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Review

46,XX/46,XY Chimerism & Human Sexual Development

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Abstract

The term chimera refers to an organism with cell lines from two or more distinct zygotes. Human chimerism may occur naturally or artificially. Although rare, advancements in genetics and genomics have resulted in the identification of additional natural human chimeras. Three forms of naturally occurring chimerism have been documented in humans: blood group chimerism, microchimerism, and fusion chimerism. Fusion chimerism may occur through several means. Sex-chromosome discordant chimerism refers to individuals with both XX and XY cell lines. There is a large amount of phenotypic variability among 46,XX/46,XY chimeric individuals. The care of people with intersex traits or DSD (Disorders of Sexual Development) is controversial due in part to a history of unnecessary surgical intervention and power-imbalances between the intersex and medical communities. As more 46,XX/46,XY chimeric individuals with intersex traits or DSD are identified, the implications for their care will need to be clarified.

Keywords
46,XX/46,XY; chimerism; human sexual development; intersex; disorders of sexual development

1. Introduction

Many know the term chimera from ancient Greek mythology. In Homer's Iliad, the chimera is described as a creature "of divine stock, not of men, in the forepart a lion, in the hinder a serpent, and in the midst a goat"[1]. The word itself has a long history of use in the life sciences, having originally been introduced in the early twentieth century by German botanist Hans Winkley, who is also credited with later coining the term "genome" in 1920 [2, 3]. In modern genetics, the term chimera refers to a single individual or organism with cell lines derived from two or more genotypically unique zygotes. This is distinct from mosaicism, which results from postzygotic genetic mutations or nondisjunction events in a single zygote. Human chimerism may occur by several means, either naturally, or artificially through organ or bone marrow transplantation [4]. Although naturally occurring congenital human chimerism is thought to be relatively uncommon, advancements in genomic technology and increased access to genetic testing has led to the identification of more of these cases [5, 6], begging questions about the actual prevalence of this form of chimerism. Three forms of naturally occurring chimerism have been documented in humans: fetal and maternal microchimerism, blood group chimerism, and fusion chimerism. Sex-chromosome discordant fusion chimerism occurs in humans when two or more zygotes carrying different sex-chromosomes fuse, resulting in a single individual with both XX and XY cell lines. There is a high degree of phenotypic variability among 46,XX/46,XY chimeric individuals. Here we will review 46,XX/46,XY chimerism as it relates to human sexual development, as well as changes in the care of people with intersex traits or Differences of Sexual Development, also known as Disorders of Sexual Development (DSD), in response to improved medical knowledge and evolving sociological understandings.

2. Blood Group Chimerism

Blood group chimerism occurs in dizygotic (DZ) twins via placental anastomosis, which allows for the transfer of hematopoietic stem cells between fetuses [7]. The first case of natural human chimerism was documented in 1953 in a 25-year-old female blood donor who was found to carry both A and O blood types [8]. Originally, it was thought that her sample had been contaminated, but repeat testing yielded the same intriguing result. Upon learning that the woman had a twin brother who had passed away in early childhood, Dr. Robert Race, a serologist and then director of the Medical Research Council Blood Group Unit in London, was reminded of a case of fraternal twin cattle who were both found to contain a mixture of their own blood and the blood of their respective twin due to placental anastomosis [2]. Race and his colleagues proposed that some of the blood of the woman's twin had made its way into her body during gestation through the same means, where it continued to circulate many years later. This is one of the same mechanisms by which twin-to-twin transfusion syndrome occurs in monochorionic twins [9]. Many cases of this type of chimerism

have been documented since the first case was published in 1953, usually through the inadvertent discovery of blood type discrepancies during routine lab work [10, 11]. Though previously thought to be a rare occurrence, a highly sensitive fluorescence assay developed by Dijk et al. was used to detect subtle blood group differences in twins and triplets, revealing that the incidence of this form of chimerism may be as high as 8% among twins and 21% in triplets [12]. Blood group chimerism has not been directly linked to intersex traits or DSD in humans and is typically confined to peripheral blood cells, though it has been shown to extend to non-haematological tissues including buccal [13] and skin cells [14].

3. Fetal & Maternal Microchimerism

During pregnancy, trace amounts of circulating fetal DNA can be found in the maternal blood. This observation is the basis of non-invasive prenatal screening, which is used to assess risk for certain genetic disorders and chromosomal abnormalities in high-risk patients [15]. It has been shown that most fetal DNA is cleared from maternal blood by 2 hours after delivery [16, 17]. Fetal microchimerism is the most common type of naturally occurring human chimerism [18]. This occurs when fetal cells are trafficked through the placenta and integrate into the maternal organs [19]. Fetal cells have been detected in the mother after as many as 27 years postpartum in one case [20]. Fetal microchimerism has been associated with autoimmune disease [21, 22]. It has also been shown to have both protective and pathogenic roles in cancer development [23, 24]. This mechanism of chimerism has not been linked to intersex traits or DSD in humans, however. Conversely, maternal microchimerism occurs when maternal cells are incorporated into fetal tissues during pregnancy, though this is less well studied [19, 25].

4. Fusion Chimerism

The third type of naturally occurring chimerism observed in humans is fusion chimerism, in which two zygotes fuse during early embryonic development, resulting in a single individual with cell lines from both zygotes. The true prevalence of fusion chimerism in humans is difficult to estimate. Although it is thought to be an exceedingly rare occurrence, it is likely underdiagnosed due to the fact that there is often no readily observable phenotype, even when the two zygotes are carrying different sex-chromosomes [26, 27]. It has been estimated that multiple pregnancies may account for as much as 12% of all naturally occurring conceptuses of which a further 12% result in singleton births [28]. Fusion chimerism may be one explanation for a subset of these singleton births, meaning that the prevalence of this phenomenon could be considerably higher than previously thought.

The first case of fusion chimerism in a human was reported in 1962 in a 2-year-old patient with suspected congenital adrenal hyperplasia who first presented for surgical reduction of an enlarged clitoris and operative correction of a branchial cleft sinus [29]. The patient was also reported to have heterochromia simplex. Through cytological studies, it was determined that the patient had a 46,XX/46,XY karyotype and, upon exploratory laparotomy, one ovotestis was identified and subsequently removed. One typical ovary was also noted. This case is an example of 46,XX/46,XY chimeric ovotesticular disorder, a condition which would have formerly been referred to as “true hermaphroditism” due to the presence of both testicular and ovarian tissue in the patient [30]. Through cytological examination and blood group studies it was determined that the most likely etiology in this case was a double fertilization event in which two ova, or an ovum and second polar

body, were fertilized by two separate spermatozoa before fusing and giving rise to a single 46,XX/46,XY zygote [29]. This is known as tetragametic chimerism, wherein a single zygote receives four gametic contributions [31]. Several other reports of this type of human chimerism have since been documented in recent years [32-34]. This case is also an example of a potentially medically unnecessary surgical procedure being performed on a child with an intersex trait or DSD, a major source of controversy in the history of intersex care [35, 36].

In contrast to tetragametic chimerism, trigametic chimerism occurs through the parthenogenetic division of the maternal genome and subsequent fertilization by two separate spermatozoa or fertilization of one cell and diploidization of the other through endoreduplication, resulting in a single zygote with three gametic contributions [37, 38]. It can also happen that the paternal pronuclei may be duplicated, resulting in a single zygote containing a paternally derived pronucleus in addition to a normal cell line containing both paternally and maternally derived pronuclei [39, 40]. Parthenogenetic and androgenetic events in mammals are associated with teratomas and hydatidiform moles [41, 42] as well as a spectrum of intersex traits and DSD [43, 44].

5. 46,XX/46,XY Chimerism & Human Sexual Development

Alfred Jost was a French endocrinologist who is most well-known for discovering the Müllerian inhibitor, now called anti-Müllerian hormone (AMH), which is expressed in Sertoli cells in early development and plays an important role in sex differentiation [45]. In the absence of AMH, the Müllerian ducts will typically develop into the fallopian tubes, uterus, cervix, and upper part of the vagina [46]. This discovery greatly improved our understanding of human sexual development by showing that the presence of primary male sex characteristics depends on the expression of testicular hormones during development. Jost's early work set the stage for the common view of sexual development as the two-step process of sex determination and sex differentiation, where sex determination refers to the path of the undifferentiated gonad into an ovary or testis as dictated by the chromosomal constitution, and sex differentiation describes the formation of the ovary or testis and the development of secondary sex characteristics as a result of hormonal secretions [47, 48]. This gonadal model of human sexual development may not be entirely comprehensive, however, as some sex characteristics have been shown to result from non-gonadal factors and may precede differentiation of the gonads [49, 50].

The Y chromosome was known to have a sex determining region and a specific testis-determining factor (TDF) based on multiple mouse and human studies of XY "females" and XX "males" but it was not until 1990, 43 years after Jost discovered AMH, that the *SRY* gene was successfully cloned and identified as the testis-determining factor in mammals [51]. Expression of *SRY* promotes formation of the testes through upregulation of *SOX9* and other target genes, signalling for differentiation of Sertoli cells while simultaneously inhibiting development of the ovaries [49, 51]. In the absence of *SRY*, a number of ovary-specific genes including *FOXI2, WNT4,* and *RSPO1* which would otherwise be supressed are expressed, resulting in the differentiation of the bipotential gonad into an ovary [52, 53]. Genetic variants and chromosomal aberrations involving *SRY* and other downstream genes may result in gonadal dysgenesis and conditions such as 46,XX ovotesticular DSD [54-56]. Since *SRY* was first isolated and characterized, many other genes involved in human sexual development have been mapped to the X chromosome and autosomes [53, 57]. It has also been suggested that epigenetics may play a role in the regulation of sex determination as well [57]. Despite these

considerable advancements in our understanding of human sexual development, the exact mechanisms of this process have yet to be completely elucidated and the majority of people with DSD do not have a molecular diagnosis [58, 59].

While studies in mice have furthered our understanding of ovotesticular DSD [60, 61], the extent to which these findings can be applied to human sexual development is uncertain. Gain-of-function mutations and copy number variants involving genes downstream of *SRY* may result in the development of testes in the absence of *SRY*, resulting in *SRY*-negative 46,XX testicular DSD [55, 61]. Conversely, pathogenic loss-of-function variants in the female sex-determining gene *SRO1* have been associated with ovotesticular DSD [62]. It is thought that the presence of *SRY* is sufficient for typical male development, so it follows that translocations involving this region of the Y chromosome commonly result in a normal male phenotype or testicular DSD without development of ovotestes [63, 64]. It is interesting, then, that the spectrum of sexual development in 46,XX/46,XY chimeric individuals ranges from typical sexual development [65, 66] to various DSD [67, 68].

At least fifty cases of sex-discordant fusion chimerism in humans have been documented since the first case was reported in 1962 [69]. Of the fifty individuals described in these cases, most had ovotesticular DSD, while only eleven showed typical sexual development [69]. Of these 11, seven were phenotypically “male” and four were phenotypically “female” and this was from a subset detected by chance in healthy individuals. Most of the remaining 39 cases came to light due to differences in sexual development (DSD) and most had both ovarian and testicular tissue. There is obvious ascertainment bias towards finding such cases, and it is possible that a much larger percentage of XX/XY chimeras are phenotypically male or female. This is true in mouse XX/XY chimeras, first developed by Beatrice Mintz in the 1960s [70], by aggregating two eight cell embryos after the zona pellucida has been removed. In this initial study, only 1% of the chimeras had both ovarian and testicular tissue. This may be due to the very small number of cells that form the embryo proper and the even smaller number that will form gonadal tissue, driving development in one direction or the other by chance [70]. Of the 99% of mice that were phenotypically normal, roughly half were phenotypically male and the other half female, with some bias toward male. This may make sense given that any presence of the *SRY* in some cells, or cells producing AMH, would lead toward a male phenotype, even in mixed XX/XY individuals. This seems likely to be true in human XX/XY chimeras, but more examples are needed to assess this.

6. Intersex and DSD

The term pseudohermaphrodite has been used in medical literature to describe individuals whose gonadal sex is consistent with their chromosomal constitution but who have atypical development of the external genitalia, while true hermaphroditism has historically referred to individuals with both ovarian and testicular tissue, regardless of their karyotype or sexual anatomy [30]. These terms, which are only concerned with anatomical and gonadal sex and do not account for other differences of sex characteristics, are now considered to be pejorative and medically obsolete [50, 71]. The term intersex in the context of sexual development was first used in 1915 by geneticist Richard Goldschmidt to describe the spectrum of sex characteristics he observed in gypsy moth studies [72]. In 1943, Greek physician Alexander Cawadias published *Hermaphroditos: The Human Intersex*, in which he describes human sex as a spectrum and proposes that the term intersex should replace hermaphrodite and its derivatives [73]. This language was adopted by many

physicians in the ensuing decades and supported by advocacy groups such as the Intersex Society of North America and Organization Intersex International.

In 2005 the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology gathered 50 international experts, including physicians and representatives from patient advocacy organizations, for the International Consensus Conference on Intersex in Chicago. Among the many proposals made by the individual working groups was the recommendation that DSD should replace terms such as intersex and hermaphroditism, which the statement describes as controversial, confusing, and potentially pejorative [71]. The statement defines DSD as congenital conditions involving atypical development of chromosomal, gonadal, or anatomical sex. In the consensus statement, 46,XX/46,XY chimeric ovotesticular disorder is given as one example of DSD. The term DSD has been criticized by leaders in the intersex community as being unnecessarily pathologizing due to its inclusion of the word "disorder"[35]. For this reason, some have offered "differences of sexual development" or "variations in sexual development" as alternatives [74, 75]. Several studies on the opinions of individuals with intersex traits have shown that these alternatives are generally preferred to DSD [76, 77]. Some critics of DSD terminology have suggested that it serves to reinstate medical authority over intersex people [35].

Before our understanding of the factors influencing gender identity had expanded beyond physical anatomy to also include genes and hormones, sex at birth was assigned largely based on the appearance of the external genitalia [78]. Surgical treatment of people with intersex traits or DSD date back to the 19th century [79], and possibly even earlier [80]. However, by the 1970s, sexual reassignment surgery in infants with atypical development of the external genitalia had become more common [81]. Early rationalization of these procedures was based on ideas popularized by psychologist and sexologist John Money who believed that gender identity was socially constructed and could be influenced through child rearing. He theorized that children were psychosexually neutral until the age of two years old, a window of time he referred to as the "gender gate," before which time parents could influence the behavioral sex of their child [82].

Money, who had gained notoriety in the fields of gender identity and sexual development through his work with intersex people, co-founded the Gender Identity Clinic at Johns Hopkins in 1966 [83]. A year later in 1967, Money was consulted by the parents of David Reimer, whose penis had been damaged beyond repair during a failed circumcision to correct his phimosis. Money's recommendation was that the child receive sexual reassignment surgery with subsequent hormone therapy and be raised as a female [82]. Although described as a success by Money [84], this work was later discredited [82, 85] and David Reimer would go on to denounce Money's practices and live his life as a male, after learning at age 14 that he was originally assigned male at birth [85]. Reimer later died of suicide at age 38. Despite the fact that Money's claims about the gender gate were never corroborated, his ideas were pervasive [86] and were even adopted by the American Academy of Pediatrics in their recommendations on the timing of elective surgery on the genitalia of male children in 1996 [87]. These recommendations and Money's account of David Reimer are presumed to have resulted in thousands of medically unnecessary and ethically dubious [88, 89] surgical procedures on intersex infants in the years following [35, 90].

7. Conclusion

Human chimeras arising from multiple possible origins may be considerably more common than previously thought, including chimeras formed by the fusion of two or more genotypically distinct zygotes. Approximately 50% of such chimeras would be predicted to be a mix of an XX and XY embryo. This type of sex-chromosome discordant fusion chimerism may result in various DSD or phenotypically normal males or females who would not otherwise come to medical attention. There is great phenotypic variability among 46,XX/46,XY chimeric individuals. The exact reasons for this variability are only partly known, but it nonetheless suggests that chromosomal constitution alone is not sufficient to predict sexual development in human chimeras. Most cases of naturally occurring human chimerism go unnoticed and are only discovered incidentally. Genotyping may lead to the identification of such individuals and clarification of the underlying mechanisms and potential outcomes of these cases, especially when sex-discordant fusion chimerism is suspected or when no diagnosis has been made and clinical findings, endocrine testing, and cytogenetic testing are not suggestive of another form of DSD.

The view of intersex traits such as an atypical appearance of the external genitalia as abnormal or medically emergent serves to uphold a gender binary which has historically contributed to the unnecessary surgical treatment of people with intersex traits or DSD. As more cases of human chimerism are detected, a review of the history of intersex traits and DSD may be warranted, which is also true for other more common causes of DSD.

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Author Contributions

Jason Tate did the primary writing and research for this review, with assistance and direction from Drs. Wei and O'Hara, who also provided editing, ideas, and conceptual framework.

Competing Interests

The authors have declared that no competing interests exist.

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