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Sexes, species, and genomes: why males and females are not like humans and chimpanzees

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Abstract This paper describes, analyzes, and critiques the construction of separate "male" and "female" genomes in current human genome research. Comparative genomic work on human sex differences conceives of the sexes as like different species, with different genomes. I argue that this construct is empirically unsound, distortive to research, and ethically questionable. I propose a conceptual model of biological sex that clarifies the distinction between species and sexes as genetic classes. The dynamic interdependence of the sexes makes them "dyadic kinds" that are not like species, which are "individual kinds." The concept of sex as a "dyadic kind" may be fruitful as a remedy to the tendency to conceive of the sexes as distinct, binary classes in biological research on sex more generally.

Keywords Comparative genomics · Gender · Genomics · Human genome · Sex · Sex differences · Species

> [O]ne often hears the statement that men and women are so genetically different that they might as well be regarded as two different species.
>
> Mid-century sex chromosome geneticist and theorist Susumu Ohno (1971)

In the 2005 issue of *Nature* announcing the complete sequence of the human X chromosome, a headline-stealing paper proclaimed that early genetic analysis of the X showed genetic differences between men and women to be far greater than previously thought (Carrel and Willard 2005). "In essence, therefore, there is not one human genome, but two—male and female" (Variation in Women's X Chromosomes 2005), stated co-author Huntington Willard. *Newsweek* featured the finding, pronouncing that, "The rift between the sexes just got a whole lot bigger. A new study has found that women and men differ genetically almost as much as

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humans differ from chimpanzees" (Guterl 2005). Male and female genomes, the article concluded, have "an altogether different arrangement of gears."[1]

In the weeks following the publication of the article, authors Carrel and Willard promoted their findings as showing that males and females, like different species, have different genomes, that contrary to politically correct visions of a shared, universal human genome, males and females are more genetically different than ever conceived, and that genetics holds the key to these "deep" differences between males and females. A *Los Angeles Times* piece quotes Willard saying, "It's not just a little variation… This is 200–300 genes that are expressed up to twice as much as in a male… This is a huge number" (Hotz 2005). And in a *New York Times* article in which Willard is quoted stating, "Men and women are farther apart than we ever knew," the *Times* writer is led to conclude that women are, indeed, "a different species" (Dowd 2005).

Recent genetic research on human sex differences evidences the emergence of a "genomic" concept of sex, analogizing sexes to "species" and "genetic populations." In this paper, I argue that comparative genetic work on sex differences would do best to dispose of analogies between sexes and species, and the corresponding construct of distinct "male" and "female" genomes. I develop a distinction between species, which are individual kinds, and sexes, which I call "dyadic kinds." Understanding sex as a dyadic kind, I argue, accurately captures the features of sexes as dimorphic yet interrelated populations within a species. Appreciating the distinction between species and dyadic kinds helps to eliminate distortions introduced by the species analogy and brings greater clarity to genomic research on sex.

Carrel and Willard's model of genetic sex differences

In their 2005 paper, Carrel and Willard advanced an "X-escapee" hypothesis of genetic differences between males and females. Humans have 22 pairs of autosomal chromosomes and one pair of "sex chromosomes." Males have an X and a Y (XY), and females have two X's (XX). One X chromosome in each female cell is permanently inactivated early in development, equalizing X chromosome dosage for males and females. Yet some genes on the female's inactivated X may "escape" inactivation. X genes with Y homologues, for example, may escape inactivation in females in order to equalize levels of gene product in males and females. The escapee phenomenon was first empirically demonstrated by Shapiro et al. (1979) for the *STS* gene, which escapes inactivation on the X and for which there is a homologue on the Y. More recently, Carolyn Brown (Brown et al. 1997), with Willard and Carrel, produced data on 33 genes that appear to escape inactivation, and predicted that as many as one-quarter of X-inactivated genes may at least partially escape inactivation.

[1] The estimate of 1–2% genetic difference between males and females, and the human-chimpanzee comparison, do not appear in the inciting 2005 *Nature* article by Carrel and Willard, but the source is certainly Huntington Willard. These ideas appear as direct quotations in the Duke Institute for Genome Sciences press release following the *Nature* publication, and in numerous interviews published in news sources. In a January 2008 interview that I conducted with Willard at Duke University, he reiterated these estimates and comparisons and confirmed that he was the source of them.

In 2005, Carrel and Willard extended this result, using data from the newly completed human X sequence to produce the first comprehensive analysis of the extent of escape from inactivation on the human X chromosome. Using an elegant experimental design—an in vitro assay of rodent/human fibroblast hybrids, which allowed genes expressing from an inactivated X to be distinguished from the active X—Carrel and Willard were able to quantify and localize escape from X-inactivation. They found a larger number of "X-escapees" than they expected. In fibroblasts, 15% of X chromosome genes permanently escaped inactivation; up to 10% more showed activity in some women. The result, that X inactivation is far from complete and is heterogeneous from one woman to another, led Carrel and Willard to suggest that X-escapee genes represent a long-ignored piece in the causal picture of sexual dimorphism. They wrote:

> Because of these heterogeneous genes and the 15% of genes that escape inactivation, the female genome differs from the male genome in at least four ways. First, the Y chromosome endows the male with at least several dozen genes that are absent in the female. Second, the incomplete nature of X-inactivation means that at least 15% of X-linked genes are expressed at characteristically higher (but often variable) levels in females than in males. Third, a minimum of an additional 10% of genes show heterogeneous X-inactivation and thus differ in expression levels among females, whereas all males express a single copy of such genes. And fourth, the long-recognized random nature of X-inactivation indicates that females, but not males, are mosaics of two cell populations with respect to X-linked gene expression. (Carrel and Willard 2005, 403)

X-escapees, Carrel and Willard concluded, "should be recognized as a factor for explaining sex-specific phenotypes both in complex disease as well as in normal, sexually dimorphic traits" (403).

The much-hyped estimate of 1–2% difference between males and females arose directly from this picture of genetic differences between males and females presented by Carrel and Willard. The reasoning goes as follows:

1. 15–25% of the genes on the inactivated female X chromosome escape inactivation, or as Willard stated, 200–300 genes.
2. "Several dozen" genes (perhaps 50) are specific to the human Y chromosome.
3. These 250–350 genes may, in large part, specify sex differences.

If the going estimate of total genes in the human genome is 20,000–30,000, and 250–350 genes differ between males and females, then it might be said that males and females differ by 1–2% of the total coding genome—more than the 1.06% difference between humans and chimpanzees.[2]

[2] Humans and chimps carry almost indistinguishable sets of chromosomes, and comparative analysis of human and chimpanzee protein structure in the 1970s found that human and chimp amino acid sequence differs by a mere 0.7% (King and Wilson 1975). Extensive analysis of aligned segments of coding DNA in the following decades expanded estimates of overall human-chimpanzee divergence to 1–3%, with 1.2% becoming the generally agreed-upon textbook statistic (Marks 2002). Analysis of the first draft sequence of the chimpanzee genome in 2005 by the Chimpanzee Sequencing and Analysis Consortium ("Initial sequence" 2005) has now increased this number to 4–5%.

A simple empirical critique may be made of the claim that males and females differ by "250–350 genes" or 1–2%. Indeed, on examination, Carrel and Willard vastly overestimated the quantitative genetic differences between the sexes. They made assumptions at each level of reasoning, and in their model of sex difference, which systematically skewed their results and overstated differences between the sexes. Rather than 250–350 genes differing in functionally significant ways between males and females, the actual number is likely closer to a dozen.[3]

My focus here, however, is the "genomic" model of biological sex differences advanced by Carrel and Willard, and uncritically embraced by many genetic researchers.[4] At issue is Willard's conclusion that, "*In essence, therefore, there is not one human genome, but two—male and female*." Do human males and females

[3] When Carrel and Willard assert that there are "several dozen," or about 50, male-specific genes, they assume that these are fully-functioning true male-specifics coding for unique proteins. Actually, there is a high rate of duplicate genes and pseudogenes on the Y. As Ross (2005) point out, that there are likely only about 15 unique male-specific genes on the Y. Carrel and Willard also imply that there is a reasonable expectation that these genes should play a role in broad phenotypic differences between the sexes. The 15 male-specific genes on the Y chromosome include many producing the same gene product or contributing to the same functional pathway. These genes also play a highly specific role in the male testes and are therefore likely to be of limited value for explaining global sex differences, as suggested by Carrel and Willard. For female-specific X-chromosomal genes, Carrel and Willard imply that escapees represent "extra" genes in females, or "double" the dosage of as many as 200–300 genes in females. But by and large, escapees express at *far* lower levels than the active copy. Talebizadeh et al. (2006) found that "gene expression levels for a distinct gene that escapes from inactivation might be as low as 25% in the inactive X compared with the active X chromosome" (680). Nguyen and Disteche (2006) found that "only a few escape genes have a significant increase in expression in females, whereas most show a modest increase, no increase or even a decrease in expression" (48–49); moreover, "only one-fifth of the human escape genes show expression from the inactive X chromosome that reaches 50% of that of the active chromosome" (51). As a result, Carrel and Willard also appear to have vastly overestimated the number of genes showing escape from inactivation. X-escapees that are candidates for explaining sex differences must not be located on the shared pseudoautosomal region of the X and Y, nor have a known identical, fully-functioning homologue on any other region of the Y. When these are ruled out, the numbers drop dramatically. Craig et al. (2004) located only *36* non-PAR escapee genes upregulated in lymphocytes, and a more extensive in vivo study by Talebizadeh et al. (2006) found only *nine* non-PAR escapee genes expressing at a higher level by at least a 1.5 female-to-male ratio in at least three human tissues.

[4] Among the leading sex chromosome geneticists who I interviewed for this project, the notion of separate male and female genomes and the greater difference between male and female genomes compared to humans and chimpanzees is taken as unproblematic. MIT Y-chromosome researcher David Page, for example, concluded the 2003 paper detailing the complete sequence of the human Y (Skaletsky et al. 2003) by arguing that males and females differ genetically by approximately "two percent" and predicting that the dogma of a single human genome would find its limit with sex. He wrote, "It is commonly stated that the genomes of two randomly selected members of our species exhibit 99.9% nucleotide identity. In reality, this statement holds only if one is comparing two males, or two females. If one compares a female with a male, the second X chromosome (160 Mb, or roughly 3% of the diploid DNA content) is replaced by the largely dissimilar Y chromosome (60 Mb, or 1% of the diploid DNA content). This common substitution of the Y chromosome for the second X chromosome dwarfs all other DNA polymorphism in the human genome" (Skaletsky et al. 2003, 836). Page continued, "The present sequence of the MSY [male-specific region of the Y chromosome], and the emerging sequence of the X chromosome, offer the near prospect of a comprehensive catalogue of genetic and sequence differences between human males and females" (Skaletsky et al. 2003, 836). Similarly, in a looser setting, a 2003 *Boston Globe* article quotes Page saying, "We all recite the mantra that we are 99-percent identical and take political comfort in it. But the reality is that the genetic differences between males and females absolutely dwarf all other differences in the human genome" (Bainbridge 2003).

have different genomes? Can human males and females be compared as we might compare species, or genetic populations?

"Thinking genomically" about sex difference

Willard suggests that rather than a single human genome, we should think of males and females as having different genomes. The question of whether it is best to think of two human genomes rather than one is more complex than it first appears. For one thing, it is not a simple factual question of whether quantitative genetic analysis shows differences between males and females that are comparable to those between humans and chimpanzees. Clearly it is possible to compare the genetic make-up of males and females using genomic technologies and data—the high-throughput and bioinformatic tools of contemporary genomics—and find some differences between them. Yet genetic and genomic differences between groups are not sufficient to establish the much stronger claim that these groups have "different genomes." In other cases in which there is substantial variation between humans (for instance, people of different continental ancestries), we do not conceive of group differences as different genomes, but as genotypic diversity within the human genome. Rather, the answer to the question is a model-theoretic choice, based not solely on the empirical extent of genetic difference between males and females, but also on the explanatory aims at hand and the values and social aims of the researcher or research community.

Part of what gives Willard's statement, "In essence, therefore, there is not one human genome, but two—male and female," its effect and significance is its startling reversal of the mantra of the 1990s Human Genome Project (HGP)—that there is a single human genome and that humans are 99.9% identical. The idea of a single, universal human genome underpinned the HGP's logic that sequencing a single human male would reveal the human genome, and that this would in turn illuminate the fundamentals of human biology and disease and unravel the natural history of the human species. From a "human genome" perspective, that female bodies have two X's, while male bodies carry X and Y, matters not at all. The idea of a "human genome" made up of 22 autosomes plus X and Y (and mitochondrial DNA), characterizing the entire genetic inheritance of the human population, accurately captures the fact that the entire hereditary material of the human species is contained in a single haploid set of chromosomes, plus one of each sex chromosome.[5] For the shared X and the autosomes, the genome is near-perfectly identical from one human to another. The power and importance of this idea of a single, shared *human* genome in late twentieth century science and liberal social discourse should not be underestimated.

[5] This concept of the "human genome" is also surely a construct, even an idealization. But it is an accurate idealization, facilitating genetic analysis and reasoning without introducing distortions or leaving out essential features of genetic ontology. Recently, human genomics has undergone a shift toward studies of human diversity, stressing the genetic differences between racial and ethnic populations and people in general, not just male and female (Armour 2009; Lahn and Ebenstein 2009; Lee 2005; Leroi 2005; Tuzun et al. 2005). The consensus that there is a single human genome, however, still holds

The first, obvious, point to be made is that Willard's construction of sex differences in the genome as "two different genomes" inaccurately implies far greater genetic differences between the sexes than is the case. Sex differences in the genome are very, very small: of 20,000–30,000 genes, marked sex differences are evident in perhaps half a dozen genes on the X and Y chromosome, and, it is hypothesized, a smattering of differently expressed genes across the autosomes. Researchers have doggedly searched for sex-based gene expression differences in dozens of tissues in the human body, including the brain, yielding limited, inconsistent results, and no strong candidate genes for sex differences (Delongchamp et al. 2005; Nguyen and Disteche 2006; Rinn and Snyder 2005; Talebizadeh et al. 2006). In DNA sequence and structure, sex differences are localized to the X and Y chromosomes. Males and females share 99.9% sequence identity on the 22 autosome pairs and the X, and the handful of genes on the Y are highly specific to male testes development. Thinking of males and females as having different genomes exaggerates the amount of difference between them, giving the impression that there are systematic and even law-like differences distributed across the genomes of males and females, and playing into a traditional gender-ideological view of sex differences.

But this is not the tack I wish to take here. Regardless of the number of genes that are found to differ between human males and females, I argue that we should resist this genomic construction of biological sex differences. "Genome" is a concept used to fix research agendas and horizons and make salient certain ontological categories in the genetic landscape. At this time, 'genome' is a powerful word with enormous authority and resonance and the ability to shape scientific research agendas. Whether the concept of "genome" is apt, clarifying, and constructive for characterizing genetic sex differences is a not a matter of whether there are quantitative genetic differences between the sexes. Rather, it depends on the role that we wish both sex difference and the concept of the "genome" to play in biological explanation and ontology. It also depends on the importance that we place on countering harmful gender-ideological thinking in science and society. Values, both empirical and contextual, have a role in our choice of ontological frameworks, models, and descriptive language in science. At present, for instance, we choose to work with a concept of a "*human genome*," and we choose *not* to call haplotypes associated with racial and continental ancestry "genomes." Analysts of genetic research on race have argued strenuously that data should not be organized and marked by race (International Haplotype Consortium 2004; see also Koenig et al. 2008), carving preconceived social ontologies into our genomic models and DNA sequence databases as the opening gestures of the human genomic era. I suggest the same with respect to sex difference.

Species have genomes

Species are the primary unit of classification in biological taxonomy. It is possible to define species and arrange them in relation to one another in multiple ways (Dupré 1993). Commonly, species are defined as reproductively isolated interbreeding

groups of organisms, as descendents of a single common ancestor arising from a speciation event, and/or by shared phenotype such as morphology (Mishler and Brandon 1998 [1987]; de Queiroz and Donoghue 1998 [1988]).

As the concept of the "human genome" reveals, in common scientific parlance a 'genome' refers to the genetic code specifying a species. Textbooks frequently define a 'genome' as the complete genetic "instructions" for a species. Species have genomes. 'Genome' refers to the complete gene complement—chromosomes, genes, and, increasingly, the relevant regulatory and epigenetic apparatus—of an individual or species (Gregory 2005, 3). This is the sense in which we can have a "Human Genome Project." The term 'genome' is used, in this context, to refer to the entire genetic content of the species. This includes, in principle, the profile of genetic diversity within a species. Individuals in a species may have different variants of a gene—for example, eye color—but they still share the same genome. In lay terms, the human genome is what people mean when they refer to "the gene pool."

Differences between species' genomes may be genetically quantified. Questions about phylogenetic relationships (time since most recent shared ancestor of two species; location on evolutionary tree) in large periods of evolutionary time drive these estimates; thus, they are referred to as "genetic distance" and "genetic divergence." Comparisons between species and between populations within a species make use of a set of highly formalized model-theoretic assumptions that permit making certain kinds of inferences about *phylogenetic distance* and *population structure*. For instance, this kind of comparative genomic work has corroborated the "Out of Africa" hypothesis of human migration by showing that human genetic diversity maps onto human linguistic diversity and flows along the historical pathways of human migration and colonization. It also validated the hypothesis that chimpanzees are among the closest living human relatives by demonstrating the high degree of similarity of their genomes. Comparative genomics of this sort may then generate hypotheses in *functional genetics*, suggesting genetic loci implicated in traits that differ between species or populations.

I argue that the genomic conception of maleness and femaleness is diagnostic of the continuing influence of implicit phylogenetic thinking in biological conceptions of maleness and femaleness (Ohno 1971). Comparative genomic, phylogenetic thinking overlays genomic models of differences between the sexes in a way that portrays the sexes as diverged descendents of a single ancestor: as different species. Nowhere is this more evident than in the presentation of human-chimpanzee differences as a measuring stick for male–female differences. The formulation of males and females as having different "genomes" is grounded in this comparative genomic approach to sex differences.

A possible objection

Before proceeding with the argument, it is necessary to consider a possible objection. The concept of the 'genome' is not, of course, indelibly tied to species.

Consider, for instance, the notion of a "cancer genome," which has emerged in recent years. "The Cancer Genome Project" at the Sanger Institute, UK, "The Cancer Genome Atlas," sponsored by the National Institutes of Health, USA, and the "Cancer Genome Anatomy Project," of the National Cancer Institute, USA, are all multimillion-dollar, multi-center research initiatives targeting the so-called "cancer genome." These projects use data from the human genome sequencing projects and the high-throughput and data analytic technologies developed for human genome analysis to search for and catalogue the genes and gene processes involved in cancerous tumor formation. If there is such a thing as a "cancer genome," it seems plausible that we might apply the concept of 'genome' to genetic sex differences in a way that does not imply that sexes are like species or lineages.

The term 'genome' is now finding many unorthodox uses, probably because it has high epistemic authority at this time and carries the power to direct resources toward particular research agendas (Lederberg and McCray 2001). In the case of the "cancer genome," the term 'genome' has two functions. First, it refers generically to a set of genes. In this case, it is a set of functionally specific genes of interest for human medical research. The "cancer genome," like other disease-specific "genome projects," is shorthand for an annotation of the human genome cataloguing all of the genes and gene processes involved in cancer. Second, these cancer initiatives are "genome projects" because they are working with the dataset of the human genome and using genomic technologies. For instance, The Cancer Genome Project's website ("The Cancer Genome Project" 2007) states that "TCGP is *using the human genome sequence and high throughput mutation techniques* to identify somatically acquired sequence variants/mutations and hence identify genes critical in the development of human cancers." The Cancer Genome Atlas website ("The Cancer Genome Atlas" 2008) similarly describes the effort as "a comprehensive, coordinated effort to accelerate our understanding of the molecular basis of cancer through the *application of genome analysis technologies*, including large-scale genome sequencing." So in the second sense, the term 'genome' here signals the data-analytic approach of the research—the project will process raw genome data, and the end result will be a specialized database of expressed sequence tags related to cancer for use by other researchers.

The "cancer genome," then, is a *genomic* catalogue of all of the genes and gene processes in the human genome involved in cancer. The analogue for sex for this usage of 'genome', then, would be the "sex genome," a genomic catalogue of all of the genes and gene processes in the human genome involved in sex determination and sex differentiation. The cancer genome and the sex genome are annotations of the human genome. Both, it seems to me, would be entirely uncontroversial functional genomics projects. (We might separately debate whether we should refer to them as "genomes," but for the time being let us allow that this is an acceptable current alternative usage of the term 'genome.')

The notion of separate "male genomes" and "female genomes," rather than one human genome, is not like the "cancer genome" construct, however. The statement, "There exists not one, but two human genomes—cancerous and non-cancerous," for instance, is non-intuitive, if not nonsensical, and certainly does not carry the exhaustive implications of the binary division of the human genome implied by

male and female genomes. The notion of two human genomes—male and female—makes a different, and quite radical, ontological claim. The idea of separate male and female genomes is not a proposal to annotate the human genome for genes involved in sex differences. It is an assertion that male and female genes are so systematically different that we should, at least in the context of sex research, set aside the idea of a single human genome and analyze males and females independently of the other. According to this view, we should treat male and female genomes, which are very similar but also very different, just like we treat human and chimpanzee genomes, which are very similar but also very different. This helps to illuminate the surfacing of the claim that "human males and females are more different than humans and chimpanzees" alongside Willard's claim that "there is not one human genome, but two.".

The projection of species concepts onto sex differences

In the present context, then, to say that males and females have different genomes is to say that the sexes are, in substantial ways, like species. More specifically, it gives a certain ontological parity to sexes and species. It also strongly asserts the ontological primacy of sex to genetic and genomic reasoning, and to biological and evolutionary reasoning more generally. In urging us to "think genomically" about sex differences, Willard situates genetic sex difference as a comparative genomics question, similar to comparative genomics of species. Pressing the idea that there is not one human genome, but two separate male and female genomes, the Willard case shows the persistence of phylogenetic thinking in the background of biological models of sex difference.

Carrel and Willard's approach to measuring and describing sex differences represents an emergent formulation of biological sex differences—positing separate "male" and "female" genomes—reflected more recently in efforts such as the Leiden University initiative to sequence the "female genome" ("Dutch Scientists" 2008). This "thinking genomically" about sex differences, I argue, is diagnostic of the projection of comparative genomics models into comparative genetic work on the sexes. In this case, the language and models of one area of inquiry (comparative genomics) shape, structure, and transform, in an often unacknowledged way, the thinking in another area of inquiry (genetics of human sex difference).[6] Representing the sexes as different genomes invites phylogenetic, populational, and general comparative genomic reasoning into comparative work on the sexes. These powerful modes of genomic reasoning shape, structure, and transform, in an often invisible way, thinking about genetic differences between the sexes.

Because species, populations, and genomes are the primary units of comparative work in biology, it seems natural, perhaps unavoidable, and possibly harmless that they surface as analogues in comparative work on sexes. Yet here a distinction between comparative genomic work leading to *functional genetics* hypotheses, and

[6] A similar example of this phenomenon of model projection in science may also be seen in the strong influence of mid-century cybernetics and informatics lingo in genetics research of that period.

comparative genomic work permitting *global estimates of difference, distance, or divergence* between classes must be appreciated. Indeed, for *functional genetics* research, which seeks information about the role of particular genes or gene pathways in an organism's development, comparative work between the sexes is very much like comparative work between the species or populations. Examining genetic divergence between the X and Y chromosomes, or comparing gene expression levels of males and females across the genome, leads to valid, testable functional hypotheses about genetic loci that may play a part in phenotypic differences between the sexes. However, while this kind of comparative work, when looking at species and populations, also permits estimates of *phylogenetic distance or divergence*, it does not permit global, whole-genome estimates of difference between sexes.

Sexes versus species

The projection of phylogenetic language and models into the study of sex differences in the genome diagnoses ontological confusion about sexes, species, and populations as biological and genetic classes. Strictly, of course, sexes are *not* accurately analogized to species. Sexes are not lineages. Males do not produce males, females do not produce females. Males and females mate, and their male and female offspring carry a random combination of paternal and maternal genetic material. Because of sexual reproduction, the sexes do not meet any of the criteria for a species, including interbreeding, shared common ancestry (monophyly), morphology, and spatial and temporal boundaries. Human males and females are biological subclasses of a sexual species. As a class, males are not descended from a common ancestor, nor do they breed only with one another; the same goes for females. Male and female morphologies are differentiated but continuous. Human male and female species-specific activity is highly integrated and cohesive. Males and females occupy the same spaces and times. They exchange genetic material through reproduction and are interrelated to a high degree. The comparative genomics reference model of phylogenetic descent and divergence is therefore, on face, not appropriate for describing sex difference.

Certainly, when pressed, most genetic researchers will readily agree that there are significant disanalogies between sexes and species. Yet, as evidenced by the lack of critical response within the genetics community to Willard's widely publicized 2005 remarks, many still see nothing wrong with comparing the global genetic differences between sexes with global genomic differences between species. I suspect that an intuition of ontological symmetry underlies this reasoning. On this view, sexes and species are similar kinds of kinds—ontologically, species and sex both hold status as low-level, core classificatory units in biology. An adherent of this view would argue, then, that while species and sexes are not the *same*, they are *comparable*. Thus, according to this view, while phylogenetic reasoning certainly does not apply to the sexes, a comparative genomics approach does not seem distortive or problematic as a background framework, or model, for comparing the sexes.

Dupré (1993), one of the few philosophers of biology to reflect deeply on the concept of sex in biological explanation, would see this view of sex and species as problematic because it flattens biological ontology, obscuring and eliding the empirical constraints of different explanatory categories in biology. As Dupré argues, as an explanatory concept in biology, "sex" both *crosscuts* and is *nested* in species. Sex may be understood, first, as a high-level generic kind in biology. Very few, if any, generalizations or laws may be made about sex at this level. For instance, among sexually reproducing species, many species with males and females have no X–Y sex-determining system. Sexual dimorphism, as well as mating, parenting, and sex-gender systems, varies so profoundly across species that sex ("maleness" and "femaleness") carries minimal explanatory value as a high-level kind. Second, sex may be understood as an empirical subdivision within a species. Here sex is a grouping that may have explanatory power with regard to many aspects of the behavior, organization, and natural history of a sexual species. Consider, for example, the diverse explanations of sex differences and reproductive roles specific to honeybees, mallard ducks, and humans.

Dupré identifies the ontological grouping of sex and species as a common conceptual confusion in biological explanation. He uses sex precisely as an instance of the tendency of biologists to "expand the relevance of explanatory categories beyond their empirically warranted limits" (1993, 79). Dupré argues for what he calls "categorial empiricism," "a plea for complete empiricism with regard to the explanatory potential of different kinds" (80). Human and woman is "a nesting of natural kinds" (72), Dupré argues, but as categorial empiricists, "it would be absurd to suppose that man and woman, say, were 'better' kinds than humans" (73), unless it is merited by the role it is playing in an explanation. Because we are constrained by the empirical facts of the mutual existence of males and females of a species, even a finding that human females and chimp females are more "genetically similar" than human males and human females would not mean that sex is prior to species, nor require the radical revision in our system of biological taxonomy hinted at by Willard's claim.

Dupré's categorial empiricist critique of analogizing sex and species provides one compelling reason why we cannot rank the differences between sexes alongside differences between species. Categorial empiricism, together with certain facts about explanatory payoff, provides good grounds for the view that human males and females can never be "more different" than humans and chimpanzees, no matter how many genes are found to differ between them. Categorial empiricism does not, however, rule out comparing the sexes globally in the *way* one might compare species globally. To see why this is inappropriate, we need to look to another type of ontological confusion at work in comparative genomic thinking about differences between the sexes.

Sex as a dyadic kind

Sex is commonly formulated as a property of individual organisms, and the sexes constituted as two different classes of organisms marked by this property. Dupré's

account, for instance, maintains a view of males and females as comprising distinct biological kinds or classes (he is agnostic and pluralistic about which category—natural kinds or classes—is most apt for sex). I suggest that sex as an explanatory concept in biology has unique and important characteristics that are overlooked and undertheorized by this conventional ontological characterization. I propose that from the perspective of population genetics and evolutionary theory, sexes are properly conceived as *dyadic* kinds—units of two. Populations and species are not—they are *individual* kinds.

Keller (1992) first articulated the persistent tendency of population geneticists to think of the sexes as separable, individual classes—which she termed the "discourse of reproductive autonomy" in theoretical population genetics. Thinking of the sexes as autonomous, rather than reproductively interdependent, introduces errors and distortions into genetic modeling. For instance, as Keller pointed out,

> even with random mating, the probability that a male will mate cannot in general be assumed to be one, but is contingent on the availability of females, and therefore depends on the proportion of males to females in the population; that is, on the relative viability of males and females. (Keller 1992, 138)

Thus, the population dynamics of one sex cannot be modeled without the other. Keller urged biologists to innovate new models that would make visible the dynamics of sex in population biology. In the last decade, there have been important steps in this direction (e.g., Roughgarden 2004, 2009). Much of biology, and even most population genetic research, however, continues to assume the reproductive autonomy of males and females, leaving sex ambiguous and undertheorized as an explanatory concept.

In developing a critique of the "discourse of reproductive autonomy," Keller's questions were different from mine. Keller was intervening in the so-called "units of selection" debate. Her concern was the way in which human evolutionary biology and population genetics models sidestep questions of sexual difference by localizing reproduction in the desexed individual, thereby making sex and reproduction invisible and obscuring an important counterargument to the predominant genic selectionist view of evolution by natural selection.

Keller argued that the failure to theorize sex as an explanatory concept in biology was due to a prevailing model of heredity as residing in, and selection as acting upon, the individual organism. In sexual species, individuals do not replicate themselves—a complicating factor for modeling population dynamics. Rather than deal with the "complications of biparental inheritance" (1992, 130), Keller showed, population geneticists folded sexual reproduction into a genic selectionist, individualist model of population genetics, represented by the Hardy–Weinberg assumptions that population size is infinite and mating is random. Keller suggested that sex has been undertheorized in biology in part because it poses an uncomfortable challenge to this predominant genic selectionist model of evolution. As she wrote, "For sexually reproducing organisms, fitness is in general not an individual property but a composite of the entire interbreeding population" (142); thus, factoring in sexual reproduction "undermines the possibility of locating the causal efficacy of evolutionary change in individual properties" (142). Were sex to

be taken into account, it would suggest a different model of the operation of natural selection in a population than the currently favored one.

Without staking ground in the units of selection debate, here I wish to build upon Keller's observations about the discursive and model-theoretic treatment of sexes as separable, autonomous classes in population genetics, carrying this important insight into contemporary questions in the genetics and genomics of sex difference. In calling for a theoretical intervention into population genetic models of sexual reproduction, Keller noted that a "*mating pair* …is a more appropriate unit of selection than the individual, but the fact is that mating pairs do not reproduce themselves any more than do individual genotypes" (1992, 140). This insight that sexes, not as individuals, but in some substantial way, *as a class*, are paired and interdependent, forms the kernel of the concept of sex as a *dyadic kind* that I suggest here as a remedy to thinking of the sexes as individual, autonomous kinds or classes.

I borrow the concept and term 'dyad' from sociology of gender e.g., (Glick and Fiske 1999). The term 'dyad' is used in sociology of gender to model social constructs of gender as arising from interactions between males and females. These dyadic interactions are prolific and stable because males and females must coexist closely for reproduction. Because biological families are made up of males and females, they share the same spatiotemporal and cultural environments and are interpersonally dependent on each other. This is unique to gender: in contrast to different races, for instance, most males and females cannot go most or all of their lives without substantial interaction with the other. The sociological concept of gender as dyadic has methodological consequences for the study of the social dynamics of gender. Gender cannot be studied by looking at one sex in isolation, but must include analysis of interaction and exchange between genders. Additionally, conceiving of gender as dyadic intervenes on social stereotypes of males and females, and social science methods, which tend to approach the sexes as coming "from different planets" and "speaking different languages." Acknowledging the extent to which males and females interact through language, share a home environment, experience the same cultural milieu, and negotiate spaces and situations, breaks down these stereotypes and counters distortive social science research models.

I suggest a similar application of the term dyad to biological sex in humans (possibly extending to mammals and other sexual species). There is a difference between properties of a population, properties of a pair, and properties of individuals. Rethinking "sex" requires paying attention to these differences. Sex is a relational property of individuals within a (sexual) population or species. From the perspective of population modeling, sex is a highly relevant property of individuals in a population. "Males" and "females" are also biological subclasses of sexual species. As such, they are frequently explicitly or implicitly analogized to populations and species. Yet sex is not simply a property of individuals, nor is it simply a subclass. Because sexual reproduction is essential to the propagation of the species, the sexes are profoundly interdependent. Specifically, the population dynamics and fitness of one sex cannot be modeled without that of the other. I argue, therefore, that sex is a dyadic concept, meaning that sex is relational. At the level of the gamete and from the perspective of evolutionary, genetic, and

populational modeling, sex is a dyad. In contrast to the notion of male and female as two different, dichotomous genetic subclasses within a population, understanding sex as a dyadic kind would systematically emphasize the interdependence, interaction, and inseparability of the sexes as biological classes.

Understanding sex as an dyadic kind makes salient a core difference between sexes and populations or species. Populations and species are, rather, usefully understood as "individual" entities.[7] Like an individual organism, populations and species are continuous, cohesive, localized in space and time, integrated, causally connected, and related to a high degree (Ghiselin 1974; Hull 1978; Mishler and Brandon 1998 [1987]). The criteria of monophyly (or shared lineage) and reproductive interbreeding, which biologists require for a group of organisms to qualify as a species or population, capture these features of continuity and interrelatedness. For these reasons, species are, substantially, "individual" entities or kinds.

Because of sexual reproduction, one sex alone cannot be an individual class in the way that species or populations might be. Two species, such as humans and chimpanzees, are not continuous, cohesive, co-localized in space and time, integrated, causally connected, and related to a high degree. Human males and human females, however, do share this degree of integration. Because of this, species and populations are individual kinds; in contrast, the sexes are a dyad. The distinction between individual and dyadic kinds spells a critical ontological difference between sex as an explanatory category and population/species as an explanatory category. If sex is dyadic, one sex cannot be treated as an autonomous class, independent of the other. Sexes cannot be separated and compared globally as species and populations might. This would misrepresent the dyadic dynamics of sex as a biological kind. Another consequence is that studying the population dynamics or biology of one sex without an adequate understanding of the other clearly emerges as methodologically unrigorous, underdocumented, and lacking in explanatory power.[8]

With the concept of sex as a dyadic kind, I seek to articulate an important disanalogy between sexes and species/populations. That sexes are not autonomous, individual classes, but interdependent, permanently coupled, interacting, binary subclasses of species, means that it is inappropriate to isolate and apply comparative genomics approaches globally to sexes as one might compare species or populations. Therefore, I recommend the notion of sex as a dyadic kind as an intervention into ontologically weak current biological thinking about sex in genetics and genomics.

[7] While the debate over whether species are best conceived as "classes" or "individuals" cannot be said to be settled in philosophy of biology, work by Hull (1978) and Ghiselin (1974) on the substantial ways in which species are like individuals is sufficient to sustain the distinction that I wish to draw here.

[8] Sex difference claims in genetics frequently fall prey to the error of treating the sexes as autonomous kinds, leading to erroneous conclusions. A survey by Patsopoulos et al. (2007) showed that common spurious comparisons in genetic sex research include "comparison of male cases directly with female cases, ignoring controls," "comparison of male vs. female cases with a given genotype, ignoring other genotypes," "comparisons of different genetic groups in male vs. female cases," and "comparisons of one sex against a subgroup of the other sex" (887–888). Idealizing the sexes as different classes, types, or kinds, rather than continuous, interdependent, interacting classes, contributes to the assumptions leading to these misconceived comparisons. The concept of sex as a dyadic kind would present a clear methodological constraint against these kinds of misleading comparisons.

An objection to conceiving sex as a dyadic kind

While the notion of sex as a "dyadic kind" in biology may address the problem of conceiving of the sexes as autonomous classes or kinds, it might be perceived as retrogressively representing the sexes as two, and only two. The concern is that the concept of biological sex as a dyadic kind takes "male" and "female" as unanalyzed, representing sex as a strict binary. As a result, the "dyadic kind" concept may contribute to reductionist and ideologically retrogressive binary thinking about the sexes in biology. As gender analysts of biology have demonstrated, binary thinking downplays the great similarities and continuities between the sexes. Binary thinking also effaces the existence of biologically intersex individuals, which may comprise as much as 1% of the human population. The notion of sex as a "dyadic kind" may also seem at odds with the plurality of arrangements of sex in relation to gender observed in human social life. Many biologists and gender analysts of biology would like to see a working concept of sex in biological research that recognizes the non-binary and diverse nature of biological expressions of sex, both genotypic and phenotypic. For these critics, the concept of sex as a dyadic kind is not nearly a bold enough intervention into current biological thinking about sex differences.[9]

Here we encounter a serious gap in both gender theory and philosophy of biology. What notion of sex is appropriate for biological explanation? The category, class, or concept of sex as it is employed in the contemporary human biosciences has been peculiarly undertheorized. Despite its ubiquity in biological explanation, the foundations of the concept of sex (unlike that of species and population, for instance) in biology have gone largely unexamined. Fehr (2001) has recently done important work parsing explanatory pluralism in evolutionary explanations of sexual reproduction, but little has been said about biological concepts of sexual dimorphism. So here we enter relatively fresh territory, with few resources to guide us. Above I recommend conceiving of sex as a dyadic kind as a remedy to the particular form of thinking of sexes as individual kinds that this case study has diagnosed. Perhaps a more expansive intervention into or revision of biological models of sex is called for. But I suspect that any such intervention, to be of use to biological researchers, would need to contend with the very substantial sense in which sex is indeed "two" in genetics.

In mammalian biology, the union of two different gametes—male and female—is required for reproduction, and the two sexes present reliably different morphology and behavior arising from their reproductive roles. A strategic conceptual intervention into biological research on sex differences must grapple with this two-ness of biological sex in a meaningful way. Intersexes have much to teach us about the continuity between biological sexes, but they do not change the assumptions of our models of sexual reproduction and mating, since they do not alter the two-gamete model of sexual reproduction, are usually sterile, and comprise a very tiny percentage of the population. And while it is essential to acknowledge the plurality and social contingency of gender forms, the irreducible necessity of

[9] I thank Donna Haraway and Joan Roughgarden, among others, for pressing these important objections.

male–female gamete pairing for reproduction requires a different approach to the biological concept of sex. While gender is, in many contexts, plastic and plural, gametic sex is dyadic.

It is not the facticity of the two biological sexes that is problematic from the perspective of critical gender theory; rather, it is *binary thinking* that carries the epistemic failure and leads to shaky reasoning about sex in biology. That sex is perceived as a binary makes it unique and troubled in biological ontology. Species and populations, for instance, exist in a dynamic multivalent field, but in mammals there are two sexes and not more or fewer than two. As gender theorists have observed, binaries invite dualistic, dichotomous thinking, so that it becomes difficult to think of two without subsuming one into the other, ranking them, implying polarity or complementarity, or posing them as opposites (Jay 1981; Bleier 1984; Fausto-Sterling 2000, 1985; Haraway 1991 [1980]). Binaries tend to imply exhaustive categories and to drive reasoning toward the detection of difference as fixed polarity. Indeed, binary thinking underpins "genomic thinking" about sex difference in biology. I suggest that the distinction between sex as a dyad—a dynamic, relational pair—and sex as a binary, answers these concerns and is a powerful construct for reorienting biological models of sex. Just as the notion of gender as dyadic intervenes on binary, complementary models of gender differences in sociology, an appreciation of sex as a dyadic kind might be a useful intervention into binary thinking about the sexes in biology.

Language and terminology matter. A well-constructed and aptly named concept can transform thinking in a knowledge field. Presently, no ontological term adequately captures sex as an interactive and interdependent property of populations. The virtue of the concept of sex as a dyadic kind is that it takes account of biological sex as a binary, in the sense of "two," but reshapes binary thinking so as to resist its most dangerous pitfalls. The concept of a "dyadic kind" conceives of the sexes as both a binary and as knitted together, as nonautonomous. The sexes are paired, they are interdependent and interact, and the dynamics of one cannot be modeled without the other. The concept of sex as a dyad therefore directs biological modeling away from sex differences—the sexes as different kinds or populations—and toward collaboration, interaction, and interdependence between the sexes—the sexes as a dyadic unit. As such, it would represent a significant advance over contemporary binary reasoning about the sexes, while presenting a meaningful concept for framing questions, structuring research agendas, and formulating and evaluating models, theories, and explanations in biology.[10]

Conclusion

I have focused on the claim that human males and females are as, or more, different than chimpanzees and humans. I focus on this claim because it poses new and challenging philosophical and biological questions, because it has received

[10] To specify this live interdependence and interaction within the dyad, perhaps the term "dynamic dyadic kind" would be more apt.

significant uptake in scientific and popular media, and because it raises the history of problematic deployments of comparisons between apes and humans.[11] The claim is not a straw man, but one put forward recently by prominent geneticists. For these reasons, I believe it requires a forceful response by critical interested thinkers working at the intersection of genetics and gender studies.

I've argued that males and females are not like different species or populations, and that comparative genomic and phylogenetic models are inappropriate for conceptualizing biological sex differences. Thinking genomically about a class of organisms implies that they are lineages or autonomous genetic populations. It invites creeping populational and phylogenetic thinking, in which difference becomes the more commanding "divergence" and "distance." Because sex is a dyadic kind, this model of sex differences is distortive. I find that there are not strong empirical, explanatory, social, or ethical reasons for genomicizing sex differences. For these reasons, it is more advisable to refer to "sex differences in the human genome" than to a "male genome" and a "female genome."

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[11] Comparisons between humans and apes have a long history in biology and a prominent position in the history of scientific racism and sexism. "Chimp" is a racial and intellectual insult. From the eighteenth to the twentieth centuries, females and blacks, as well as other minorities and marginalized groups, such as the Irish and the disabled, have been frequently claimed to be phylogenetically or morphologically closer to chimps, or otherwise chimp-like (Marks 2002, 70). In the eighteenth century, women were typified as closer to nature—and thus to apes. Popular and scientific narratives and imagery depicted anthropomorphized female apes acting out gender-specific roles (Schiebinger 1993, 97–98). In the nineteenth century, physical anthropologists asserted that female brains are "closer in size to those of gorillas than to the most developed male brains'" (Gould 1996, 104), and that female skull structure was simian. On the "Great Chain of Being," women sat below men, closer to the apes. This painful history of human-chimpanzee comparisons underscores the importance of carefully interrogating contemporary reprisals of such comparisons.

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