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

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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
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 [24,35,36]. Establishing environmental contingency in 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 organisational 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: HINTW1 and DMRT1 [reviewed in [34,45,126]]. HINTW1 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].
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 car-

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

<table>
<thead>
<tr>
<th>Sex chromosome dimorphism</th>
<th>References</th>
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<tr>
<td>Physical length (W &lt; Z)</td>
<td>[12,142]</td>
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<tr>
<td>Physical shape</td>
<td>[12,143]</td>
</tr>
<tr>
<td>Centromere position</td>
<td>[12,143]</td>
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<tr>
<td>Protein body size</td>
<td>[144]</td>
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<td>DNA methylation</td>
<td>[49]</td>
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<tr>
<td>Lampbrush condensation (W &gt; Z)</td>
<td>[12]</td>
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<tr>
<td>Tandem repeats at terminal chromomere</td>
<td>[145,146]</td>
</tr>
<tr>
<td>Telomere length</td>
<td>[89,146]</td>
</tr>
<tr>
<td>DNA sequence</td>
<td>[147]</td>
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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 Myrmeleontetitix maculatus [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 fulfills 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.

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 Ca²⁺) 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; E2 = estradiol; GSK-3 = glycogen synthase kinase-3).

<table>
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<th>Meiotic phase</th>
<th>Evidence for epigenetic effects on chromosome segregation in oocytes</th>
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<tr>
<td>Meiotic spindle formation</td>
<td>BPA affects microtubule organization</td>
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<td></td>
<td>BPA interacts with centrosome proteins</td>
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<td></td>
<td>FSH widens the spindle, possibly via GSK-3</td>
<td>[85]</td>
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<td></td>
<td>BPA may target motor proteins</td>
<td>[95]</td>
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<td></td>
<td>eCG and FSH affects centrosome number</td>
<td>[80]</td>
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<td></td>
<td>eCG and FSH affects microtubule organization</td>
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<td></td>
<td>Glutathione widens spindle poles and increases spindle length</td>
<td>[149]</td>
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<tr>
<td></td>
<td>E2 affects spindle organization</td>
<td>[105]</td>
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<td></td>
<td>Telomerase-negative mice have compromised chromosome bouquet formation</td>
<td>[88]</td>
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<tr>
<td></td>
<td>BPA affects chromosome alignment in vitro</td>
<td>[82]</td>
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<tr>
<td></td>
<td>Estrogen affects microtubule motor proteins</td>
<td>[94]</td>
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<tr>
<td></td>
<td>FSH increases spread of chromosomes at congression, possibly by inactivation of GSK-3 and destabilization of the spindle</td>
<td>[95]</td>
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<td></td>
<td>LHB(CTP transgenic female mice show abnormal chromosome alignment as a result of endocrine environment of maturing oocytes</td>
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<td></td>
<td>XY(15) sex-reversed female mice show abnormal chromosome alignment as a result of endocrine environment of maturing oocytes</td>
<td>[94]</td>
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<td></td>
<td>Telomerase-negative mice have aberrant chromosome alignment</td>
<td>[132]</td>
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<td>Microtubule attachment and chromosome segregation</td>
<td>BPA mediates microtubule attachment to kinetochores</td>
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<td>Reduced sensitivity of checkpoint at microtubule attachment in older individuals due to hormone exposure of maturing oocytes</td>
<td>[150-152]</td>
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Box 2: Avian sex-determination: II. Meiosis

Avian germ cells are induced from epiblast cells during the first 20th of development, migrate individually to the area pel-lucida 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 6h before ovu-

lation, 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 chromo-

some at the kinetochores on the chromosome centromeres [93]. The first meiotic spindle consists of two poles and the micro-

tubules and is perpendicular to the surface of the germinal disc [Fig. 1 in [17]]. The directionality determines which of the chro-

mosome 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 seg-

regation. For example, in several taxa, telomere length affects chromosome position during the clustering of chromatids at the nuclear envelope [85–88]. In birds, differences in telomere sequences and lengths between sex chromosomes are well doc-

umented. 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 hor-

mones, 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 mei-

otic 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 distur-

tion of sex chromosomes. Indeed, there is now direct evidence that the oocyte growth, which is linked to the endocrine envi-

ronment 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 Ca2+ 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...
2.3. Microtubule capture, attachment and chromosome segregation

Microtubule attachment to chromosome kinetochores creates the force that enables and initiates chromosome segregation network, leading to a biased chromosome position relative to the poles. Alternatively, the concentration of microtubules 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.

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, [77]]—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 1 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 oogenesis and sex-determination in birds (Box 3) provides a mechanism for the apparent integration of the mechanisms of oogenesis and sex-determination in birds [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.

Acknowledgements

We are grateful to David Crews for the invitation to contribute and helpful suggestions and to Renee Duckworth, Philip Bergmann, Caroline Isaksson, Kevin Oh, and Libby Landeen for insightful discussion and comments on this manuscript. This work was supported by a Fulbright Foundation Fellowship to TU and the David and Lucille Packard Fellowship to AVB. Empirical work on sex-determination in the house finch was funded by the grants from the National Science Foundation (DEB-0075388, IBN-0218313, and DEB-0077804).

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