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Review

Evolution of "determinants" in sex-determination: A novel hypothesis for the origin of environmental contingencies in avian sex-bias

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ABSTRACT

Sex-determination is commonly categorized as either "genetic" or "environmental"—a classification that obscures the origin of this dichotomy and the evolution of sex-determining factors. The current focus on static outcomes of sex-determination provides little insight into the dynamic developmental processes by which some mechanisms acquire the role of sex determinants. Systems that combine "genetic" pathways of sex-determination (i.e., sex chromosomes) with "environmental" pathways (e.g., epigenetically induced segregation distortion) provide an opportunity to examine the evolutionary relationships between the two classes of processes and, ultimately, illuminate the evolution of sex-determining systems. Taxa with sex chromosomes typically undergo an evolutionary reduction in size of one of the sex chromosomes due to suppressed recombination, resulting in pronounced dimorphism of the sex chromosomes, and setting the stage for emergence of epigenetic compensatory mechanisms regulating meiotic segregation of heteromorphic sex chromosomes. Here we propose that these dispersed and redundant regulatory mechanisms enable environmental contingency in genetic sex-determination in birds and account for frequently documented context-dependence in avian sex-determination. We examine the evolution of directionality in such sex-determination as a result of exposure of epigenetic regulators of meiosis to natural selection and identify a central role of hormones in integrating female reproductive homeostasis, resource allocation to oocytes, and offspring sex. This approach clarifies the evolutionary relationship between sex-specific molecular genetic mechanisms of sex-determination and non-sex-specific epigenetic regulators of meiosis and demonstrates that both can determine sex. Our perspective shows how non-sex-specific mechanisms can acquire sex-determining function and, by establishing the explicit link between physiological integration of oogenesis and sex-determination, opens new avenues to the studies of adaptive sex-bias and sex-specific resource allocation in species with genetic sex-determination.

Contents

1. Evolution of "determinants" in sex-determination

Despite being a focus of debate for centuries [1–5], the link between developmental origin and evolutionary persistence of sex-determination remains poorly understood. An intermediate solution – the classification of sex-determination as either "genetic" or "environmental" – distracts from the understanding of both

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the origin of this dichotomy and the evolution of sex-determining factors. Consequently, empirical documentations of environmental contingency of sex-bias in taxa with genetic sex-determination and of genetic inheritance of sex-determination in taxa with environmental sex-determination are often greeted with great skepticism [6–11].

The developmental cascade leading to sex-determination combines highly modular genetic mechanisms with an epigenetically regulated machinery that compensates for chromosome morphology and influences chromosome movements [3,12–18]. Although the "genetic" and "environmental" classifications elevate different aspects of this composite process to the role of causal mechanism, *both* exclude environment from the actual determination of sex and reduce the role of environment to either regulation of expression of invariant modules (in environmental sex-determination) or to sorting among their outcomes (in genetic sex-determination) [4,19–23]. The implicit assignment of natural selection to the role of a guiding developmental force is evident in both genetic and environmental sex-determination classifications: in environmental sex-determination systems the external environment acts as an initiator of the sex-determining cascade [4,24,25] whereas in systems with genetic sex-determination the environment is assumed to interfere with canalized sex-determination systems to produce environment-specific disruption of otherwise context-invariant sex-determination [8,9,26–28]. Furthermore, although both environmental and genetic sex-determination require genetic modules of sex-determination [29–32], neither addresses the origin of these modules, instead focusing on their maintenance and modification, thereby confounding the roles of development and natural selection in the determination of sex. Crucially, both views assume an evolved sensitivity to the environmental input, but neither addresses the evolution of this sensitivity and therefore fail to explain the developmental and evolutionary relationship between genetic and environmental sex-determining systems.

In birds, sex-determination is based on a female heterogamety sex chromosome system that involves modular sex-specific genetic pathways (Box 1) that result in the consistent expression of sex according to chromosome configuration – ZW for females and ZZ for males [33,34]. The sex-determining chromosome segregation that occurs at first meiosis just prior to ovulation is a multistage process with several regulatory mechanisms ("checkpoints") that maintain correct cytological and molecular configuration and prevent unequal or biased transmission of chromosomes to daughter cells [Fig. 1; [35,36]]. Establishing environmental contingency of sex-determination at meiosis requires a mechanism that links the physiological responses of females to breeding conditions with sex chromosome segregation without disrupting meiotic fidelity. We propose that regulatory checkpoints of meiosis play a crucial role in this process. Consistent and recurrent natural selection on integration of such regulatory meiotic checkpoints with organismal response to environmental variation can result in reliable, directional and context-dependent environmental sex-determination [37,38].

We suggest that explicit consideration of the origin of sex-determining factors provides novel insights into the evolutionary relationship between genetic and environmental sex-determination. Specifically, we propose that sex chromosome degeneration associated with genetic sex-determination in birds leads to the exposure of cryptic epigenetic variation in meiotic regulatory mechanisms to natural selection and their subsequent integration with oogenesis (Fig. 2). This, in turn, forms a basis for the evolution of environmental contingency in avian sex-determination. We evaluate this hypothesis first by showing that avian sex chromosome degeneration sets the stage for significant effects of epigenetic regulatory mechanisms on sex chromosome segregation. Second, we examine variation in epigenetic mechanisms of chromosome segregation during meiosis and whether the exposure to natural selection and compensatory interactions with downstream regulatory mechanisms are evident in patterns of plasticity in resulting sex-determination. Third, we address whether the evolutionary origin of epigenetic regulators of sex-determination in birds is due to modification of pre-existing meiotic regulators or developmental co-option of novel environmental inputs. Finally, we argue that chromosome degeneration and newly expressed variation in regulatory mechanisms of meiosis facilitates integration among a physiological response to environmental input in the breeding female, resource allocation to growing oocytes, and offspring sex, and that such integration enables precise and environmentally sensitive sex-determination in species with sex chromosomes.

Box 1: Avian sex-determination: I. Sex-specific genetic pathways

Birds share a genetic pathway of embryonic sexual differentiation of the gonads that involves a non-recombining part of the genome confined to a pair of sex chromosomes (ZW), originated from an ancestral pair of autosomes [33,34,45,124]. Females carry one Z and one W chromosome whereas males have two Z chromosomes. The region of suppressed recombination extends across much of the W chromosome and, in most species, has resulted in a reduction in the number of functional genes and divergence in chromosome size and morphology in a process of chromosome degeneration [46,51]. The W chromosome is usually much smaller and shows differences in size and position of the centromere, epigenetic markings, and telomere length compared to the Z chromosome (Table 1), and there is large variation in chromosome degeneration within carinate birds [12]. Unusually among birds, the sex chromosomes are relatively similar in size in ratites [125]. The molecular mechanisms of embryonic sex-determination in birds are not well understood. Two main candidate genes of major effects have been proposed: HINTW and DMRT1 [reviewed in [34,45,126]]. HINTW is a W-linked gene that encodes a derived version of a histidine triad nucleotide binding protein [126]. It is evolutionarily conserved in carinate birds, reiterated some 40 times on the chicken W, and seems to be under positive selection. It is widely expressed during embryonic development, including in the gonads, indicating its involvement in female sex-determination. However, it is absent in the ratites [126], suggesting differences in the sex-determining cascade between the two avian clades. An alternative candidate sex-determining gene – DMRT1 – is a Z-linked gene with ancestral involvement in gonadal differentiation in vertebrates [15,127]. DMRT1 encodes a nuclear transcription factor with a DNA-binding motif and, in contrast to HINTW1, also maps to the Z-, but not the W-chromosomes in ratites [45]. Because there is little evidence for dosage compensation in birds [128], the differential expression in ZZ and ZW individuals could thus be the basis for testis versus ovary differentiation. However, both candidate genes are expressed before any signs of gonad differentiation and also in other tissues during development [45].

2. Chromosome degeneration and the expression of environmental contingency in avian sex-determination

Sex-determination in birds exhibits a combination of phylogenetically conserved and novel features (Box 1). Ancestrally, avian sex-determination may have been sensitive to temperature during embryonic development [39, but see 40], as in crocodilians [41], but temperature no longer functions as a sex determinant under normal incubation conditions. This could be a result of either parental buffering of temperature variation or evolved canalization

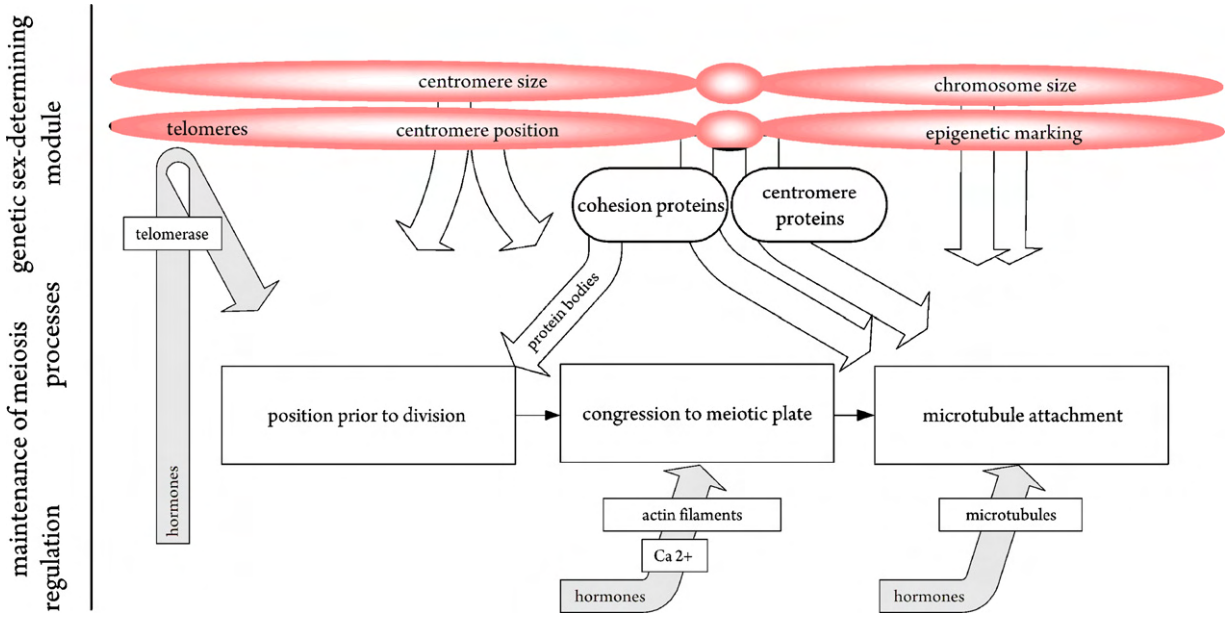

Fig. 1. Schematic illustration of the relationships between sex chromosomes ("genetic sex-determination", shown in red) and regulators of meiosis [modified from [17]]. White arrows indicate characteristics of chromosomes that affect their behavior at all stages of meiosis. Meiosis processes are shown by boxes and proceed from left to right. Gray arrows show hormonal regulation of meiotic stages and processes.

Table 1
Differences between avian sex chromosomes (Z and W) that may enable sex-determining function of epigenetic regulatory mechanisms of meiosis.

Sex chromosome dimorphism	References
Physical length (W < Z)	[12,142]
Physical shape	[12,142]
Centromere position	[12,143]
Protein body size	[144]
DNA methylation	[49]
Lampbrush condensation (W > Z)	[12]
Tandem repeats at terminal chromomere	[145,146]
Telomere length	[89,146]
DNA sequence	[147]

of sex determining cascades and temporal separation of sex-determination and incubation onset [28,42, but see 43,44]. All birds studied to date share a chromosome-specific region of suppressed recombination (the female heterogamety ZW sex chromosome system) that has a major effect on gonadal differentiation [reviewed in [33,34]]. The origins of the genetic sex determinants and the reasons for initial suppression of recombination are not fully understood [34,45–48] and the primary sex determinant could either be W- or Z-specific and, in the latter case, express sex-determining function via dosage dependence [33,34,49,50]. Regardless of the origin of recombination suppression, reduced recombination sets the stage for degeneration of the W chromosome through accumulation of deleterious mutations and retrotransposons [46,51–53]. Reduced recombination is evident in evolutionary changes in the avian W-chromosome's structure, DNA content, and function, including: (1) regional differences in DNA sequences, increased amounts of repetitive DNA, and an overall reduction in coding regions in W compared to Z; (2) reduced chromosome length of W compared to Z; (3) differences in shape, including the size and position of the centromere; and (4) differences in epigenetic markings, including chromatin structure and DNA methylation (Table 1). Sex chromosome degeneration seems to have occurred discontinuously over evolutionary time [54,55] resulting in pronounced differences among taxa in chromosome structure; although degeneration is evident in all carinate birds, the dimorphism of Z and W chromosomes is minor in the ratites (Box 1).

The chromosome segregation that results in sex-determination takes place during first meiosis that generates haploid daughter cells from a single diploid mother cell and determines whether the oocyte will receive a Z or W chromosome (Box 2). Meiosis is maintained by several processes that prevent aneuploidy (i.e., unequal transmission of chromosomes to daughter cells) by regulating chromosome segregation in relation to a set of molecular and cytological configurations [Fig. 1; [35,36,56]]. Variation in these regulatory processes provides insights into environmental effects on segregation distortion of sex chromosomes [17]. For example, non-random segregation of chromosomes requires asymmetric cell division, as well as functional asymmetry between the poles and between chromosome homologues [57]. Asymmetry of cell division is a general feature of female meiosis and pronounced differences in the spindle of the different poles have been described in several species [58]. For example, the spindle on the oocyte side is substantially larger than on the polar body side in the grasshopper *Myrmeleontettix maculates* [59]. Although differences in the size or length of microtubules was not observed in Japanese quail (*Coturnix japonica*) [60,61], both the presence of non-random segregation of chromosomal rearrangements to the oocyte in chickens [62] and substantial evidence for epigenetic effects on spindle position, size and morphology (see below) indicate that functional differences in the spindle itself are likely to be present under some conditions [63]. Further, polar asymmetry resulting from within-oocyte gradients of morphogens is well established in vertebrates [64–67], including birds, and could form the basis for preferential segregation towards one pole rather than the other.

Importantly, degeneration of the W chromosome fulfils sufficient criteria for segregation distortion by creating asymmetry between chromosome homologues (Table 1) whilst large differences in the size and morphology of Z and W chromosomes compromise chromosome movement, alignment, attachment and segregation [see also 68,69]. Thus, chromosome degeneration, in the absence of compensatory mechanisms, increases the probability of biased chromosome segregation. However,

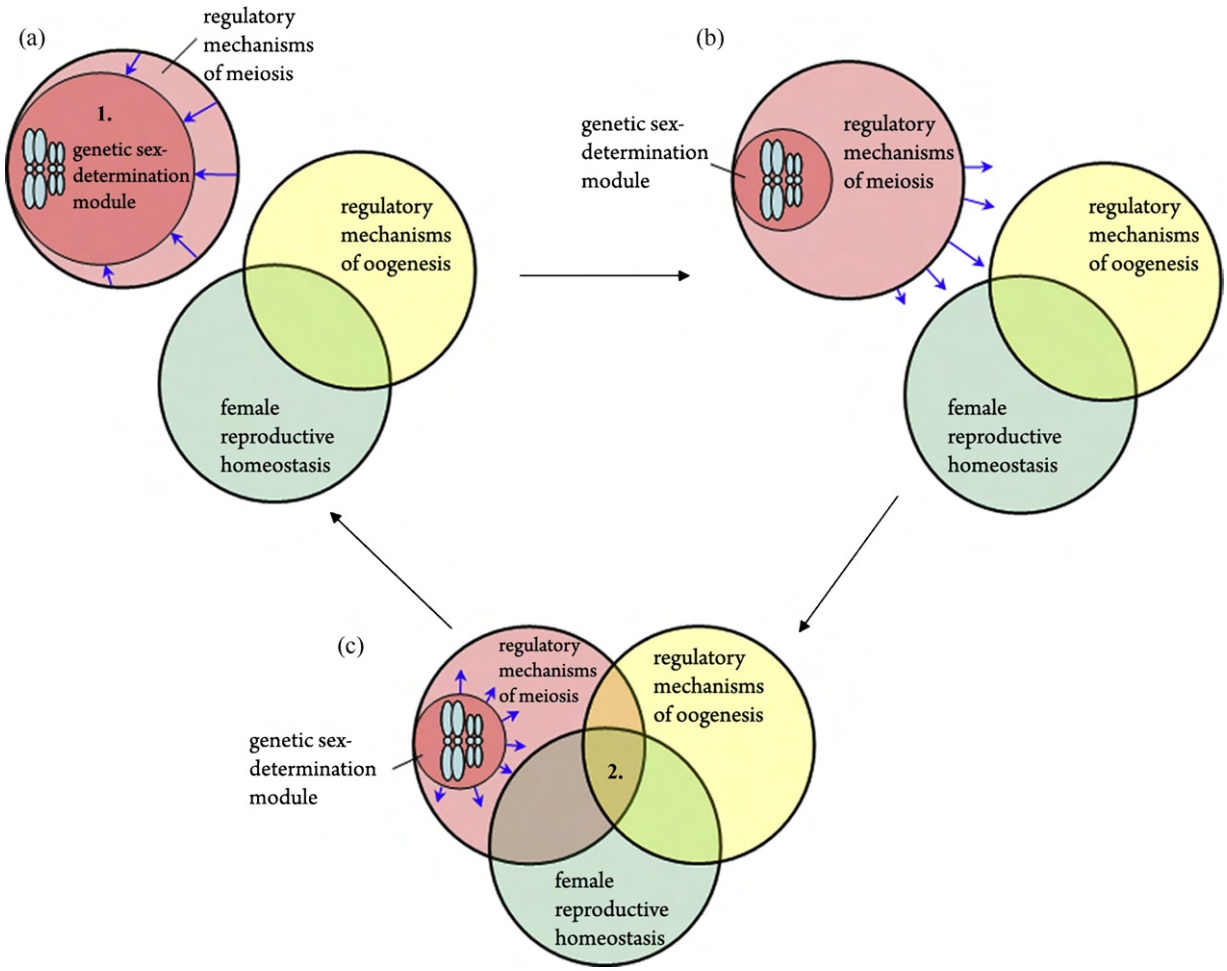

Fig. 2. Conceptual overview of the proposed evolutionary relationship among the genetic sex-determination module (1. sex chromosomes), regulatory mechanisms of meiosis and oogenesis, and female reproductive homeostasis. (a) Degeneration of sex-chromosomes (blue arrows) exposes epigenetic regulators of meiosis to natural selection. (b) Natural selection favors physiological integration (blue arrows) of meiotic regulators with oogenesis and reproductive homeostasis, resulting in (c) partial overlap (2.) of regulatory mechanisms of meiosis, oogenesis, and reproductive homeostasis. Consistent integration of meiotic regulators with a particular set of organismal functions results in larger genetic sex-determination module (blue arrows), i.e., genetic integration of chromosomal sex-determination with recurrent aspect of reproductive homeostasis or oogenesis. Context-dependency in regulators of oogenesis and reproductive homeostasis leads to variation in genetic sex-determining module (arrow from (c) to (a)). Greater integration of variation in female reproductive homeostasis in relation to the environment of breeding with regulators of meiosis and oogenesis (2.) as a result of natural selection accounts for adaptive environmental contingency in sex-determination. Transition in modularity of sex-determining functions depends on interchangeability of epigenetic and genetic links between elements of areas in (1.) and (2.) and sex-determination.

chromosome degeneration also leads to the expression of novel sex determinants by exposing existing, but previously cryptic, variation in meiotic regulation that over evolutionary time can acquire a sex-determining function via integration with processes regulating maternal responses to the breeding environment (Fig. 2, Box 3).

Endocrine regulation of female responses to the breeding environment is likely to be particularly important in this process [70,71]. This is because hormone uptake and synthesis by avian oocytes closely covaries with both the stage of oogenesis and with breeding female's reproductive homeostasis [71–74] (Box 3). Hormonal sensitivity of regulatory mechanisms assuring fair meiosis can thus provide a basis for the evolution of environmental contingency in sex chromosome segregation [17] and account for observed effects of circulating maternal hormones on avian sex-determination [70,75–77]. Below, we explore the role of the meiotic regulatory mechanisms in sex-determination by reviewing hormonal effects on: (1) spindle morphology and position, (2) chromosome movement, alignment and congression to the meiotic plate, and (3) mictrotubule attachment and segregation.

2.1. Spindle formation, morphology and position

Although the spindle asymmetry by itself is insufficient for segregation distortion of sex chromosomes, the size, shape, and position of the spindle plays a central role in enabling differential attachment and directional segregation of sex chromosomes [36]. Further, several hormones affect intracellular molecular gradients (e.g., of Ca^{2+}) and cytoskeleton morphology and function in general [64,78] and spindle morphology and position in particular [[79,80], Table 2]. For example, recent *in vitro* and *in vivo* studies have shown that bisphenol-A (BPA), a xenobiotic estrogenic compound that interacts with estrogen and androgen receptors, affects the shape and position of the spindle via its effect on centrosome function, possibly by acting on the protein-kinase-pericentrin domain or motor proteins associated with microtubules [81–84]. Moreover, hormones can bind to and affect microtubule function directly enabling within-oocyte hormone gradients to play an important regulatory role in determining spindle shape and position (Table 2). Such asymmetries can result in differential attachment of Z and W chromosomes with respect to the poles, ultimately resulting in segregation distortion of sex chromosomes.

Table 2
Epigenetic effects on spindle formation, chromosome movement, alignment, congression, and segregation in vertebrates (BPA = bisphenol-A; FSH = follicle-stimulating hormone; eCG = equine chorionic gonadotropin; E_2 = estradiol; GSK-3 = glycogen synthase kinase-3).

Meiotic phase	Evidence for epigenetic effects on chromosome segregation in oocytes	References
Meiotic spindle formation	BPA affects microtubule organization	[81,82]
	BPA interacts with centrosome proteins	[81,83]
	FSH widens the spindle, possibly via GSK-3	[95]
	BPA may target motor proteins	[81]
	eCG and FSH affects centrosome number	[80]
	eCG and FSH affects microtubule organization	[80,148]
	Glutathione widens spindle poles and increases spindle length	[149]
	E_2 affects spindle organization	[105]
Chromosome movement, alignment and position	Hormonal regulation of telomerase activity	[86,92]
	Telomerase-negative mice have compromised chromosome bouquet formation	[88]
	BPA affects chromosome alignment *in vitro*	[82]
	Estrogen affects microtubule motor proteins	[94]
	FSH increases spread of chromosomes at congression, possibly by inactivation of GSK-3 and destabilization of the spindle	[95]
	LHβCTP transgenic female mice show abnormal chromosome alignment as a result of endocrine environment of maturing oocytes	[94]
	XY^{POS} sex-reversed female mice show abnormal chromosome alignment as a result of endocrine environment of maturing oocytes	[94]
	Telomerase-negative mice have aberrant chromosome alignment	[132]
Microtubule attachment and chromosome segregation	BPA mediates microtubule attachment to kinetochores	[82]
	Reduced sensitivity of checkpoint at microtubule attachment in older individuals due to hormone exposure of maturing oocytes	[150–152]

Box 2: Avian sex-determination: II. Meiosis
Avian germ cells are induced from epiblast cells during the first 20 h of development, migrate individually to the area pellucida where they aggregate, divide mitotically, enter newly formed blood vessels a few hours later, and are carried by blood circulation towards the site of future gonads [Box 1 in [106]]. After the establishment of functioning gonads some germ cells undergo apoptosis whilst others are promoted by hormonal and cellular factors to further development and maturation [129,130]. During the breeding season, the ovary contains a large group of small pre-recruitment follicles, few of which are advanced into a hierarchy of rapidly growing pre-ovulatory follicles, undergo rapid yolk accumulation, and ovulate sequentially [130,131].
The first meiotic division that results in an egg that contains either a Z or a W chromosome takes place in the germinal vesicle situated at the periphery of the oocyte [reviewed in [17]]. Approximately 24 h before ovulation, the upper surface walls of the vesicle begin to dissolve and the protoplasm of the germinal disc and the content of germinal vesicle mix and spread beneath the vitelline membrane. At 6 h before ovulation, chromosomes in post-lampbrush form appear at the centre of the germinal vesicle [(Fig. 1 in [17] [60,61]). Spatial organization of chromosomes is mediated by telomeres that become embedded in the inner nuclear membrane [86,88] such that chromosomes form a cluster around the centrosome [85]. Oocytes' telomerase activity is high before and during the first meiosis, suggesting that telomere length is important for chromosome pair formation and movement [88], corroborating observations of meiotic disorders in telomerase-deficient mice [132]. Chromosomes are subsequently delivered to the division plate by the contraction of an actin network and attach to the meiotic spindle via microtubules that anchor the chromosome at the kinetochore on the chromosome centromeres [93]. The first meiotic spindle consists of two poles and the microtubules and is perpendicular to the surface of the germinal disc [Fig. 1 in [17]]. The directionality determines which of the chromosome bivalents will remain in the ovum and be transferred to the offspring and is therefore crucial for sex-determination (Fig. 1). Finally, chromosome segregation occurs by shortening of the attached microtubules driven by motor proteins at the attachment sites of the kinetochores [Fig. 1, reviewed in [17]].

2.2. Chromosome movement, alignment, and congression

Morphological differences between Z and W chromosomes can affect their movement and position prior to the onset of segregation. For example, in several taxa, telomere length affects chromosome position during the clustering of chromosomal ends at the nuclear envelope [85–88]. In birds, differences in telomere sequences and lengths between sex chromosomes are well documented. For example, a very long (2.8 Mb) telomere has been identified on the chicken W chromosome [89,90], which can result in different movements of Z and W chromosomes during meiotic prophase I. Furthermore, telomere length in birds and other taxa is affected by telomerase activity, which is expressed in the germinal vesicle and during metaphase of the first meiotic division [88,91]. In turn, telomerase activity is modulated by several steroid hormones, including oestrogens, progesterone and androgens, via gene transcription, alternative splicing and post-translational modifications [92]. Thus, the hormonal milieu of the germinal vesicle should have pronounced effects on the position of sex chromosomes at prometaphase I (Table 2).

Once the chromosome bivalents have aligned along the axis of the spindle they are delivered to the metaphase plate of the meiotic spindle by the contraction of actin filaments in the process of congression [93]. In turn, the alignment of the chromosome homologues affects the probability of chromosome segregation to the polar body versus the oocyte, which suggests that the contraction of actin filaments, together with the initial positioning of the chromosomes, are important determinants of segregation distortion of sex chromosomes. Indeed, there is now direct evidence that the oocyte growth, which is linked to the endocrine environment of oocyte development, affects congression in mice [94]. Furthermore, hormonal effects on chromosome alignment have also been shown *in vitro* (Table 2). For example, in a study of mouse oocytes, follicle-stimulating hormone (FSH) affected chromosome alignment: higher exposure to FSH led to widely dispersed chromosomes [95]. More generally, the widespread involvement of actin filaments throughout meiosis [93,96] and their sensitivity to hormones and hormone-mediated intracellular Ca^{2+} gradients [79,97], suggests that hormonal gradients across the germinal vesicle are well placed to induce differences between the sides of the spindle equator, resulting in a difference in the contraction of the actin

Box 3: Hormonal integration of oogenesis and avian sex-determination: an example with the house finch

Evolutionary co-option of regulatory mechanisms of meiosis into sex-determination relies upon the establishment of a link between variation in these mechanisms and females' reproductive homeostasis under variable environments of breeding. In turn, involvement of non-sex-chromosome-specific epigenetic regulatory mechanisms of meiosis might account for both context-dependency of sex-biases documented in birds [133–136] and the diversity of mechanisms and levels at which such sex-bias can be accomplished [17,26,28]. Studies of the house finch (*Carpodacus mexicanus*) document close integration of endocrinological mechanisms involved in female reproduction, oogenesis, interactions among oocytes, and sex-determination. Such integration enabled pronounced environmental contingency in offspring sex-determination across populations recently established in distinct climatic conditions, as well as phenotypic accommodation and inheritance of novel environmental inputs in the sex-determining process [137].

Recent documentation of a close association between oocyte sex-determination, oocyte growth dynamics, and ovarian steroidogenesis in the house finch [71,138] raises several arguments in support of the assertion that hormonal integration of oogenesis and sex-determination might be more widespread than is currently realized. First, depending on the time of their sequestration to the ovulatory sequence and corresponding development in different hormonal milieus, house finch oocytes accumulate and synthesize distinct concentrations of several hormones [70]. Second, similarity in the exposure to hormonal milieus (largely a function of the timing of sequestration in relation to a female's hormonal profile) along with growth-inhibiting interactions among growing oocytes lead to the formation of clusters of oocytes destined to become the same sex [72,139]. Third, the formation of the same sex oocyte clusters can be induced by distinct environmental cues and in different environments [109]. Such a consistent outcome is likely mediated by the effects of temporal hormonal fluctuations in female's plasma on the hormonal exposure of growing oocytes, subsequent accumulation and synthesis of distinct hormonal concentrations, and biases of the sex-determining meiotic division of oocytes. Fourth, close alignment of sex-specific steroidogenesis in oocytes and sex-determination of the oocytes is under natural selection—a mismatch between these processes results in hormone accumulation incompatible with normal sex-specific growth of offspring [72,135]. Involvement of the same hormonal mechanism – pituitary prolactin – in all stages of this process, from regulation of maternal reproductive decisions in response to environmental cues to regulation of oocyte proliferation and maturation [70,108,140,141] can form a proximate link between sex-determination and accumulation of maternal products. Evolution of such a link under natural selection can explain both the gradual decrease in environmental contingency of sex-bias and an increase in the precision of locally adaptive sex-bias in house finch populations following establishment in novel environments [109,137].

network, leading to a biased chromosome position relative to the poles. Alternatively, the concentration of morphogens at the time of chromosome segregation may have different effects on sex chromosome movement as a result of variation in sex chromosome size, epigenetic markings, or telomere lengths and thereby cause biased chromosome delivery by actin filaments with respect to the poles.

2.3. Microtubule capture, attachment and chromosome segregation

Microtubule attachment to chromosome kinetochores creates the force that enables and initiates chromosome segregation [98–100]. A large number of kinetochore proteins are required for successful attachment [99,101] and failure of microtubules to properly attach to kinetochores results in either meiotic arrest or meiotic delay by activation of the meiotic checkpoint signaling proper chromosome attachment and alignment on the division plate [35,56]. Consequently, differences in centromere size and morphology affecting microtubule attachment may activate the spindle attachment checkpoint leading to repeated attachment and release of microtubules and thereby causing non-random sex chromosome segregation. Furthermore, larger kinetochores produced by an increase in the centromere array of satellite repetitive DNA can increase the number of attached microtubules, affecting the probability of sex chromosome segregation to the oocyte versus polar body [102]. Centromere sequences, epigenetic markings and its consequences for biased chromosome segregation towards poles evolve rapidly [58,102,103] and may even show context-dependence within species as exemplified by differences between mouse strains in the bias of segregation [58]. Such effects may be enhanced by differences between Z and W chromosomes in cohesion protein aggregation on the kinetochores [104] and by epigenetic modification of kinetochore proteins that affect microtubule attachment and orientation of the centromere towards the poles [57]. Additionally, *in vitro* experiments have shown that estrogen or estrogen-like compounds act via direct binding on microtubules and modify their attachment to the kinetochore [82,105]. Such binding could not only counterbalance the effect of different-size bivalents, but also interfere with centromere and cohesion proteins of Z and W chromosomes, and ultimately modulate the directionality of sex chromosome segregation.

3. From expression of epigenetic mechanisms to the evolution of environmental sex-determination

Even this brief survey of the literature reveals substantial evidence for a role of hormones as both transcription factors and modifiers of cell cytoskeleton and cellular gradients during oogenesis, the roles central to meiotic regulation in vertebrates, including birds [Table 2, [79]]. Thus, hormones not only have considerable capacity to disrupt meiosis, but also are an essential part of the normal regulatory mechanisms of meiotic fidelity *in vivo*. However, there is little evidence for a time- and site-specific effect of hormones on chromosome segregation [Table 2, [17]]—a specificity that would have been expected if hormones were part of evolved mechanisms of sex-determination (Fig. 1). This molecular and cytological evidence for hormonal involvement in meiotic regulation corroborates well-established effects of hormonal induction of offspring sex-bias in birds, and the lack of consistency and directionality of observed patterns [e.g., [76,77]].

We therefore propose that non-random sex chromosome segregation in birds represents modification of regulatory mechanisms (meiotic checkpoints) that involve hormonal gradients in the vicinity of the germinal vesicle. Consequently, hormonal effects on sex chromosome segregation likely represent a modification of pre-existing regulation of oogenesis, rather than an evolved mechanism that translates environmental variation into sex-determination *per se*. Thus, environmental contingencies in genetic sex-determination in birds are expected to be accompanied by differences in the growth environment of the developing oocytes [71], such as hormone exposure during chromosome prophase I and variation in yolk uptake. Importantly, this also provides a basis for the evolution of sex-specific maternal effects in birds [71,106,107].

Whereas sex chromosome degeneration provides the necessary requirements for the initial expression of variation in the epigenetic mechanisms of sex chromosome segregation, evolutionary co-option of non-sex-specific regulators in sex-determination

at meiosis can be facilitated by integration of hormonal regulation of oogenesis and responses to the environment of breeding [70,108,109]. In particular, integrated homeostatic systems where single hormones have multiple targets in both regulation of breeding and oogenesis should be most likely to account for environmental contingency in segregation distortion of sex chromosomes in birds (Fig. 2). Consistent and recurrent natural selection on newly expressed regulatory mechanisms of meiosis, enabled by sex chromosome degeneration, may ultimately lead to integration of a physiological response to the environment in the breeding female, resource allocation to growing oocytes, and determination of offspring sex, producing precise and adaptive environmental contingency in sex-determination (Fig. 2, Box 3).

Our hypothesis proposes that the evolution of environmental contingency in avian sex-determination capitalizes on cryptic variation in non-sex-specific mechanisms of oogenesis and meiosis that is exposed to natural selection as a result of changes in other parts of the sex-determining cascade (i.e., chromosome degeneration). Similar processes via epigenetic effects on cell proliferation or growth of early embryos may form the basis for sexual differentiation and embryonic sex-determination in species with poorly differentiated sex chromosomes [110–112]. Furthermore, the lack of time- or site-specific sensitivity to hormones throughout meiosis might be conceptually similar to the wide window of sexual lability in species classified as having environmental versus genetic sex-determination [10,113–115] – a perspective that emphasizes the interactive roles of epigenetic and genetic regulators of development in the evolutionary origin of sex determinants over mutations in single elements in genetic pathways [16,116].

The exposure to natural selection of multiple meiotic regulators – the mechanisms involved in a wide diversity of meiotic stages – and subsequent acquisition of sex-determining functions by these regulators, may explain the staggering diversity of factors that cause sex-bias in species with sex chromosomes, the diversity of environmental correlates of sex-determining factors within and across populations, and the lack of consistent patterns thereof in field and experimental studies [e.g., 117–119]. It also provides a working hypothesis for the kinds of environmental inputs most likely to be co-opted as sex determinants [19,120]. Further, our perspective provides a mechanism for the apparent integration of the mechanisms of oogenesis and sex-determination in birds (Box 3) which is evident in both sexual dimorphism in yolk, albumen, and hormone allocation and in the precise control of sex-biased maternal investment, often in close concordance with the social and ecological environment of breeding [e.g., 121–123].

In conclusion, our review suggests that environmental contingency of genetic sex-determination is enabled by chromosomal reorganization that leads to the exposure of epigenetic regulatory mechanisms of oogenesis and meiosis to natural selection. In turn, close integration of such mechanisms with mechanisms that regulate female responses to environmental conditions during breeding results in environmental contingency of genetic sex-determination. Over evolutionary time, such contingency should lead to the evolution of a novel sex-determining system in which the mechanisms of meiosis acquire sex-determining functions under particular set of environments.

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