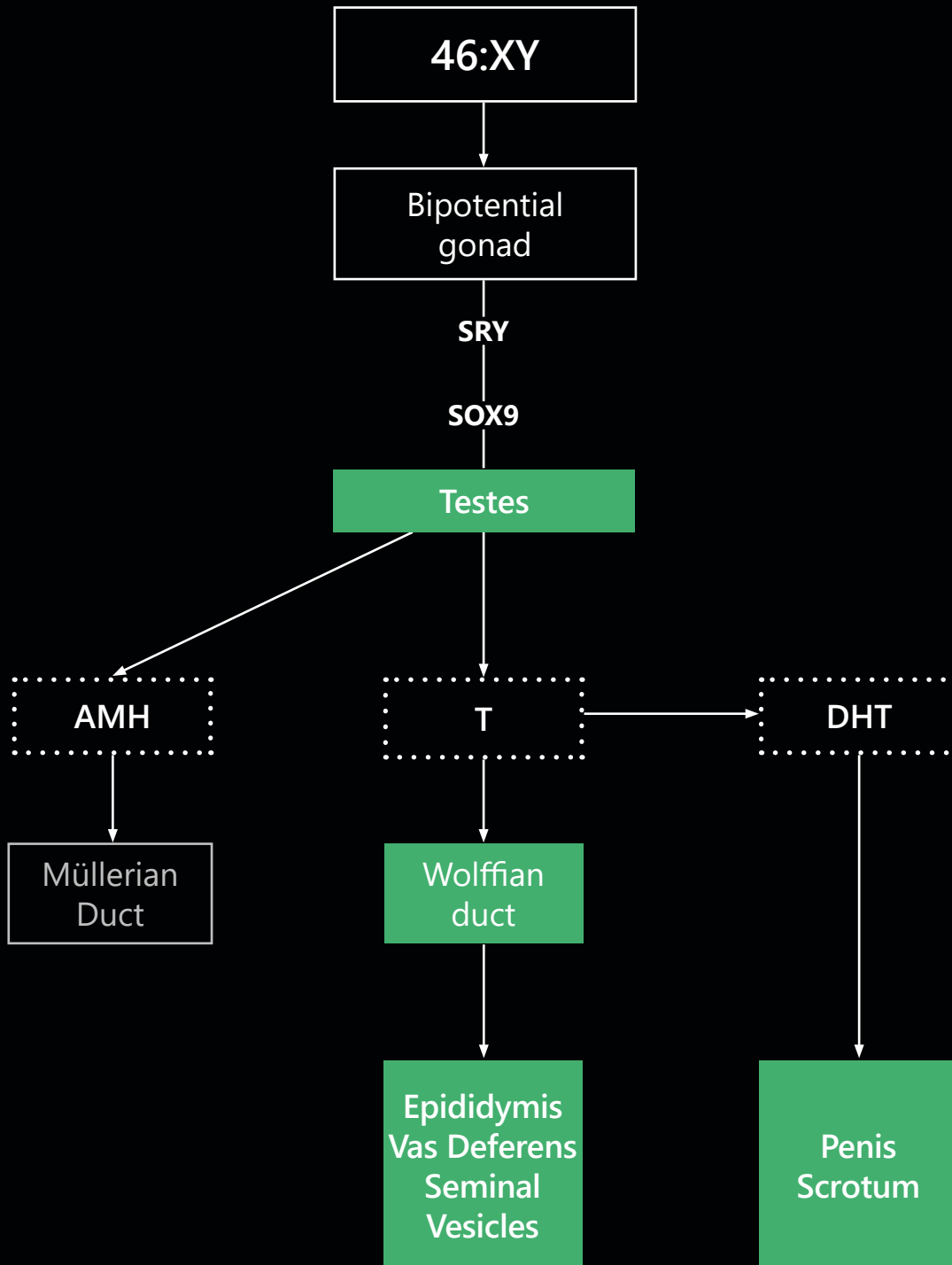
of the genitalia becomes externally apparent around the 11th week, where early ultrasound can predict sex with 90% accuracy (Gharekhanloo, 2018). Once the genitalia is established by the 20th week, sex can be observed in utero with more than 99% accuracy. Genetic testing can also be done as early as six weeks, and this is even more accurate.

Once the reproductive system is differentiated, determined by the gene profile, the male or female pathway is fixed for life. Unlike certain species, where sex change can occur in response to environmental cues, mammals exhibit low anatomical plasticity and therefore cannot change sex. While secondary sex characteristics can be altered through hormones later in life, the reproductive system remains fixed once the human embryo initiates the male or female genetic program (Warr et al. 2012).

The final step of sex development is mature gamete production to fulfill the role of the sexes. This is achieved during puberty, where a pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus travels to the anterior pituitary, stimulating the production of gonadotropins called luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH stimulate the gonads of both sexes to increase production of sex hormones and initiate the process of gamete maturation (Breehl & Caban, 2023). This brain-to-gonad feedback loop is called the hypothalamic-pituitary-gonadal axis, or HPG axis. It is active in utero and for a brief period in the first year of life before becoming more dormant. Its resurgence during puberty is essential for proper sexual maturation, maintenance of the reproductive organs, and gamete production.

In sum, chromosomes hold genes that transform the gonad into testes or ovaries, and the sex-specific hormone profile from the gonad directs the genital ducts to form the male or female genitalia. Next, we will explore the typical path of sex development for males and females in detail. Then, we will move to the various ways this process can be disrupted due to disorders of sex development.

46:XY TYPICAL MALE



46:XY TYPICAL MALE

Scientific discussion

A **Typical Male** has XY chromosomes. The Y chromosome holds the SRY gene. SRY causes testes development. Testicular hormones then form the internal and external male genitalia.

Around the sixth week of gestation, the male sex-determining gene on the Y chromosome, known as SRY, tells the neutral gonad to differentiate into testes (Kashimada and Koopman 2010). SRY sends a signal to many male-making genes, telling them to increase their expression and encode proteins required for testes development. This begins the first step of male development.

While this process starts, the primordial germ cells (or PGCs) migrate into the developing testes. These PGCs can be thought of as the raw material that the gamete factories (the gonads) will fashion into mature sperm or eggs (Hansen and Pelegri, 2021). Their initial fate, whether they will differentiate into young sperm or egg cells, depends on the gonadal tissue environment they reside in: testes or ovaries (McClaren et al. 1995; Kocer et al 2009).

As SRY signals to male-making genes like SOX9, the testes develop Sertoli cells. These specialized cells then help nurse the PGCs into young sperm called spermatogonia (Rey et al 2020). The transformation of spermatogonia into their mature and fertile form requires the AZF genetic region from the Y chromosome. If this region is mutated or missing, the male can experience arrested sperm development or death of the young sperm cells.

While SRY is upregulating male-making genes, female-making genes such as WNT4 and FOXL2, which guide ovary development, are being suppressed (Warr et al. 2012; Witchel 2017). This reveals the push and pull dynamic between the genetic networks of males and females (Estermann and Smith 2020).

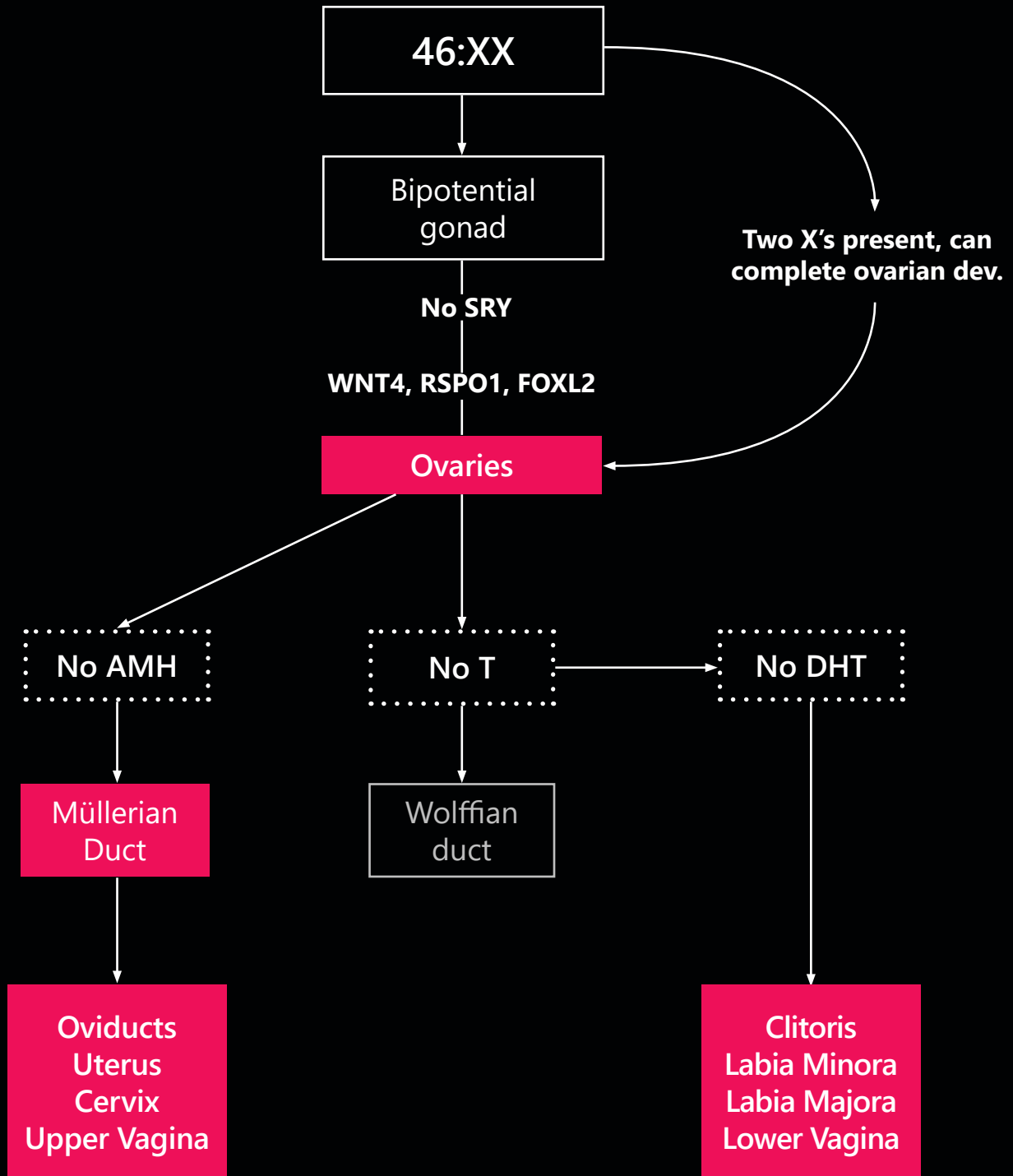
As the gonads develop into testes, we enter the hormonal stage of sex differentiation. To build the male's genitalia, the testes secrete two hormones: testosterone and anti-Müllerian hormone (AMH). Testosterone is produced by the testes' Leydig cells and builds the Wolffian ducts, forming the sperm transportation systems of the epididymis, vas deferens, seminal vesicle, and ejaculatory duct. (Jones and Lopez 2014). While testosterone builds the internal male system, anti-Müllerian hormone is in charge of removing the primordial female ducts. AMH is a special protein produced from the Sertoli cells in the fetal testes. When activated, AMH initiates programmed cell death in the Müllerian ducts, causing them to degenerate (Mullen and Behringer 2014). These ducts would develop into the oviducts, uterus, cervix, and upper vagina if AMH from the testes was absent.

Once the internal ducts are formed, some testosterone is converted into the more potent dihydrotestosterone (DHT) along the external genitalia. The surge of DHT descends the testes, forms the scrotum, and enlarges the penis (Kinter and Anekar 2021).

During adolescence, the sustained increase of GnRH secretion from the hypothalamus stimulates the pituitary to produce LH and FSH. LH stimulates the Leydig cells to create a surge of testosterone, whereas FSH stimulates the Sertoli cells to produce sperm.

This surge in testosterone across development, 15-20 times higher than in females, forms the male secondary sex characteristics (Handelsman et al., 2018). Not only does this surge cause a deeper voice and facial hair, but it also creates larger skeletal structures, greater muscle mass, stronger tendons and ligaments, and larger hearts and lungs. These permanent structural differences remain even when comparing to females of the same height, weight, and age—forming the basis of the male performance advantage in sports (Pike, Hilton, & Howe, 2021).

46:XX TYPICAL FEMALE



46:XX TYPICAL FEMALE

Scientific discussion

A **Typical Female** has two X chromosomes. Autosomal genes initiate the development of ovaries, while genes on both Xs maintain them. Lack of male sex hormones then activates gene networks that build the female genitalia.

The absence of the Y chromosome and its SRY gene allows the female genetic program to dominate. With no male program to suppress them, autosomal genes FOXL2, WNT4, and RSPO1 differentiate the neutral gonads into young ovaries while suppressing testes development (Biason-Lauber 2012). As the initial steps of ovarian differentiation occur, the primordial germ cells (PGCs) arrive inside the gonads. Signals from the female tissue environment then fashion the PGCs into oogonia, the first stage of egg cell development. As these egg cells develop, they are surrounded by Granulosa cells, which nurse them. This layered system for each egg cell is called a follicle.

By week eight, the ovaries have about 600,000 developing egg cells known as oogonia, which will eventually become oocytes. The oocytes are the primary egg cells that will form into a mature egg (ovum) during ovulation. At birth, the typical female contains 500,000 oocytes in each ovary, the only ones she will have for the rest of her life (Jones and Lopez 2014).

While ovarian development can be kickstarted by genes on the autosomes in the absence of SRY, the young egg cells developing inside the ovaries need more to survive. To maintain their health so that many survive through puberty, large amounts of proteins are produced from genes on the female's two X chromosomes that express themselves in double copy (Fukami 2023). Without these proteins the oocytes will experience accelerated cell death, decimating the egg reserve before the female is even born. And if the oocytes die in large numbers, so too will the ovaries. Unlike testes,

which do not need sperm cells to survive, the eggs that comprise the follicles are essential for keeping the ovaries from degenerating (Yao 2005).

The double gene expression does not occur in every X-linked gene, however. In fact, only around 20% of genes in the X chromosomes express themselves in both Xs (Katsir and Linial 2019). What about the other 80%? The answer is found in a phenomenon unique to female mammals called X chromosome inactivation (or XCI). XCI silences one of the X chromosomes in every cell except the gametes. Some genes, like those involved in maintaining the health of the eggs, have evolved to escape this process of inactivation, but most genes on the silenced X remain dormant. If this second X was not inactivated, females would have double the gene products across all X-linked genes, which could result in lethal diseases and cancers.

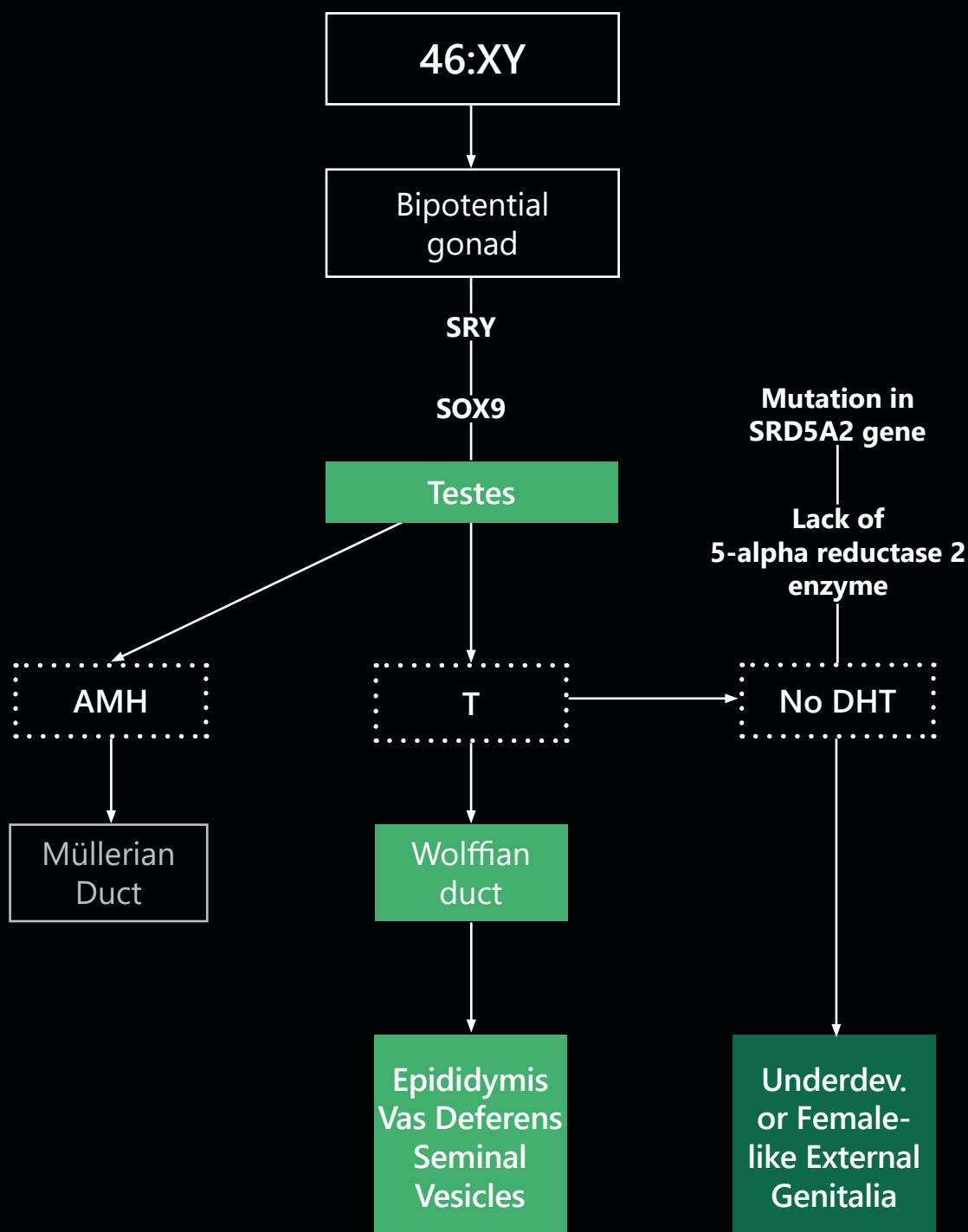
As the ovaries develop, no high testosterone is secreted, and so gene networks eliminate the Wolffian duct. Since no high anti-Müllerian hormone is secreted either, a network of WNT and HOX genes develop the Müllerian ducts into the oviducts, uterus, cervix, and upper two-thirds of the vagina (Mullen and Behringer 2014). Then, since testosterone is low—and thus, the level of DHT is also low—the external genitals differentiate into the clitoris, the labia minora, labia majora, and lower vagina (Baskin et al. 2018).

During adolescence, the increase of GnRH secretion from the hypothalamus stimulates the pituitary to produce LH and FSH. LH stimulates the Theca cells of the ovary to create androgens, whereas FSH stimulates Granulosa cells to convert some of these androgens into estrogen while preparing follicles for cyclical ovulation. The rise in estrogen develops the female's secondary sex characteristics, resulting in breast growth, hip widening, and fat redistribution. Estrogen also builds the uterine endometrium, and the beginning of its cyclical fluctuation causes the first menstruation (menarche).

5-ALPHA REDUCTASE DEFICIENCY

Affects males only | Rare globally; common in D.R. and North Africa | Often fertile

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5-ALPHA REDUCTASE DEFICIENCY

Scientific discussion

5-ARD is an enzyme deficiency in males, impairing conversion of testosterone into the more potent dihydrotestosterone used for the development of the male's external genitalia.

In the 1970s, Dr. Julianne Imperato-McGinley trekked into the remote villages of the Dominican Republic. She was there to investigate strange reports of girls transforming into boys, locally known as the guevedoces (“penis at 12”).

Careful genetic analysis revealed that such people were actually males, and they were missing a crucial enzyme called 5-alpha reductase type 2 (5a-R2). This enzyme converted testosterone into dihydrotestosterone (DHT). During sex development in utero, the male fetus uses DHT to develop the external genitalia: growth of the penis and descending of the testes from the abdomen into an external scrotal sac (Marks, 2004). Without DHT, these male fetuses were born with genitalia that appeared female-like, along with testes inside their abdomens, and no receding hair line or acne as they grew up. The surge of testosterone at puberty, however, was often strong enough to descend the testes, grow the scrotum, and enlarge the penis. Now, the reports that Dr. Imperato-McGinley heard finally made sense.

Scientists in the pharmaceutical industry already knew that DHT was also a major driver of prostate cancer since the 1960s, but a method to inhibit the hormone was unknown. That was until the mechanisms behind the guevedoces were discovered. Pharma companies quickly took advantage of this new discovery: if they could inhibit 5a-R2, they could block the production of DHT. Soon after, the 5-alpha reductase inhibitors known as finasteride and dutasteride were invented (Gurram & Ashley, 2016).

5-ARD begins when both parents pass down the mutated gene, SRD5A2, to the XY embryo. The

expression of the syndrome is autosomal recessive, so one needs two copies of the mutated gene for the disorder to manifest (Kumar & Barboza-Meca, 2022). It is also a sex-limited disorder, meaning that it only affects one sex. In this case, it only affects XY males. While XX females can also inherit 5-ARD, blocking their body’s ability to produce DHT, there are little to no side effects. This is because females do not use DHT for sex development, whereas males do, requiring it for the development of the penis and scrotum. The level of external genital development in XY 5-ARD depends on the level of impairment to the 5-alpha reductase type 2 enzyme. Some cases show complete impairment, and others show more mild impairment.

Fertility can also be impacted, with lower sperm counts and semen volume compared to controls. Low DHT may impair the growth and differentiation of sperm cells and the growth of the prostate. Males with 5-ARD often have a prostate that is 1/10th the healthy size. Small prostates mean that semen volumes are low, harming sperm transport and motility. Undescended testes can also disrupt the careful balance of temperature for sperm creation (Kang, Imperato-McGinley, Zhu, & Rosenwaks, 2014).

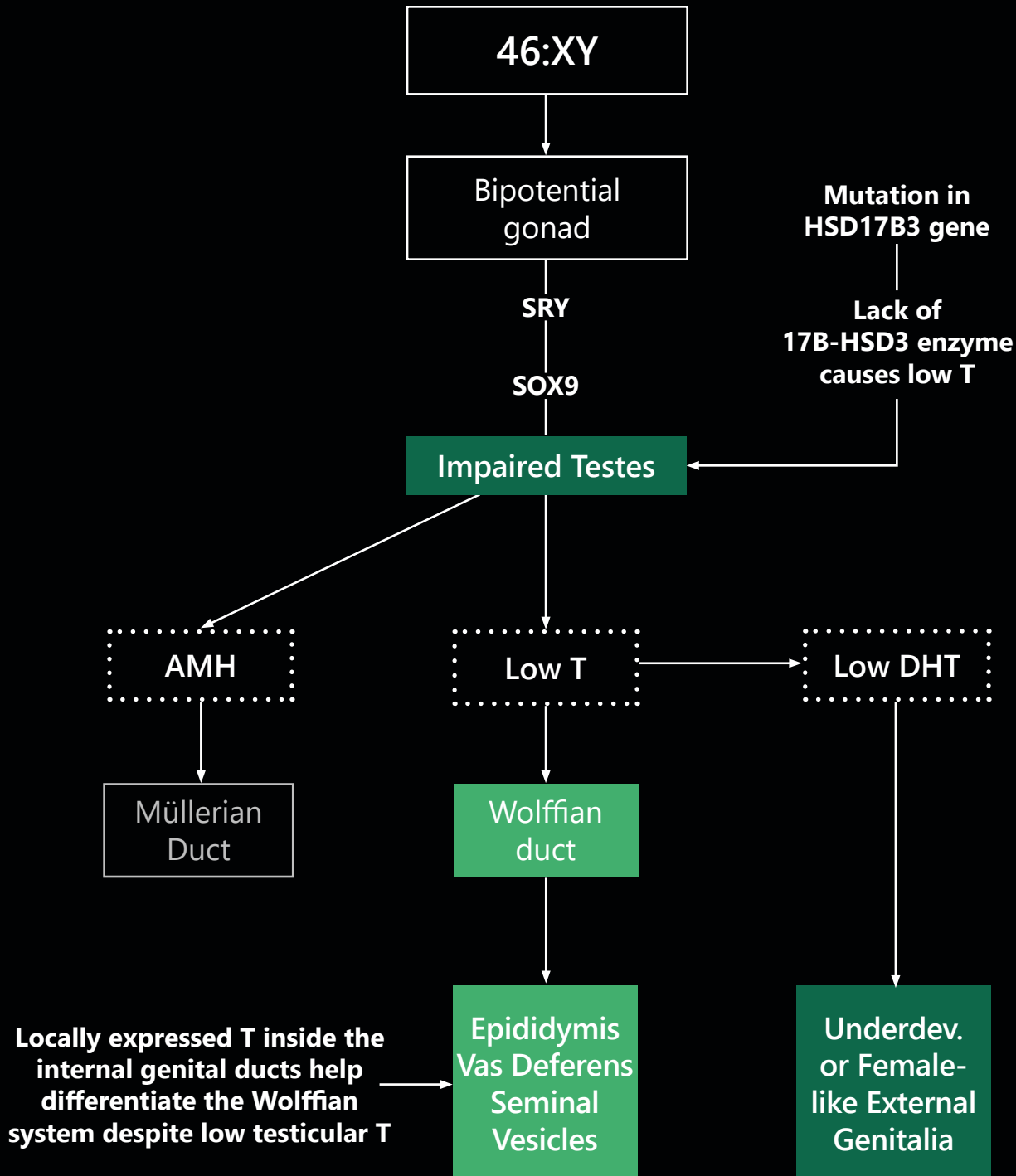
Incidence rates for the condition are difficult to pin down, as they differ depending on the region. In the first world, 5-ARD is very rare, but in other parts of the world, such as isolated communities in the Dominican Republic, Papua New Guinea, Turkey, and Egypt, rates are much higher. This is largely due to isolated populations and the resultant inbreeding, which increases the rates of SRD5A2 mutations.

The treatments for 5-ARD sometimes involve testosterone and DHT supplementation to help the development of the genitalia and secondary sex characteristics. Sperm extraction and IVF practices are also common to restore fertility if genital development and semen volume are inadequate.

17-BETA HYDROXYSTEROID DEHYDROGENASE 3 DEFICIENCY

Affects males only | 1 in 147,000 globally; 1 in 250 in Gaza | Usually infertile

.....



17-BETA HYDROXYSTEROID DEHYDROGENASE 3 DEFICIENCY

Scientific discussion

17B-HSD3 deficiency is an enzyme disorder in males that impairs the body's ability to convert a weak androgen called androstenedione into the more potent testosterone.

The production of sex hormones in our bodies requires a long, multi-step conversion process, where certain molecules are reduced to different forms through the actions of enzymes. The conversion of androstenedione into testosterone is one of the last steps in this process, and when enzymes cannot properly accomplish this step of the conversion process in XY males, 17B-HSD3 deficiency is the result.

It begins when the male is conceived with two mutated copies of the HSD17B3 gene. Sex development proceeds normally at first, with the gonads differentiating into testes. However, inside the testes, the mutated gene cannot provide the appropriate code for the 17B-HSD3 enzyme, resulting in non-functional or only partially functional enzymes. While the male is still able to produce some level of testosterone in other tissues using four other 17B-HSD enzymes, the testes are unable to produce testosterone in large amounts. This is because the enzyme they are missing (the type 3 enzyme) is the primary catalyst of testosterone creation in the testes.

Despite the presence of testes, the lack of testosterone creation causes the male's external genitalia to be underdeveloped, ranging from undescended testes and absent penile development to partial testicular descent and a micropenis or hypospadias (failure of the underside of the penile shaft to fully close).

The internal genital ducts, however, usually develop fully. This is due to locally expressed testosterone from the other enzymes in the internal genitals, helping the Wolffian ducts form and creating the internal sperm transport systems (Mendonca et al., 2017).

In the developed world, 17B-HSD3 is usually diagnosed at infancy due to “ambiguous” genitalia. Infants are thoroughly evaluated and screened for various disorders to determine the diagnosis. Because the genital phenotype of males with 17B-HSD3 is often similar to males with PAIS or 5-ARD, it can sometimes be misdiagnosed. Accurate diagnosis requires not only a measure of testosterone to androstenedione ratio, but also molecular genetic testing that can reveal mutations in the HSD17B3 gene. This is required to confirm the diagnosis (Mendonca et al., 2017).

As the patient grows up, masculinization of the genitalia can often happen at puberty due to a conversion of androstenedione into testosterone by tissues outside the testes due to the other unaffected 17B-HSD enzymes. Testes can also produce a surge in T if the type 3 enzyme is only partially affected, further contributing to masculinization.

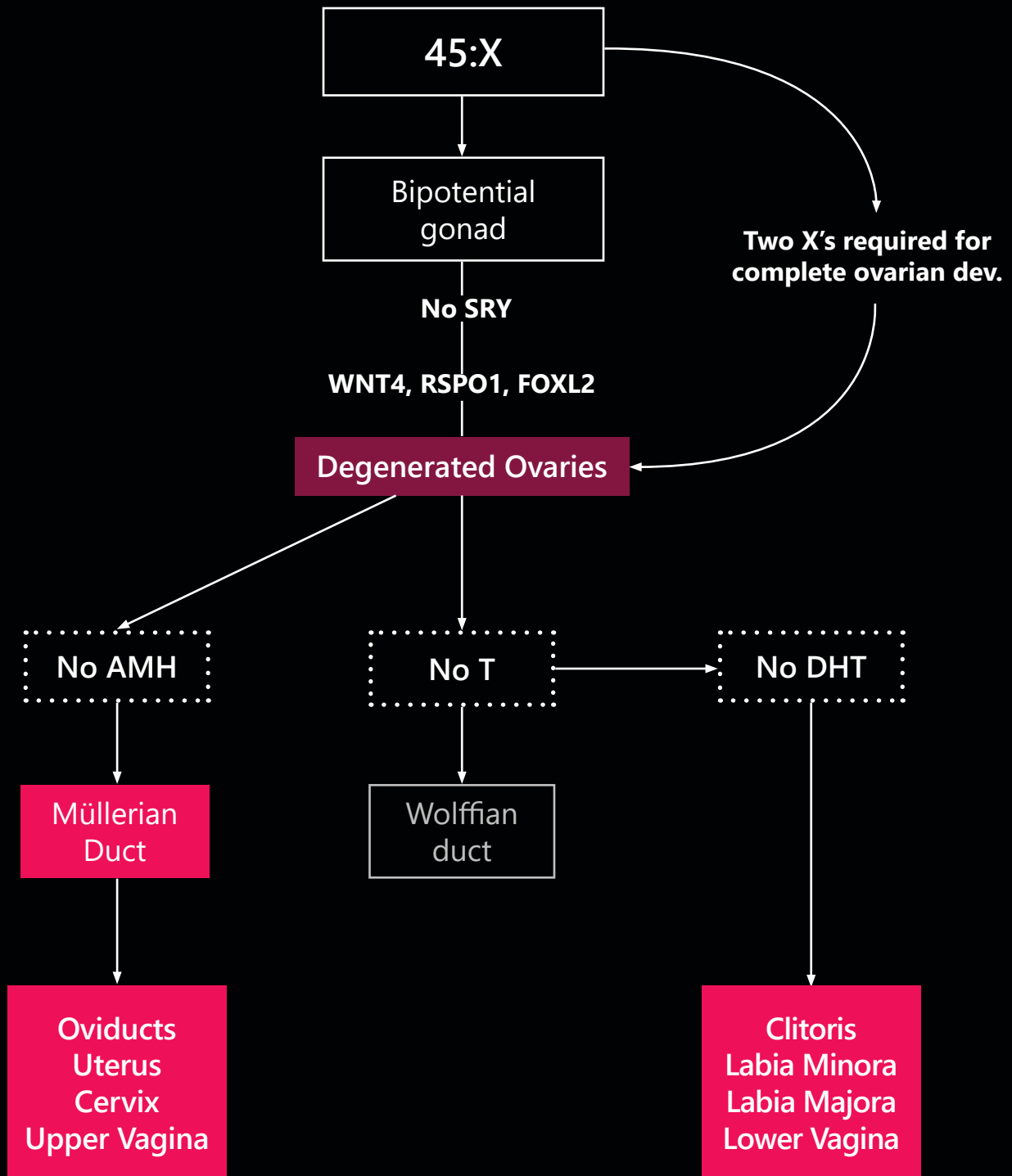
Due to earlier diagnosis of this condition and better treatment options, it is more common to raise males with 17B-HSD3 as males and provide treatment plans that help maintain and improve the health of their male-specific anatomy and physiology. Treating earlier with testosterone replacement therapy, for example, has yielded positive results in many patients (Wang et al., 2024).

Historically and in the third world, lack of medical infrastructure and detailed screening causes many males with 17B-HSD to be identified as females at birth. This delays diagnosis and treatment. Many who are raised as girls adopt a male identity as they begin to recognize the reality of their biology when puberty begins and progresses, masculinizing their bodies and genitalia.

17B-HSD3 reveals that a single mutation in an enzyme along the chain of sex hormone creation can cause severe, sex-specific development abnormalities.

45:X (MONOSOMY X / TURNER SYNDROME)

Affects females only | 1 in 2,500 | Usually infertile



45:X (MONOSOMY X / TURNER SYNDROME)

Scientific discussion

Turner Syndrome is a female chromosomal disorder resulting from the complete or partial loss of one X chromosome. It typically causes short stature, ovarian failure, and heart defects.

Healthy embryos require two sex chromosomes: XX or XY. Most female mammals have XX chromosomes, and humans follow this pattern. But what happens if a female only receives one X chromosome? Not XY. Just X. This is the reality that females with Turner Syndrome face, a sex chromosome disorder that most often results in a karyotype of 45:X.

The disorder is usually caused by nondisjunction, which results in atypical distribution of chromosomes in the parents' sperm or egg cells. At conception, a sperm or egg may be missing the necessary X, or the second X may be defective.

About half of all females with the condition have a 45:X karyotype (known as Monosomy X), while the other half exhibit X chromosome mosaicism, where some of their cells are 45:X and others may be 46:XX or 46:XY. Detecting Y chromosome material, which is found in a small minority of females with Turner syndrome, is clinically important because its presence increases the risk of developing gonadal cancer.

Surviving with 45:X is rare. 3% of all pregnancies begin with 45:X, yet only 1% survive to term (Urbach & Benvenisty 2009). Turner Syndrome is unique in that it is the only monosomy condition that is not always lethal; losing an autosome (non-sex chromosome) is always lethal. This is because development requires the double gene expression from all autosome pairs.

If no early miscarriage occurs, the first step of sex development begins like normal. Just like XX females, with no SRY pathway to suppress the formation of ovarian cells, the WNT genetic network is prioritized, and the gonads begin differentiating into ovaries. As

the ovaries are differentiating, 500 to 1300 primordial germ cells (PGCs) migrate into the gonad (Cox & Takov 2023). These PGCs will proliferate into the millions and become the young egg cells, or oocytes, that the ovarian Granulosa cells will help mature (Nicol et al. 2022). Thus, the *initial* steps of ovarian differentiation do not require two Xs. Something critical is missing, however.

To survive through puberty, the oocytes need appropriate concentrations of proteins from the gene products of two Xs. While one of the Xs is inactivated in the cells of normal females, certain genes escape the process of X-inactivation and express themselves in double copy (see commentary for 46:XX female). This is how the oocytes are maintained. But because there is only one X in 45:X cases, the double gene dosage does not occur. While 46:XX females are born with 1 to 2 million oocytes and are able to maintain about 300,000 of them by puberty, the lack of the second X in 45:X results in a quick exhaustion of the oocyte reservoir. At only 20 weeks, the 45:X female has lost 70% of her egg cells (Fukami 2023). This is in contrast to 46:XX females, who by 20 weeks have only lost 3-5%. Because ovarian health is directly tied to the oocyte health, the death of the oocytes also leads to the degeneration of the ovarian tissue. The fetus then experiences premature ovarian failure. Much of this results in the formation of fibrous tissue called “streak gonads.” Although the ovaries have degenerated, the Müllerian duct still differentiates into oviducts, uterus, cervix, and vagina.

Due to the missing X and the subsequent lack of gene dosage, affected females will often be shorter than average, have extra folds of the skin on the neck, puffiness or swelling of the hands and feet, kidney problems, and heart defects. Treatment involves estrogen replacement therapy to induce puberty and maintain healthy sex hormone levels, while careful monitoring of the heart, kidneys, bones, and thyroid is essential to ensure long-term health and wellbeing.

END OF SAMPLE

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