Transitions Between Sex-Determining Systems in Reptiles and Amphibians

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Abstract

Important technological advances in genomics are driving a new understanding of the evolution of sex determination in vertebrates. In particular, comparative chromosome mapping in reptiles has shown an intriguing distribution of homology in sex chromosomes across reptile groups. When this new understanding is combined with the widespread distribution of genetic and temperature-dependent sex-determination mechanisms among reptiles, it is apparent that transitions between modes have occurred many times, as they have for amphibians (particularly between male and female heterogamety). It is also likely that thermosensitivity in sex determination is a key factor in those transitions in reptiles, and possibly in amphibians too. New models of sex determination involving temperature thresholds are providing the framework for the investigation of transitions and making possible key predictions about the homologies and sex-determination patterns expected among taxa in these groups. Molecular cytogenetics and other genomic approaches are essential to providing the fundamental material necessary to make advances in this field.

INTRODUCTION

We are in the midst of a revolution in understanding of vertebrate sex determination. This revolution has emerged from important technological advances in genomic analyses, particularly whole-genome sequencing, and from critical advances in knowledge of sex determination in the relatively conserved mammals and birds. Key milestones in this revolution include identification of a dominant master sex gene, *SRY*, on the Y chromosome in most therian mammals (48, 81); a strong indication that sex in birds is determined by dosage (rather than dominance) of a gene, *DMRT1*, on the Z chromosome (82, 85); comparative mapping of monotreme and bird sex chromosomes to reveal common retention of an ancestral amniote sex chromosome (30, 97); and mapping of homologous syntenic chromosomal regions of the bird and therian mammal to show that the mammal sex chromosomes were derived independently (24, 58, 61).

At a finer scale, comparative chromosome mapping in snakes, a turtle (*Pelodiscus sinensis*), a gecko (*Gekko hokouensis*), and a dragon lizard (*Pogona vitticeps*) has shown that sex chromosomes, particularly in ZW species, are not homologous across reptile groups (19, 43–45, 51, 53). Four genes that are sex linked in *G. hokouensis* are autosomal in *P. vitticeps* (19) and snakes (44, 51), whereas five snake and chicken sex-linked genes are autosomal in *P. vitticeps* (19). Thus, although there is conservation in chromosomal homology and that of broad syntenic regions in vertebrates (31), there appears little conservation across Reptilia in those chromosomes enlisted as ZW.

Given this general lack of homology among sex chromosomes in reptiles, it is perhaps remarkable that six orthologous genes map on the Z chromosomes of chicken and *G. hokouensis* with only two rearrangements even though these species diverged more than 285 Mya. This suggests that chickens and *G. hokouensis* have more likely retained the primitive condition of a common ancestor (17, 44), whereas other squamates (snakes and lizards) (98) show more recent and independently derived states (17). Alternatively, it may be that labile evolution in reptile sex determination has, coincidentally and convergently, enlisted the same chromosome pairs as sex chromosomes in birds and *G. hokouensis* but with a fundamentally different underlying mechanism (20). There may well be fundamental but not fully understood reasons for such convergence to occur more frequently than by chance alone (31). Perhaps more extraordinary is the recent finding that the complex XY chromosomes of the platypus show striking homology to the chicken Z chromosome (97). The spectacular homology between the sex chromosomes of birds, a gecko, and monotreme mammals could mean that a common amniote ancestor had a birdlike ZW system that has been independently retained in distantly related vertebrates over many hundreds of millions of years (97). This remarkable conservation is at odds with the equally remarkable lability of sex chromosomes in extant reptiles, a conundrum that we will explore further in this review. In particular, we will focus on how these transitions may occur, what biases appear to exist in reptiles and amphibians, and how new genomic tools can provide robust tests of predictions for those mechanisms.

THE HOMEOTHERM-HETEROTHERM DIVIDE

Sex determination in mammals and birds is extraordinarily conserved compared with that of reptiles, amphibians, and fish. In therian mammals (placental and marsupial), development as a male depends on the presence or absence of the Y chromosome, a conclusion drawn from studies of various deviations in development, primarily in humans and mice (91), and by experimental manipulation of expression in what is now known to be the mammalian sex-determining gene, *SRY* (48, 81). In marsupials, the formation of testes is determined by the Y-dominant mechanism, whereas the other traits characteristic of males and females depend on X-chromosome dosage (27).

Deterioration of the Y chromosome occurs through processes that are now reasonably well understood (9, 29) and leads to heteromorphy of the X and Y chromosomes of most mammals—taken to extreme in mole voles (*Ellobius* sp.) and spiny rats (*Tokudaia* sp.) in which the Y chromosome, including *SRY*, is lost altogether (42, 87, 88). The mechanism of sex determination in these species is not known. In birds, development as a female depends on the presence or absence of a W chromosome, but in this case, dosage rather than dominance is suspected, probably involving the gene *DMRT1* (83). Heteromorphy in the ZW sex chromosomes occurs in most birds (but not ratites, where Z and W are almost identical) (79), and thus they are as conservative in their mode of sex determination as mammals.

It is against this background that we measure the truly impressive and contrasting diversity in sex-determining modes among reptiles. Among those with genotypic sex determination (GSD), male and female heterogamety (XY and ZW) are known in turtles, female heterogamety (ZW, ZZW, or ZWW) is known in snakes, and both are known in lizards [including XXY and ZO (66, 86)]. Many species have a form of environmental sex determination—temperature-dependent sex determination (TSD)—based on the temperature of egg incubation (5, 12, 15, 22, 35). In two recently discovered instances, temperature and genotype interact to determine sex in two species of lizards (a dragon lizard and a skink) (71, 73). In contrast to mammals and birds, most reptiles with GSD lack heteromorphic chromosomes, at least at the level that can be detected using traditional cytological techniques, and they may involve microchromosomes. As such, their sex chromosomes are cryptic. The diversity of sex-determining mechanisms in the ectothermic reptiles, compared with that of the homeothermic birds and mammals and the typically poikilothermic amphibians and fish, may have arisen because of a unique predisposition to the development of TSD, acting as an intermediary in the evolution of GSD in its various forms (26).

The distribution of sex-determination mechanisms among the reptiles and the lack of sex chromosome homology suggest that transitions between modes have occurred many times (**Figure 1**). The predominant direction of change is not known, and where both modes of sex determination exist, neither GSD nor TSD can necessarily be regarded as the derived state in a related group of organisms (although see 38 for an alternative perspective). Reptiles are particularly intriguing. There is an almost haphazard distribution of TSD across the reptile phylogeny, with sister taxa at all levels exhibiting alternative modes of sex determination. Tuatara exhibit TSD (12). Crocodiles exhibit TSD (22), whereas birds do not. Snakes have a ZW form of GSD, whereas lizards exhibit TSD as well as multiple chromosomal forms of sex determination (39). TSD is common and widespread among turtles, but absent in two families (Trionychidae and Chelidae; but see 49) and present in their sister taxa (Carettochelyidae and Pelomedusidae, respectively) (16, 92), while at least three families (Bataguridae, Emydidae, and Kinosternidae) contain both GSD and TSD species (16). Both male and female heterogamety are widespread among lizards. Of the 181 species for which sex chromosomes have been detected, approximately two-thirds have male heterogamety (20), while both male and female heterogamety occur in at least one family (Gekkonidae) along with TSD (25). This fascinating diversity of sex-determining mechanisms shows no clear phylogenetic segregation (40, 67, 70).

Amphibians also exhibit variation in their sex-determination mechanisms, with either XY or ZW sex chromosomes identified in many species (37, 99). The recent discovery of the *dmW* gene in *Xenopus laevis* (101), which exhibits a high identity with the DNA-binding domain of *dmrt1* in that species and probably functions as a suppressor of autosomal *dmrt1* dosage (100), is the most likely early candidate for a sex-determining gene in this group. Most amphibians karyotyped do not have cytologically distinguishable sex chromosomes (36, 37, 76), and of the 4% of amphibians that do, most are ZW (37). However, they do show considerable diversity, with both male and female heterogamety occurring within families (37) and even within the same species. The best known of these is the Japanese wrinkled frog (*Rana rugosa*), which exhibits a ZZ/ZW system in the north of its range, whereas each of the three southern forms exhibits XX/XY chromosomes (56, 62). There is some consistency in the particular chromosomes that act as the sex pair, with chromosomes 4, 7, 8, 11, or 13 taking this role in many species (14, 76), although the homology of these chromosomes remains undetermined in most cases. Morphological differences between sex chromosomes of different amphibians tend to be the product of relatively trivial changes, including heterochromatin accumulation, pericentric inversions, insertions or deletions, and the presence of supernumerary chromosomes rather than the extreme degeneration of sex chromosomes observed in mammals and nonratite birds. Phylogenetic analysis of amphibian sex chromosomal systems suggests that a ZW system is ancestral (37; **Figure 1**) and that male heterogamety has evolved independently at least seven times. There is only a single known case of XY-to-ZW transition (37). Amphibians also exhibit other sex chromosome systems, with a multiple-sex-chromosome system identified in one species [*Eleutherodactylus maussi* (77)], and an OO male/OW female system,

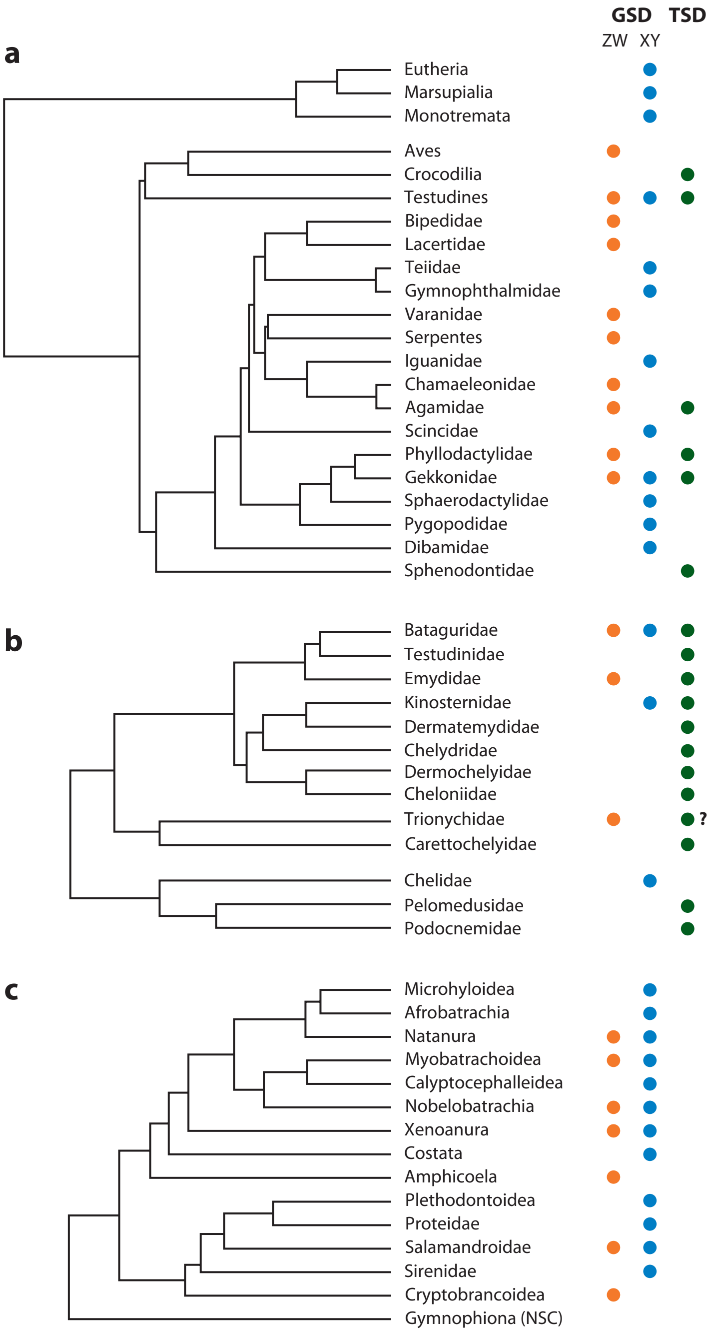

Figure 1

The distribution of male and female heterogamety and temperature-dependent sex determination (TSD) among (*a*) squamates and other reptiles, (*b*) turtles, and (*c*) amphibians. We note that ZW and XY sex chromosomes do not coexist in reptile families unless TSD is also present and that, in most cases, the ancestral state for XY taxa is ZW. Data for turtle families are insufficiently known to provide a reliable assessment of the distribution of sex-determining mechanisms or clearly involve highly devolved states (panel *b*). Abbreviations: GSD, genotypic sex determination; NSC, no sex chromosomes apparent. Data are from References 20, 21, 93, and 94. Turtle phylogeny follows that of Reference 78.

where Z chromosomes are absent from both males and females and the W chromosome is present only in females, in the endemic New Zealand frog [*Leiopelma hochstetteri* (32)].

Although reports of amphibians with environmental or polygenic sex determination in the wild are few, some species show spontaneous sex reversal, and others show a temperature effect in the laboratory (8, 99). Rearing the ZZ/ZW salamander *Pleurodeles waltl* at high temperatures produced viable ZW males, and several other anuran species produce sex-reversed males at high temperatures and females at low temperatures. Sex reversal in amphibians (where genetic XX females become phenotypic males) is also possible using hormonal treatments, but unlike those caused by high or low temperatures, sexes reversed by hormonal treatment are not maintained into adulthood (99). Sex reversal in the field occurs in one frog, *Rana temporaria* (2). When this species, which has an XX/XY system, is exposed to subarctic temperatures during development in nature, it exhibits a female sex bias (1) and produces single-sex clutches from XX males and XX females. Given that less than 0.2% of amphibian species have been examined for their response to incubation temperature, it is possible that temperature effects may be more influential than is conventionally thought.

Thus, among tetrapods, a clear distinction emerges between the homeothermic mammals and birds (with their conservative patterns of sex determination and typical heteromorphy in the sex chromosomes) and the ectothermic or poikilothermic reptiles and amphibians (with their diversity in patterns of sex determination and prevalent homomorphy in the sex chromosomes). As all species are extant, this is not a primitive-versus-advanced distinction. The distinction may have arisen because of the deeper divergencies and therefore greater phylogenetic diversity among reptiles and amphibians compared with that among mammals and birds, or because ectothermy and endothermy place quite different constraints on the potential for transitions among sex-determination mechanisms (26).

MODES OF GENOTYPIC AND TEMPERATURE-DEPENDENT SEX DETERMINATION: CHALLENGING THE PARADIGM OF DISCRETE AND MUTUALLY EXCLUSIVE STATES

One of the most widely and strongly held views on the evolution of vertebrate sex determination has the various modes of vertebrate sex determination as discrete and mutually exclusive states, with fundamentally different underlying mechanisms (5, 70, 95). Intermediate forms between these distinct adaptive peaks—XY GSD, ZW GSD, and TSD—are seen as brief, transitory, and suboptimal. This view has almost certainly been driven by the vastly superior knowledge surrounding mammalian XY sex determination (34, 47, 48, 81) and to a lesser extent the ZW system in birds (82, 84, 85). These two mechanisms, XX/XY and ZZ/ZW, appear fundamentally different in that one is a dominance system and the other a dosage system, and the sex chromosomes of birds and mammals are not homologous, suggesting independent origins for their mode of sex determination (60). In medaka fish (*Oryzias latipes*), one of the few non-mammalian vertebrates in which the master sex-determining gene has been identified, transitions between mechanisms of sex determination have occurred via evolution of de novo genes and chromosomes (89). This work has reinforced the perception that different modes of sex determination in GSD species are discrete, independently derived states.

GSD and TSD are believed to have fundamentally different underlying mechanisms. Transitions from GSD to TSD are thought to occur through the acquisition of thermosensitivity, and through the rapid elimination of the Y or W chromosome from the population via lethal or sublethal YY or WW chromosomal combinations (6) or under frequency-dependent selection (7). Loss of the Y or W equates to loss of any dominant master sex gene, effectively removing the underlying genetic influence and severing the connection with GSD.

Thus, pure TSD is considered to be where phenotypic variation (male or female) results only from environmental variation, with no directing genetic influence on whether an individual develops as male or female (95), and pure GSD where phenotypic and genetic sex correlate perfectly (subject to low levels of abnormality) (33, 95).

This paradigm, in which sex of TSD species is determined entirely by temperature as a consequence of having lost or failed to gain any genetic influence on sex, held sway for many decades. However, recent work has challenged the proposition that the various modes of vertebrate sex determination are discrete, mutually exclusive states on independent evolutionary trajectories. In particular, it has been argued that GSD and TSD are not dichotomous states, as is commonly believed, but rather are extremes in a continuum that includes species for which genotype and environment interact to determine sexual outcomes (74). This continuum has been particularly clear in lizards, with temperature effects evident in species with GSD and known sex chromosomes (71, 73, 80), suggesting that the division between GSD and TSD may not be as clear as previously thought (74, 80). In particular, the dragon lizard (*P. vitticeps*) has a cryptic ZZ/ZW genetic mode of sex determination (18) that is overridden by temperature at higher extremes (71) and does not require the W chromosome for female development. Similarly, the skink (*Bassiana duperreyi*), has XY chromosomes, yet XX males are produced at some temperatures (73, 80). There have been few attempts to examine gene-environment interactions in sex determination of reptiles, so these two cases are likely to represent a much wider phenomenon and greater scope for transitions between modes of sex determination than previously thought.

CONVENTIONAL TRANSITIONS BY CHROMOSOMAL HIJACKING

Sex chromosomes are generally thought to evolve from an autosomal pair by the acquisition of a male- or female-determining gene that defines a non-recombining region. That non-recombining region is progressively extended, promoting degeneration of the sex-specific chromosome (9, 57, 64). The lack of recombination around the sex-determining gene then causes an erosion of genes on the chromosome upon which the sex-determination gene resides. This in turn leads to a gradual loss of functional genes on the sex-determining chromosome and an eventual reduction in chromosome size (as in the mammalian Y chromosome), perhaps even to the point of being lost altogether, such as in the mole vole (41) and spiny rats (87, 88).

Although the Y chromosome in mammals probably arose only once (28), and probably originated from a gene that was already on the autosomes that are currently the mammalian X and Y, it is clear from sex chromosome distribution in reptiles and amphibians that heteromorphic chromosomes have evolved from autosomes many times in many lineages and have almost certainly arisen in different ways at different times. Medaka fish (*Oryzias latipes*) provide the best example of the development of incipient sex chromosomes in vertebrates (**Figure 2**). A duplicated copy of the *dmrt1* gene is sex specific in two strains of the medaka, while another copy of this gene resides on an autosome in a gene cluster with its paralogs *dmrt2* and *dmrt3* (52, 59). The Y-linked copy of *dmrt1* (*dmY* or *dmrt1Y*) shares close identity with the autosomal *dmrt1* gene, suggesting that this gene has undergone duplication onto a different autosome only relatively recently (52, 59).

The evidence for a central role for *dmY* in sex determination in medaka is strong (59). The Y chromosome is largely homologous with the X and has a large pseudoautosomal region that recombines over almost the entire length of the chromosome. The exception is a 250-kb fragment adjacent to the sex-determining region that contains the *dmY* gene, corrupted copies of three other genes whose autosomal homologs are also linked, and a high number of repetitive elements and transposons—a characteristic that is consistent with the genetic degeneration and recombinational isolation expected around a sex-determining region (10).

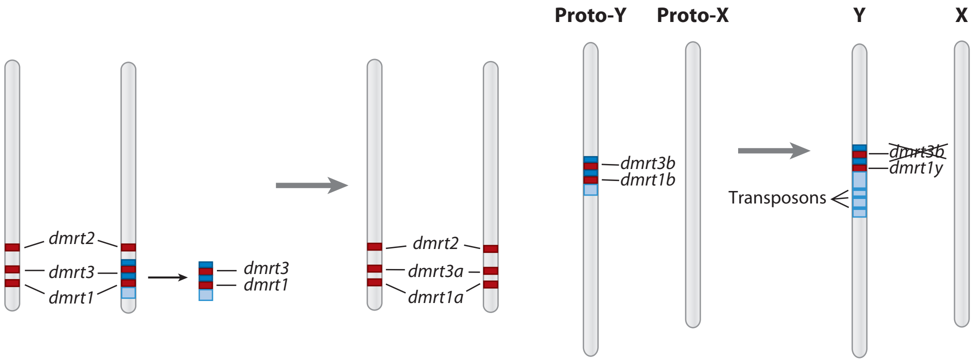

Figure 2

A model for the evolution of the Y chromosome in medaka fish (*Oryzias latipes*). A segment from the chromosome containing *dmrt1* (possibly an autosome) and related genes was duplicated and inserted into another autosome, which became the proto–Y chromosome in which the duplicated *dmrt1* adopted a male sex-determining function (68). As the segment of DNA containing *dmrt1* was translocated to a different chromosome, it has no homolog on the proto–X chromosome and therefore enables the suppression of recombination. Transposable elements accumulate on this segment and the allied chromosome, reinforcing the suppression of recombination and enabling other genes from the duplicated fragment (e.g., *dmrt3*) to become nonfunctional by mutation. In this way, sex determination in medaka was captured by the gene *dmY* from the as yet unidentified sex-determining gene in the ancestor. Figure modeled after Reference 75.

Phylogenetic comparisons among *dmY* genes from different species of medaka revealed that this particular sex-specific duplication is found in only one small clade of medaka (46), and molecular clock estimates suggest that the duplication took place approximately 10 Mya (102). The clear implication from these data is that new sex chromosomes in these species were formed by the duplication and transposition of *dmrt1* onto an unrelated chromosome, which effectively hijacked the sex-determination function (46).

The process of degradation of the chromosome exposed in the heteromorphic sex is well documented in mammals, where the Y chromosome holds only 23 protein-coding genes. This is as compared with the approximately 1,000 genes held on each of the chromosomes common to both sexes (X in mammals, Z in birds), which are freed up by the same process to expand and to acquire genes with sex-related functions (4).

Evolution of novel sex chromosomes through the hijacking of sex determination by genes with a sex-differentiation function provides the classical view of how transitions in sex-determination mechanisms can occur (64, 65). However, alternative evolutionary pathways may exist. In particular, thermolabile sex in reptiles, and potentially other ectotherms or poikilotherms, provides opportunity for a complex interplay between environmental temperature and sex determination (26). That in turn provides the potential for novel transition pathways between sex-determining forms.

NEW MODELS OF TRANSITION

Viewing reptile sex determination under environmental influence as a threshold trait provides particular insight into novel transitions. Thresholds exist in any system where a dichotomous outcome, such as sex, is determined by a continuously varying factor (such as temperature) or by multiple interacting genetic factors, which for practical purposes can be regarded as continuous in their influence (54). Such thresholds are well established in reptiles with TSD (15, 35). A sex-determining threshold is the minimum regulatory signal required to shift the balance between the competing signals directing the opposing male and female developmental programs (3, 26). Positive feedback loops, cross-program suppression, and reciprocal antagonism between genes in their expression reinforce any imbalance in those competing signals so that gonadal differentiation becomes committed to one fate only (13). Depending on the species or on the coincident presence or dosage of a master sex gene, temperature has the initial primary influence on the direction of the imbalance. Genetic variation will establish different set points for the sex-determining threshold, so that it can be subjected to selection and therefore is evolutionarily labile.

A number of recent papers have addressed the idea that movement in thresholds provides a potent force in transitions among sex-determining modes (33, 69, 72) where transitions in sex determination are facilitated by the interaction between genes and the environment (33). Quantitative shifts in a regulatory threshold for male or female development (depending on the underlying sex chromosome arrangement) enable transitions between heterogametic states via intermediate states of genotype-environment interaction. Shifts in a threshold could result from direct selection for increased (or decreased) thermosensitivity (11, 69), from genetic variants in the regulatory sex network hitchhiking with linked genes that themselves are undergoing positive selection, or from drift in the frequencies of those variants.

Quinn et al. (72) proposed a general model that does not require de novo evolution of sex-determining genes or sex chromosomes for transitions between TSD and GSD and between male and female heterogamety. Under that model, transitions can occur solely (although not always) through evolutionary change in a gene regulatory threshold, while retaining the same master genes and sex chromosomes. A key prediction of the model is that some species with thermolabile sex will retain the Y or W chromosome at a low frequency, driven down by Fisher's frequency-dependent selection in response to overproduction of one sex by natural sex reversal of the ZZ or XX genotype. Many of these species will traditionally have been regarded as TSD but may have sex chromosomes undetected because they are homomorphic or involve microchromosomes (18, 21).

A second key prediction arising from the Quinn model (72) is that male and female heterogametic sex-determination systems, particularly in closely related forms, may involve homologous genes and sex chromosome pairs. That is to say, a switch between types of heterogamety (ZW to XY or vice versa) can occur without significant change to the genomic machinery involved. An example of where that appears to have happened is in the Japanese wrinkled frog (*Rana rugosa*), which is the only vertebrate known to have both ZZ/ZW and XX/XY populations and thus provides the first evidence that such transitions between XY and ZW systems can occur (55, 63). Elegant gene-mapping work in this species has demonstrated that the X and W chromosomes are homologous, as are the Z and Y (56, 90)—in perfect agreement with the predictions of the Quinn model. The model further predicts that in one population, sex will be determined by the presence of a dominant gene on the heterogametic chromosome (Y or W), whereas sex determination in the other populations will depend on double dosage of that same gene in the homogametic sex—a proposition yet to be examined in *R. rugosa*.

The central question arising from these models and from the sparse data currently available is whether transitions in reptiles and amphibians between the modes of sex determination have been affected by the evolution of independent and fundamentally unique genetic mechanisms or by more subtle and possibly reversible modifications of some conserved underlying mechanism of sex determination.

In summary, homologous or nonhomologous states for sex chromosomes among sister and more distantly related taxa may be arrived at by a number of different pathways. We identify seven such routes (**Table 1**). First and best understood are the ancestrally homologous sex chromosomes, such as the XY system seen in most mammals. These sex chromosomes were

Table 1 Seven transitional pathways between different sex chromosomal forms among sister and more distantly related taxa, with proposed predictive tests using genomic features for the transitional pathways involved

	Homologous (group 1)				Nonhomologous (group 2)		
Mode of transition	Transition 1a (ancestral): XY or ZW	Transition 1b: XY ↔ XY XY ↔ ZW ZW ↔ ZW	Transition 1c: XY ↔ ZW	Transition 1d: XY ↔ ZW	Transition 2a: XY ↔ ZW	Transition 2b: ZW ↔ ZW	Transition 2c: |← ———— →| ← XY ↔ TSD ↔ ZW →
Mechanism	Function captured by allelic differences	Function captured independently through gene capture on homologous chromosomes	Function captured by an autosomal modifier on sex chromosomes	Function attained by a different autosomal modifier acting on the same master gene on homologous sex chromosomes	Function captured by gene duplication and transposition leading to the evolution of novel sex chromosomes	Function captured by novel gene independently	Function captured independently by novel genes, allelic differences, or threshold and dosage sensitive to temperature (gene-environment interaction)
Examples	*SRY* as an allelic form of *SOX3* Most mammals	Gecko and birds (shared homology between birds and geckos, but not other reptiles)	No known examples	Japanese wrinkled frog (*Rana rugosa*; homology shared between W and X)	*DMY/DMW* Medaka (*Oryzias latipes*) *Xenopus*?	Agamids (*Pogona vitticeps* and *Ctenophorus fordi*)	Agamids, geckos, skinks, turtles?
Test of transitional mechanism using genomic features	Homologous sex-determining gene on homologous sex chromosomes	Homologous sex chromosome but nonhomologous sex-determining genes	Homology between X and W and Z and Y but different sex-determining genes	Homology between X and W and Z and Y but same master sex-determining gene	Homology absent in sex chromosomes but present in master sex-determining gene	Homology absent in sex chromosomes and in master sex-determining gene	Absence of clear phylogenetic signal in sex chromosome and sex-determining gene homology

Abbreviation: TSD, temperature-dependent sex determination.

derived by capture of allelic differences at the *SOX3* locus in the ancestor to therian mammals. This followed either the acquisition of a testis-determining role and its subsequent evolution into the *SRY* gene (ancestral transition 1a) or the differentiation of the Y chromosome from the X initiated at a different, now lost, sex-determining locus on the Y [transition 1b (23)]. Other homologous forms may be derived through multiple modes of transition, where the function is captured independently by a gene on the sex chromosomes changing the master sex-determining gene but not the sex chromosomes or where the function has been captured by an autosomal modifier, either on the sex chromosomes or elsewhere in the genome (transitions 1c or 1d).

Nonhomologous sex chromosomes can evolve through the capture of the sex-determining function by an initial duplication followed by its transposition to an autosome and subsequent development into a sex chromosome (as seen in the medaka fish above), or where the function is captured by a novel gene quite independently of the genetic machinery on the existing sex chromosomes. This appears to be the case for the agamids *Ctenophorus fordi* and *P. vitticeps*, where nonhomologous ZW chromosomes have assumed the sex-determining function (19). Finally, nonhomologous sex chromosomes may arise from the effectively neutral state of pure TSD where sex chromosomes are reset as autosomes (ZZ or XX) and genetic sex determination arises independently of the former sex chromosomes.

We can expect to gain a clearer understanding of how frequently and by how many paths sex chromosomes have developed as homologies among sex chromosomes are tested using genomic data and chromosome painting (79) as well as other similar approaches.

RESIDUAL OR UNDERLYING PREDISPOSITION

A further prediction arising from the Quinn model is that reptile species with an underlying ZZ/ZW system will follow the egg incubation pattern where females are produced at low and high temperatures and males (or both males and females) are produced at intermediate temperatures (72). This particular pattern of temperature incubation is common among reptiles. The reverse pattern expected for XY species (males produced at high and low temperatures and females produced at intermediate temperatures), has not been observed in reptiles [although it is present in platyfish (*Xiphophorus maculatus*) (50)]. Furthermore, it is likely that ZW systems in lizards act via dosage mechanisms, which may be more susceptible to temperature influences than dominant gene systems and are therefore more likely to evolve from TSD than those systems that act via male dominance (72). Thus, it seems likely that ZW reptiles will be linked with temperature influences on incubation more so than those exhibiting XY heteromorphy. The distribution of heterogamety and TSD among reptile families supports just such an association [**Figure 1*a*,*b*** (20)], where, with one confirmed exception, ZW sex chromosomes have evolved only in those families in which TSD species occur. This is not the case with XY systems. The exception, Gekkonidae, includes examples of all three modes (XY, ZW, and TSD), providing the possibility that temperature interactions upon ZW forms have acted as the transitional mechanism for the evolution of XY heterogametic forms in that family. The ability to move along a continuum of sex-determining states, mediated by temperature or other environmental influences, provides a pathway to transitions between sex-determining modes that is alternative to those where pure TSD or sex chromosomal forms are hijacked by novel sex-determining genes.

A bias in sex-determination transitions similar to that observed in lizards is also apparent in amphibians, where transitions from ZW to XY have occurred at least seven times compared with a single XY-to-ZW transition [**Figure 1*b*** (37)]. This directional pattern of independent transitions from ZW to XY sex determination suggests that XY amphibians have passed through a ZW form. Given the possible thermal influences on amphibian sex

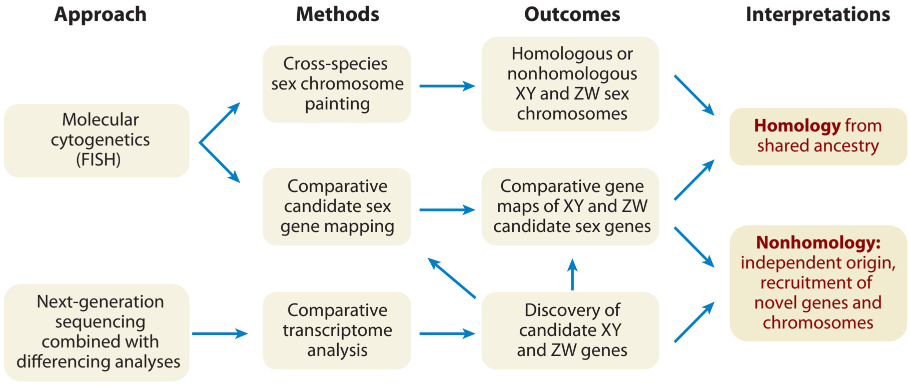

Figure 3

Schematic diagram linking the approaches and methods necessary to identify the modes of transitions in sex-determining mechanisms occurring in reptiles and amphibians. These approaches and methods test the hypothesis of shared ancestry between sex chromosomes from different taxa, and in doing so will determine the cytogenetic and molecular basis of transitions between XY and ZW sex-determination systems. Abbreviation: FISH, fluorescence in situ hybridization.

determination observed in the laboratory and now in the field (1, 2, 8, 99), it is tempting to speculate that temperature also plays a role in transitions between sex-determining modes in this group even though TSD itself is not a recognizable mode. A more comprehensive and fine-scale understanding of the phylogenetic relationship in these groups will assist in teasing apart the ancestral state changes.

Irrespective of the potential role of temperature in facilitating transitions in sex-determination modes, the widespread and frequent apparent retention of a residual W chromosome in TSD species may well allow for a rapid evolution back to a ZW system should circumstances such as climate change make this an advantage. As such, TSD systems that have not shed the W (or the Y) are likely to be predisposed to evolution to a GSD state, having retained the fundamental underlying ZW machinery (31).

CONCLUSIONS

Although the potential for temperature influences on sex determination in reptiles and amphibians has been known for some time, investigation of sex-determination transitions has really become possible only since the arrival of modern genomics. The key to those investigations lies in the identification of homology, and hence ancestry, among sex chromosomes, and in the identification and characterization of sex-determining genes in multiple taxa. Only with such a mechanistic approach can we hope to tease apart the different possibilities for the types of sex-determining mechanisms in nonmodel organisms such as reptiles and amphibians. Such an approach will shed light on the way in which transitions between mechanisms occur. In particular, a clearer picture of the relatedness among sex chromosomes will enable discrimination between homologous and nonhomologous transitions in sex chromosomes (**Table 1**) and between the sex-determination process itself, through the genes involved and the role of temperature in influencing the action of those genes.

There exists a substantial armory of approaches, including comparative genomics and chromosome painting, that have fostered much recent progress in understanding the evolution of sex chromosomes (**Figure 3**). Molecular cytogenetics in particular has generated much clarity in identifying the patterns of homology among vertebrate XY and ZW chromosomes and will continue to play a central role as this picture unfolds. The increasing amount of genomic information around key species like the green anole, painted turtle, chicken, *Xenopus*, and other reptile and amphibian species is generating, and will continue to generate, the critical comparative data required to focus on the elements that are common and different across the variety of sex-determination mechanisms seen in nature. The application of next-generation sequencing of DNA and complementary DNA (cDNA) to the identification of sex markers and sex genes will accelerate this process, providing a much clearer picture of sex genome evolution and mechanisms involved in many transitions observed in reptiles and amphibians.

DISCLOSURE STATEMENT

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