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REVIEW

Dynamics of vertebrate sex chromosome evolution: from equal size to giants and dwarfs

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Abstract The Y and W chromosomes of mammals and birds are known to be small because most of their genetic content degenerated and were lost due to absence of recombination with the X or Z, respectively. Thus, a picture has emerged of ever-shrinking Ys and Ws that may finally even fade into disappearance. We review here the large amount of literature on sex chromosomes in vertebrate species and find by taking a closer look, particularly at the sex chromosomes of fishes, amphibians and reptiles where several groups have evolutionary younger chromosomes than those of mammals and birds, that the perception of sex chromosomes being doomed to size reduction is incomplete. Here, sex-determining mechanisms show a high turnover and new sex chromosomes appear repeatedly. In many species, Ys and Ws are larger than their X and Z counterparts. This brings up intriguing perspectives regarding the evolutionary dynamics of sex chromosomes. It can be concluded that, due to accumulation of repetitive DNA and transposons, the Y and W chromosomes can increase in size during the initial phase of their differentiation.

Keywords Heterochromatin · Sex chromosome · Degeneration · WZ/ZZ · XX/XY · Homomorphy · Heteromorphy

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Introduction

Irrespective of the contrasting chromosomal sex-determining mechanisms, the small sizes of the mammalian Y and the chicken W chromosomes perfectly illustrate a prominent aspect of their evolutionary history. Suppression of meiotic recombination between X and Y as well as Z and W chromosomes undoubtedly is one of the first events in the evolution of sex chromosomes. This is the precondition for genetic and morphological differentiation and maintenance of sex chromosome identity (Bergero and Charlesworth 2009; Rice 1996). In making the Y and W different from the X and Z, many possibilities have been realized: inversions, accumulation of heterochromatin, deletion of heterochromatin, suppression of meiotic recombination by interference, fusions between sex chromosomes and autosomes, etc. All such mechanisms act in a very dynamic way to decrease recombination, and a general evolutionary rule seems not to exist. Because of the absence of recombination in the sex-specific region of those chromosomes, genetic alterations cannot be purged. For sex chromosomes, only the presence and functionality of the major sex-determining gene counts. Thus, although the vast majority of mutations have a negative effect on gene function, those occurring in genes linked to the sex-determining gene are not cleared during meiosis. This accumulation of deleterious changes in the Y or W is easily tolerated due to the fact that the X and Z provide corresponding intact copies, which are sufficient to fulfil the gene functions. Once a gene on the W or Y has lost its biological function, it will rapidly degenerate and its DNA sequence will disappear in the further evolution in a process described as "Muller's ratchet". Its space may be filled transiently by selfishly propagating transposable elements or DNA pieces inserted from autosomes, but in the long run, this process will force the Y and W to shrink to the miniature size seen in mammals and

birds. The general view is that Y and W sex chromosomes will continuously decrease in gene content and in size and end up as degenerated elements which are small, gene depauperated and heterochromatic (Bachtrog 2013; Charlesworth and Charlesworth 2000; Graves 2006). Extrapolating the loss of DNA content for the mammalian Y since it originated from a chromosome similar in size to the X has led to the prediction that the human Y (and all other Ys and Ws as well) finally even will fade to total disappearance (Charlesworth and Charlesworth 2000; Graves 2006).

Taking a closer look at evolutionary younger sex chromosomes of fishes and amphibians, it clearly appears that this perception is incomplete. In these vertebrate classes, contrary to birds and mammals, sex-determining mechanisms show a high turnover and new sex chromosomes appear again and again (Ellegren 2011; Ezaz et al. 2006; Mank and Avise 2009). Also in reptiles, where some groups (Serpentes) have a conserved sex determination system, others show a high diversity (Squamata, Testudines) (Ezaz et al. 2009; Gamble 2010; Kawagoshi et al. 2014; Matsubara et al. 2013). Phylogenetically closely related species or even different populations of one and the same species may have ZW and XY sex chromosome systems. Interestingly, many of these Y and W chromosomes are considerably larger than their corresponding X and Z counterparts, sometimes being the largest chromosome of the karyotype. In the present review, cytogenetic and molecular data that exemplify this observation are compiled. It can be concluded that in the initial phase of sex chromosome evolution and sometimes for quite a long period, the Y and W sex chromosomes increase in size, and that size diminishing may be only a late attribute in the evolutionary history. As an explanation for this process, there is evidence that accumulation of repetitive DNA and transposons, often regarded as epiphenomena of genetic degeneration, plays important roles during the establishment of a sex chromosome in the first phase. Amassing such functionless sequences is a fast and effective way of making an emerging Y or W genetically different from its counterpart and preventing meiotic pairing and crossing over.

Vertebrate sex chromosome structure elucidates their evolutionary history

Currently, deep sequencing approaches in several model vertebrates are shedding light in greater depth on the evolutionary steps involved in shaping specialized Y or W sex chromosomes (Chen et al. 2014; Hughes and Rozen 2012; Hughes et al. 2010; Soh et al. 2014; Zhou et al. 2014). However, for the majority of vertebrates, the information on sex chromosomes accumulated from classic cytogenetic studies is still extremely important for determining the extent of differentiation of sex chromosomes in the heterogametic sex. The

transformation from a pair of ordinary homomorphic autosomes to highly heteromorphic sex chromosomes endured a long evolution. This involved the accumulation of constitutive heterochromatin and/or the occurrence of structural changes (e.g. inversions) leading to the suppression of recombination between the homologous chromosome pairs, finally retaining a variable extent of autosomal segments in heterogametic chromosomes in different vertebrates. Remarkably, this evolutionary process can still be visualized among the karyotypes of basal vertebrates where the sex chromosomes exist either in incipient or in advanced forms. In the former case, both sex chromosomes appear homomorphic with limited meiotic isolation whereas in the latter case, they are structurally diverged by possessing small or large segments of heterochromatin in the Y or W chromosomes. In some instances, the sex chromosomes may lack any heterochromatic regions but can achieve some level of structural difference through inversions. Thus, cytological information of sex chromosomes provides a valuable help for evaluating evolutionary relationships of sex chromosomes in a wide range of vertebrates. It is a common belief that in most vertebrates, the Y and W chromosomes tend to become shorter over time compared to their counterpart (X and Z). However, exceptions to this reasoning, especially in groups with high sex chromosome turnover, have not been adequately evaluated. A detailed comparison of the cytological structure of sex chromosomes in vertebrate karyotypes may provide information whether the Y and W chromosomes always follow the general rule in evolving to small heterochromatic elements whereas the X or Z chromosomes always retain their original sizes.

Unusually structured Y chromosomes in mammals

The highly heteromorphic sex chromosomes of mammals evolved from an ordinary autosomal pair. When exactly this happened is still a matter of debate, and the estimates range from a maximum of 300 to a minimum of 166 million years ago (Bachtrog 2013; Bellott et al. 2014; Cortez et al. 2014; Lahn and Page 1999; Livernois et al. 2012). Strikingly, the X-linked genes, contrary to the genes in all autosomes, are mostly conserved in all eutherian mammals. To a large extent, the same is true for the Y chromosome, although some Y-linked genes experienced a lineage-specific loss (Bellott et al. 2014). Thus, given the remarkable conservation and long evolutionary history, the mammalian X and Y chromosomes are considered as "old" sex chromosomes.

In the vast majority of karyotypes, the so-called original-type X chromosome of most mammals constitutes approximately 5 % of the female haploid karyotype, a phenomenon consistent with the conservation of its gene content. In contrast, the Y chromosome generally is small and mostly heterochromatic, i.e. at an evolutionary endpoint largely owing to

the steady decay of the ancestral Y chromosome. The process of ancestral Y chromosome degeneration may have started early on in the evolution of the Y. In basal eutherian lineages like Afrotheria (elephant) and Xenarthra (armadillos and sloths), the Y chromosomes are small and highly differentiated from the X alike the situation in the vast majority of other mammals (Table 1).

However, classical cytogenetic studies already pointed out that in several species, the X and Y can have an unusual organization (Fredga 1970). In the Chinchilla rat, *Chinchilla lanigera* and fin whale, *Balaenoptera physalus*, the X chromosome is extraordinarily large but the Y chromosome did not change and remained very small. The Y can appear as a small dot-like chromosome, being completely heterochromatic in the karyotypes of dog (Carnivora), sheep (Artiodactyla)

and sable (Carnivora). On the contrary, in some rodents, like hamsters and some voles (*Microtus*) and also a few species of Artiodactyla, both X and Y are exceptionally large due to accumulation of heterochromatin. The Y can be from half the size of the X up to reaching the same size or can even be larger as in the tufted deer, *Elaphodus cephalophus* (Table 1).

The variability of the structure and/or size of the Y chromosome is most pronounced in rodent karyotypes. In the majority of mammalian species, the Y remains small and heterochromatic. But in some karyotypes, the Y becomes enlarged due to accumulation of constitutive heterochromatin, while in others, it is drastically reduced to a dot-like chromosome without exhibiting visible amounts of constitutive heterochromatin (Table 1). In the Transcaucasian mole vole, *Ellobius lutescens*, and two spiny rats, *Tokudaia tokunoshimensis* and *Tokudaia*

Table 1 Examples of extreme variation of Y chromosome length within the superorder or in different orders of placental mammals

Species	Order	Sex chromosomes	Y chromosome size	Heterochromatin accumulation	References
Trichechus manatus latirostris	Sirenia (Afrotheria)	XX/XY	Smallest	Heterochromatic	(Gray et al. 2002)
Elephas maximus	Proboscidea (Afrotheria)	XX/XY	Small	Heterochromatic	(Houck et al. 2001)
Microgale cowani	Afrosoricida (Afrotheria)	XX/XY	Tiny	N.A.	(Gilbert et al. 2007)
Bradypus torquatus	Pilosa (Xenarthra)	XX/XY	Small	Poor	(Azevedo et al. 2012)
Chaetophractus villosus	Cingulata (Xenarthra)	XX/XY	Small	Poor[a]	(Rossi et al. 2014)
Suncus murinus	Soricomorpha	XX/XY	Large (3/4th of X)	Partial heterochromatic[a]	(Raman and Nanda 1986)
Talpa romana	Soricomorpha	XX/XY	Smallest	Poor	(Gornung et al. 2008)
Hemiechinus auritus	Erinaceomorpha	XX/XY	Smallest	Poor	(Arslan et al. 2009)
Canis familiaris	Carnivora	XX/XY	Smallest	Heterochromatic	(Graphodatsky 1989)
Martes zibellina	Carnivora	XX/XY	Tiny	Heterochromatic	(Graphodatsky 1989)
Lutra lutra	Carnivora	XX/XY	Large (1/2 of X)	Heterochromatic	(Graphodatsky 1989)
Tapirus indicus	Perissodactyla	XX/XY	Large (1/2 of X)	Large part heterochromatic	(Houck et al. 2000)
Tapirus pinchaque	Perissodactyla	XX/XY	Small	Poor	(Houck et al. 2000)
Cervus elaphus	Artiodactyla	XX/XY	Small	Heterochromatic	(Goldoni et al. 1984)
Elaphodus cephalophus	Artiodactyla	XX/XY	Largest (larger than X)	Heterochromatic	(Cao et al. 2005)
Microtus agrestis	Rodentia	XX/XY	Extreme large	Heterochromatic	(Borodin et al. 1995)
Microtus guentheri	Rodentia	XX/XY	Small	Heterochromatic	(Borodin et al. 1995)
Cricetulus griseus	Rodentia	XX/XY	Large	Heterochromatic[a]	(Vistorin et al. 1977)
Dendromus mesomelas	Rodentia	XX/XY	Large (nearly equal to X)	Yq heterochromatic	(Solano et al. 2014)
Chiromyscus chiropus	Rodentia	XX/XY	Tiny (smallest)	Poor	(Chen et al. 1995)
Ctenomys maulinus	Rodentia	XX/XY	Large (nearly equal to X)	Poor	(Suarez-Villota et al. 2014)
Myotis frater	Chiroptera	XX/XY	Tiny	Heterochromatic	(Ando et al. 1980)
Hipposideros larvatus	Chiroptera	XX/XY	Large (half of the X)	Heterochromatic	(Xiu-Guang et al. 2010)
Saguinus midas niger	Primates	XX/XY	Small/medium	Mild heterochromatic	(Nagamachi and Pieczarka 1988)
Saguinus mystax mystax	Primates	XX/XY	Tiny	Heterochromatic	(Dantas and Barros 1997)

N.A. not available

[a] Synapsis or chiasmatic association between the X and Y during meiosis

osimensis, the existence of a Y chromosome in the karyotype is even hard to visualize (Honda et al. 1977; Matthey 1953) or might have been lost (for review and in depth discussion see (Just et al. 2007; Murata et al. 2012)).

The laboratory mouse is known for its relatively large Y, which comprises a full 3 % of the whole mouse genome. Sequencing of the Y chromosome revealed that it is almost entirely euchromatic and that only 2 % of the male-specific region on the Y derives from the ancestral autosome that gave rise to the mammalian sex chromosome. The majority of the sequences that make up its current size are recently acquired and massively amplified families of testis expressed genes, which are lineage specific (Soh et al. 2014).

Even more intriguing is the situation in an Argentinian rodent, *Ctenomys maulinus*, where the Y appears completely euchromatic and has the same size as the X (Suarez-Villota et al. 2014). Despite these features, the Y does not show extensive pairing with the X during meiosis. Thus, remarkable expansion or contraction of Y chromosome length occurred rapidly within this clade because many species of *Ctenomys* have heteromorphic sex chromosomes with a small heterochromatic metacentric or subtelocentric Y.

A number of other mammals, such as the Asian house shrew *Suncus murinus* and some hamster species, have large X and Y chromosomes with few heterochromatic regions (Table 1). However, they show extensive synapsis during meiosis, which may imply retention of a large pseudoautosomal region in some Y chromosomes. On the contrary, it may be conjectured that some autosomal segments may have been transposed to both X and Y chromosomes resulting in autosomal-like traits on the differentiated sex chromosomes. Indeed, in Zoo-FISH analysis of the chromosomes of the South African climbing mouse, *Dendromus mesomelas*, both large X and Y chromosomes were simultaneously labelled with mouse (*Mus musculus*) chromosome 15 paint (Solano et al. 2014). This indicates a scenario where both X and Y become enlarged through the acquisition of an autosomal segment, which creates a "neo-pseudoautosomal region" on the sex chromosome pair.

Y chromosome size reduction also occurs on the young neo-Y chromosomes. For example, the neo-Y chromosomes of the mongoose *Herpestes sanguineus* can be distinguished from *X*2, which is somewhat smaller with a longer p- and a shorter q-arm. In a related species, *Herpestes auropunctatus*, the neo-Y can hardly be detected in mitotic metaphases (Fredga 1970; Raman and Nanda 1982).

The present survey of karyotypes from many mammalian orders shows that tiny Y chromosomes are not rare (Table 1). In many instances, these tiny Ys are non-heterochromatic. The sequencing of the Y chromosome revealed that it is 99.9 % euchromatic consisting of ampliconic sequences that are expressed in the testes and distinct from what is typically

referred to as repetitive sequences that constitute heterochromatin (Soh et al. 2014). Hence, though heterochromatin accumulation is considered an important step for the differentiation of sex chromosomes, it may eventually become disconnected with some differentiated Y chromosomes. They can be entirely heterochromatic with all intermediate stages up to being almost completely euchromatic (C-band negative).

In summary, mammalian Y chromosomes show quite some heterogeneity in size, ranging from tiny, dot-like Ys to unexpectedly large elements which can even reach the size of the X chromosome.

Differing extent of W chromosome degeneration in birds

As in mammals, sex determination in birds is accomplished through a stable sex chromosome system. Both Z and W chromosomes, like the mammalian XY pair, have evolved from a pair of autosomes, but from a different pair than the mammalian sex chromosomes (Marshall Graves and Shetty 2001; Nanda et al. 1999). Similar to the mammalian Y chromosome, the avian W is generally small in size, highly heterochromatic and contains palindromic sequences (Davis et al. 2010). Based on the uniform size and morphology of the Z chromosome in various avian species, Ohno (Ohno 1967) first proposed that the Z was highly conserved throughout the avian lineages, which was later confirmed by comparative FISH mapping (Nanda et al. 2008; Nishida-Umehara et al. 2007). Thus, the bird sex chromosomes like those of mammals are defined as old sex chromosomes. Though both avian Z and mammalian X chromosome derived from opposite sex-determining systems (♂ birds: homogametic ZZ, ♀ birds: heterogametic ZW; ♂ mammals: heterogametic XY, ♀ mammals: homogametic XX), both have acquired testis-specific genes and display many comparable features, which can be explained by convergent evolution (Bellott et al. 2014). Similar to the mammalian Y, the avian W evolved by losing most of its ancestral genes through recombination arrest and after continuously accumulating repetitive DNA sequences. Subsequent deletions of these highly reiterated DNA sequences apparently led to the distinctly reduced size of the W chromosome in extant avian species. Recent DNA sequence analysis in 17 bird species undoubtedly disclosed that the evolution of Z and W chromosomes, complementary to the mammalian X and Y, occurred in several strata involving inversion and recombination suppression between the two sex chromosomes (Zhou et al. 2014).

Comparative avian cytogenetics, in particular detailed comparisons of karyotypes in the two sister groups, the palaeognathous and the neognathous birds, revealed that in these vertebrates, the evolution of sex chromosomes occurred in discrete stages (Fig. 1a). In general, Z and W chromosomes
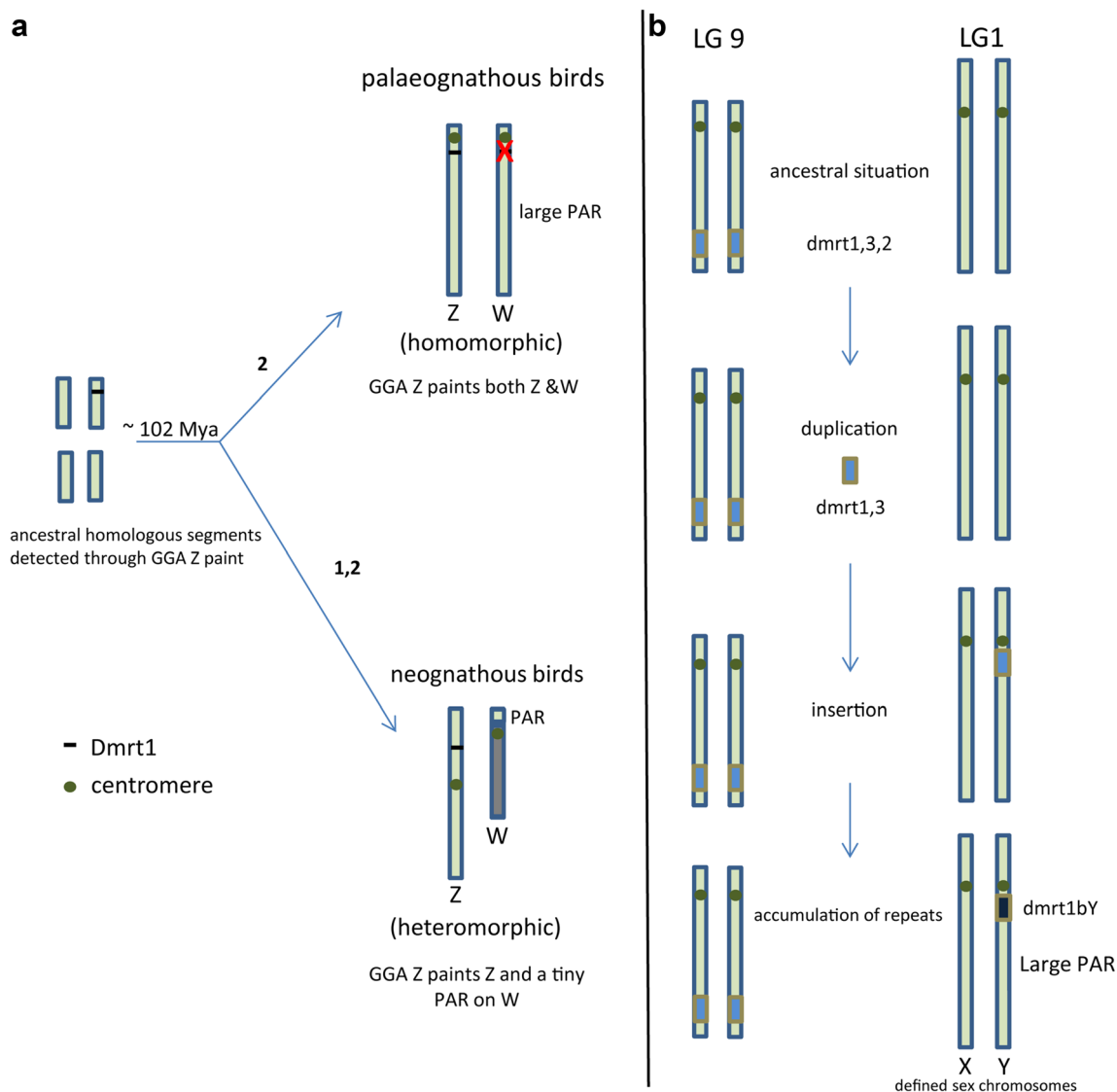
Fig. 1 Evolutionary pathways of old and young sex chromosomes as exemplified in birds (**a**) and medaka (**b**). **a** Outline of the evolution of homomorphic and heteromorphic sex chromosomes in ratite (palaeognathous) and carinate (neognathous) birds. The rearrangement of ancestral sex linkage group (proto sex chromosome) through inversion and accumulation of heterochromatin may be a common mechanism underlying the evolution of "old sex chromosomes" in birds and mammals. **b** Unique mode of sex chromosome evolution in medaka involving duplication and insertion of a tiny chromosomal segment containing sexual regulatory locus. This mode of evolutionary strategy may contribute to rapid generation of "young" sex chromosomes. *PAR* pseudoautosomal region, *1* heterochromatin accumulation, *2* inversion

of all palaeognathous birds are largely homomorphic and euchromatic. This status appears to correspond to the ancestral situation and indicates the existence of a large pseudoautosomal region in the W chromosome (Nishida-Umehara et al. 2007). However, an initial step towards the differentiation of W chromosome by heterochromatin accumulation was cytogenetically detected in the elegant crested tinamou (Tinamiformes) in which the W chromosome is partially heterochromatic and the size is already slightly diminished (Tsuda et al. 2007).

In the karyotypes of most neognathous birds, the W chromosome is distinctly smaller than the Z and, as a result of continuous accumulation of repetitive DNA sequences, has often acquired a completely heterochromatic structure. Since this is also the case in basal lineages as the Anseriformes and Galliformes, a rapid degeneration of the ancestral W chromosome could be deduced. However, in a comparative analysis of 200 bird species, a gradual shrinkage of the W chromosome during avian evolution was not evident and the length of the W chromosome can vary due to amplification of non-coding regions without any phylogenetic pattern observed (Rutkowska et al. 2012).

Though in many neognathous bird karyotypes, the W chromosome is generally smaller than the Z but there are some

exceptions. Notably, in two species, the crimson finch, *Neochmia phaeton* (Passeriformes), and the paddy bird, *Ardeola grayii* (Pelecaniformes), the W is larger than the Z chromosome (Table 2). The W chromosome in the crimson finch is completely heterochromatic suggesting that the pseudoautosomal region is disrupted by stretches with enormous amplification of non-coding DNA. Interestingly, in the karyotypes of some hawks, eagles and kites (Accipitriformes) and owls (Strigiformes), the W chromosome is large but can be completely or only partially heterochromatic. It is noteworthy to mention that the karyotypes of most species belonging to the family Accipitridae are derived. Compared to other neognathous birds, they possess a reduced diploid chromosome number, only few microchromosomes but many bi-armed chromosomes. All these facts indicate that a process of fusion between microchromosomes and between micro- and macrochromosomes has occurred during the chromosome evolution in the Accipitridae. Hence, stretches of non-heterochromatic regions in the W chromosome of some of these species could be the result of a shift of microchromosomal DNA sequences. Such an inter-chromosomal rearrangement involving both sex chromosomes has been shown in the great reed warbler, *Acrocephalus arundinaceus* (Pala et al. 2012).

Further dynamics in W chromosome differentiation is evident in two parrots (the yellow-faced parrot, *Salvatoria xanthops*, and short-tailed parrot, *Graydidascalus brachyurus*) where a large part of the W chromosome is not heterochromatic although it is smaller than the Z (Caparroz and Duarte Barbanti 2004).

Similar to the mammalian Y chromosome, the avian W chromosome was subjected to extraordinary structural changes during evolution. In mammals, Y chromosome degradation seems to have been a rapid evolutionary process and in many karyotypes, the tiny Y chromosomes appear as euchromatic or poor in heterochromatin content (C-band negative). In contrast, the degradation of the ancestral W chromosome of birds was relatively slow as the W chromosomes of palaeognathous and neognathous birds demonstrate. Recent molecular analysis highlights that the pace of W chromosome degeneration also varies considerably among neognathous birds, i.e. each species has different genes retained in the non-recombining region (Zhou et al. 2014).

Large Ys and Ws among reptiles with different sex chromosome systems

Unlike mammals and birds, the sex-determining mechanisms among reptiles are extremely divergent. They range from genotypic sex determination (GSD), with either male or female heterogamety to temperature-dependent sex determination (TSD) in different lineages. Essentially, all snakes exhibit GSD with female heterogamety, whereas some lizard and turtle species are characterized by both male and female heterogamety. Some of the lineages with different modes of GSD have recently separated from their last common ancestor, as shown for the Agamidae (Ezaz et al. 2009), and given the frequent transition of sex chromosomes, it is likely that their sex chromosomes are "young" sex chromosomes. On the other hand, in Iguana lizards, the sex chromosomes appear to be evolutionary quite old (Rovatsos et al. 2014).

Historically, snakes represented important model organisms for studies on vertebrate sex chromosome evolution. The predominating hypothesis on the origin of sex chromosomes from a pair of autosomes emulated from cytogenetic studies, which demonstrated the presence of homomorphic and heteromorphic sex chromosomes in different groups of snakes (Ohno 1967). In general, Z and W chromosomes are undifferentiated and homomorphic in species of the families Boidae (Becak et al. 1964) and Pythonidae (Singh et al. 1976). An evolutionary series in which the increasing structural complexity of the sex chromosomes in the karyotypes of snakes with differing stages of W chromosome morphological

Table 2   Examples of avian species where the W chromosome is either of equal size or larger than the Z chromosome

Species	Order	Sex chromosomes	W chromosome size	Heterochromatin accumulation	References
Struthio camelus	Struthioniformes	ZZ/ZW	Equal to Z	Poor	(Nanda et al. 2008)
Dromaius novaehollandiae	Casuariiformes	ZZ/ZW	Equal to Z	Poor	(Nishida-Umehara et al. 2007)
Elanus caeruleus	Accipitriformes	ZZ/ZW	Equal to Z	p-arm is heterochromatic	(Bed'Hom et al. 2003)
Pulsatrix perspicillata	Strigiformes	ZZ/ZW	Equal to Z	Heterochromatic	(Yamada et al. 2004)
Nyctibius griseus	Caprimulgiformes	ZZ/ZW	Equal to Z	Heterochromatic	(Nieto et al. 2012)
Neochmia phaeton	Passeriformes	ZZ/ZW	Larger than Z	Heterochromatic	(Christidis 1986a)
Lonchura flaviprymna	Passeriformes	ZZ/ZW	Large but slightly smaller than Z	Heterochromatic	(Christidis 1986b)
Ardeola grayii	Pelecaniformes	ZZ/ZW	Larger than Z	N.A.	(Mohanty and Bhunya 1990)

N.A. not available

differentiation was initially recognized by Becak et al. (1964). Exceptionally, the W chromosome in the Madagascar boa *Acrantophis dumerili* (Boidae) is structurally differentiated from the Z by a pericentric inversion that may appear as an initial structural barrier for recombination between two homomorphic sex chromosomes (Mengden and Stock 1980). Z and W in colubrid snakes were long considered to represent an intermediate stage of chromosome differentiation, but a much higher degree with complete cessation of recombination was recently shown at the molecular level (Vicoso et al. 2013). Highly degenerated and heterochromatic W chromosomes are documented in snakes belonging to the Elapidae and Viperidae.

Highly differentiated W chromosomes of snakes are usually smaller than the Z chromosomes and are enriched with repetitive DNA sequences (Jones and Singh 1985). An exception is found in two species, the Trans-Pecos rat snake *Elaphe subocularis* (Colubridae) and the Sind krait *Bungarus walli* (Elapidae), where the W chromosome is substantially larger than the Z and completely heterochromatic (Table 3). A further peculiarity is that the W chromosome can be completely differentiated from the Z but may not be entirely heterochromatic, still maintaining some level of homology with the Z as seen in the Okinawa habu *Trimeresurus flavoviridis* (Viperidae) (Matsubara et al. 2006).

Interestingly, the Z chromosome of snakes, like the avian Z, appears to be evolutionarily conserved (Matsubara et al. 2006). A similar situation has been found in birds, which would suggest that the ZW sex chromosomes of snakes behave similar in evolutionary terms as the ZW chromosomes of birds. However, it became clear from gene mapping studies that sex chromosomes in different reptilian groups have evolved from different ancestral autosomes. Comparative gene mapping experiments showed the existence of homoeologies between the avian Z chromosome and various autosomes of snakes, but no apparent homoeologies between the Z chromosomes of birds and snakes (Srikulnath et al. 2009).

Many lizards and some turtles have highly differentiated sex chromosomes. Contrary to the stable ZZ/ZW sex chromosomes of snakes, frequent transitions between different types of heterogamety (XY♂ → ZW♀ and vice versa) and even TSD is observed (Ezaz et al. 2009; Gamble 2010). This is conspicuously evident among lizards, especially in the family Gekkonidae, which includes species having both male and female heterogamety as well as TSD. Additionally, in lizards, the XY and ZW sex chromosomes can be homomorphic as well as heteromorphic. This diversity in sex chromosome morphology and differentiation is the result of inversions, fusions and heterochromatin accumulation (Cole et al. 1967; King 1977; Matsubara et al. 2014; Moritz 1984; Olmo et al. 1987). Furthermore, in many species, a degeneration of the Y or W chromosomes took place by deletions in their heterochromatic segments making these chromosomes distinctly smaller than the X and W chromosomes (Matsubara et al. 2013). Finally, both Z and W chromosomes show different morphological forms in different races of the purplish dtella *Gehyra purpurascens*, implying that the structure of sex chromosomes is subjected to rapid change (Moritz 1984).

Table 3 Examples of large heterogametic sex chromosomes and their heterochromatin status in reptilian lineages

Species	Order	Sex chromosomes	Y/W chromosome size	Heterochromatin accumulation	References
Thecadactylus rapicauda	Squamata	ZZ/ZW	W is larger than Z	Partially heterochromatic	(Schmid et al. 2014)
Delma inornata	Squamata	XX/XY	Y is the largest	N.A.	(King 1990)
Varanus acanthurus	Squamata	ZZ/ZW	W is slightly larger than Z[a]	Heterochromatic	(Matsubara et al. 2014)
Varanus rosenbergi	Squamata	ZZ/ZW	W is slightly larger than Z	Heterochromatic	(Matsubara et al. 2014)
Underwoodisaurus milii	Squamata	ZZ/ZW	W is larger than Z	Heterochromatic	(Pokorná et al. 2014)
Elaphe subocularis	Squamata	ZZ/ZW	W is larger than Z	Heterochromatic	(Mengden and Stock 1980)
Naja naja	Squamata	ZZ/ZW	W is slightly larger than Z	Heterochromatic	(Singh et al. 1980)
Elaphe radiata	Squamata	ZZ/ZW	W is slightly larger than Z	Heterochromatic	(Singh et al. 1980)
Bungarus walli	Squamata	ZZ/ZW	W is larger than Z	Heterochromatic	(Singh et al. 1980)
Boiga forsteni	Squamata	ZZ/ZW	W is larger than Z	N.A.	(Singh 1972)
Boiga trigonata	Squamata	ZZ/ZW	W is larger than Z	N.A.	(Singh 1972)
Notechis scutatus	Squamata	ZZ/ZW	W is larger than Z	Repeat accumulation	(O'Meally et al. 2010)
Apalone spinifera	Testudines	ZZ/ZW	W is larger than Z[a]	Heterochromatic	(Badenhorst et al. 2013)
Pelodiscus sinensis	Testudines	ZZ/ZW	W is larger than Z	Heterochromatic	(Kawai et al. 2007)
Furcifer oustaleti	Squamata	ZZ/ZW	W is larger than Z	Heterochromatic	(Rovatsos et al. 2015)

N.A. not available

[a] Both Z and W are of microchromosome size

In several instances, the Y and W chromosomes of reptiles are larger than their X and Z counterparts (Table 3). The Y chromosome is the largest chromosome in the karyotype of the patternless delma, *Delma inornata*. The W chromosome of the turnip-tailed gecko, *Thecadactylus rapicauda*, is larger than the Z, and this size difference is caused exclusively by the presence of an interstitially located heterochromatic segment in the W. A more striking situation is the extreme reduction of the size of the Z chromosome in the fat-tailed gecko, *Underwoodisaurus milii* (Pokorná et al. 2014), and the Malagasy giant chameleon *Furcifer oustaleti*, whereas the large W chromosome is completely heterochromatic (Rovatsos et al. 2015). Furthermore, in monitor lizards (*Varanus* spp.), the differentiated sex chromosomes have the sizes of microchromosomes. Due to accumulation of constitutive heterochromatin, the W is somewhat larger than the Z (Matsubara et al. 2014).

Although TSD is the common mode of sex determination in turtles, a few species with heteromorphic sex chromosomes are known. These sex chromosomes are found in both males and females with no common phylogenetic roots which forces the conclusion that evolutionary transitions of sex-determining modes took place in these vertebrates. In parallel, turtle sex chromosomes have also experienced considerable structural changes leading to large homomorphic XY chromosomes in the black marsh turtle *Siebenrockiella crassicollis* and to microchromosome-sized and differentiated Y and W sex chromosomes in the eastern long-necked turtle, *Chelodina longicollis*, the spiny softshell turtle, *Apalone spinifera*, and the Chinese soft shelled turtle, *Pelodiscus sinensis* (Badenhorst et al. 2013; Kawai et al. 2007). In both *A. spinifera* and *P. sinensis*, the W chromosomes appear to be larger even in these microchromosome-sized ZW chromosomes (Table 3). Moreover, the long segments in the large Y chromosomes of *S. crassicollis*, the Mexican giant musk turtle, *Staurotypus triporcatus*, and the giant musk turtle, *Staurotypus salvinii*, are not heterochromatic (Kawagoshi et al. 2012; Kawagoshi et al. 2014) indicating that the sex chromosomes are still in an early stage of structural differentiation. In fact, recent mapping studies exemplify the amplification of microsatellite repeat motifs is strongly correlated with the extent of differentiation and heterochromatinization of Ys and Ws in many sauropsids (Matsubara et al. 2015; Pokorná et al. 2011).

In conclusion, reptiles display a remarkable variety of different sex chromosomes and sex-determining systems. This is reflected by dynamic changes in the cytological morphology and molecular structure of the sex chromosomes. An enlargement of the W and Y chromosomes by accumulation of repetitive DNA sequences (as visible constitutive heterochromatin) has occurred in some species of snakes, lizards, turtles.

Large Y and W chromosomes in amphibians

In the vast majority of amphibians, sex is determined genotypically through either male or female heterogamety. ESD or polygenic modes of sex determination in natural populations are rare or a matter of debate (Hillis and Green 1990). Phylogenetic analyses suggested that female heterogamety was the ancestral state of sex determination and male heterogamety is thought to have subsequently and independently evolved several times in different lineages (Hillis and Green 1990). It has been proposed that the amphibian sex chromosome systems can go through transitions not only on the inter-species but also on the intra-species level. This hypothesis is based on very detailed studies in one frog species, the Japanese wrinkled frog, *Rana rugosa,* which exhibits ZW and XY, as well as undifferentiated sex chromosomes in different populations (Uno et al. 2008). Gene mapping data suggest that these sex chromosomes existing in different populations are largely homoeologous indicating their common origin.

Cytogenetic analyses so far revealed that most amphibian species lack morphologically differentiated sex chromosomes implying that they still have not developed supramolecular differences to an extent that this becomes evident on the cytological level. Such homomorphy, which is taken as an indication of structural collinearity and high molecular similarity, is evident in the recently diverged hylid frogs where casually recombination can occur all along the sex chromosomes (Stöck et al. 2011). In the African clawed frog *Xenopus laevis*, the sex-determining gene *DM-W* is located on the W chromosome. It is a duplicated but truncated version of the autosomal *dmrt1* gene and most likely acts as a dominant negative version that abrogates the male-determining function of Dmrt1 (Yoshimoto et al. 2008). However, besides this W chromosome-linked sex-determining gene, no further evidence for molecular or cytological differentiation of the ZW sex chromosomes of *X. laevis* was demonstrated. In the genome of the closely related Western clawed frog, *Silurana tropicalis*, DM-W is not present and a different sex-determining gene appears to be in action. Again, the homomorphic sex chromosomes seen in this species do not show any sign of differentiation. Highly sensitive methods (RAD-tags and SNP analyses) failed to detect any differences on the molecular level in this species (Bewick et al. 2013), which was taken as evidence for the existence of a large pseudoautosomal region and a young age of the sex chromosomes. Recently, it was shown that in this species, even three types of sex chromosomes co-exist, which despite being indistinguishable by morphology or molecular markers act as strong genetic sex determiners either as W, Z and Y (Roco et al. 2015).

A compilation of homomorphic and heteromorphic sex chromosomes found in amphibian species was presented by

Schmid et al. (Schmid et al. 2010). Although most amphibian species possess homomorphic sex chromosomes, in some anuran and urodelan species, subtle structural changes, which indicate an initial stage of morphological differentiation of sex chromosomes, are apparent. For example, in the otherwise homomorphic sex chromosomes of the edible frog, *Rana esculenta*, the Y chromosome can be differentiated from the X by having a late replicating region (Schempp and Schmid 1981). Likewise, in some *Triturus* species (Table 4), the terminal region of the Y chromosome shows heterochromatin accumulation that is not observed on the morphologically identical X chromosome (Schmid et al. 1979). Interestingly, some of the highly differentiated Y or W chromosomes detected in few amphibian species resemble those found in birds and mammals, as they are heterochromatic and are distinctly much smaller than the X and Z. For instance, the W chromosomes in the African bullfrog, *Pyxicephalus adspersus*, and Y chromosomes in several species of salamanders (*Necturus* sp.) are small and heterochromatic (Schmid 1980; Sessions 1980). Exceptional cases of XY sex chromosomes are found in the Walker's marsupial frog, *Gastrotheca walkeri* (Schmid et al. 2002a; Schmid et al. 2010). In this hemiphractid frog, the Y chromosome contains less amounts of constitutive heterochromatin than the X chromosome.

The W chromosome in the common bell-ring frog, *Buergeria buergeri*, is found to be practically free of heterochromatin and only slightly smaller than the Z (Schmid et al. 1993). These cases provide evidence that the differentiation of amphibian sex chromosomes can proceed through very different ways and that there is not a general evolutionary rule which can be hypothesized.

As observed in many reptiles, some amphibian karyotypes show highly differentiated sex chromosomes with Y or W chromosomes, which are either slightly larger or even distinctly larger than their X or W chromosomes (Table 4). In *Triturus* species, both X and Y appear equal in length in conventionally stained karyotypes but after demonstration of the constitutive heterochromatin by the classical C-banding technique, the Y chromosomes turned out to be slightly larger. Several species from the genus *Eleutherodactylus* have W or Y chromosomes that are distinctly larger than their Z and X counterpart. Yet, it is interesting to note that the large W may be either fully or partially heterochromatic. In two closely related species, *Pristimantis euphronides* and *Pristimantis shrevei*, the W chromosome is the largest chromosome in the karyotype and is completely heterochromatic. Furthermore, in the karyotype of the South American marsupial frog, *Gastrotheca riobambae*, Y is the largest chromosome in the karyotype (11.5 % of the haploid genome) and is completely heterochromatic. A totally reverse pattern is seen in another anuran species, *Physalaemus ephippifer*, with a W larger than the Z but which is not heterochromatic. Of note, seven out of approximately 150 *Eleutherodactylus* species examined showed W chromosomes that were larger than the Z chromosomes indicating an explosive amplification of repetitive DNA sequences in the W chromosomes (Schmid et al. 2010).

Table 4 Examples of large heterogametic sex chromosomes and their heterochromatin status in amphibian lineages

Species	Order	Sex chromosomes	Y/W chromosome size	Heterochromatin accumulation	References
Triturus a. alpestris	Caudata	XX/XY	Y is slightly larger than X[a]	Distal heterochromatin on Y	(Schmid et al. 1979)
Triturus. v. vulgaris	Caudata	XX/XY	Y is slightly larger than X[a]	Distal heterochromatin on Y	(Schmid et al. 1979)
Gastrotheca riobambae	Anura	XX/XY	Y is the largest	Heterochromatic	(Schmid et al. 1983)
Eleutherodactylus casparii	Anura	ZZ/ZW	W is larger than Z	Heterochromatic	(Schmid et al. 2010)
Eleutherodactylus turquinensis	Anura	ZZ/ZW	W is larger than Z	Heterochromatic (interstitial)	(Schmid et al. 2010)
Eleutherodactylus cuneatus	Anura	ZZ/ZW	W is larger than Z	Large part is heterochromatic	(Schmid et al. 2010)
Eleutherodactylus oxyrhyncus	Anura	XX/XY	Y is larger than X	Poor	(Schmid et al. 2010)
Eleutherodactylus glamyrus	Anura	ZZ/ZW	W is larger than Z	Poor	(Schmid et al. 2010)
Eleutherodactylus albipes	Anura	ZZ/ZW	W is larger than Z	Heterochromatic	(Schmid et al. 2010)
Eleutherodactylus emiliae	Anura	ZZ/ZW	W is larger than Z	Heterochromatic	(Schmid et al. 2010)
Pristimantis euphronides	Anura	ZZ/ZW	W is the largest	Heterochromatic	(Schmid et al. 2002b)
Pristimantis shrevei	Anura	ZZ/ZW	W is the largest	Heterochromatic	(Schmid et al. 2002b)
Crinia bilingua	Anura	ZZ/ZW	W is larger than Z	Partial heterochromatic	(Mahony 1991)
Physalaemus ephippifer	Anura	ZZ/ZW	W is larger than Z	Partial heterochromatic	(Nascimento et al. 2010)
Pseudis tocantins	Anura	ZZ/ZW	W is larger than Z	Large part is heterochromatic	(Busin et al. 2008)
Leiopelma archeyi	Anura	ZZ/ZW	W is larger than Z	Long arm is free of heterochromatin	(Green 2002)
Proceratophrys boiei	Anura	ZZ/ZW	W is large and equal to Z	Most part heterochromatin	(Ananias et al. 2007)

[a] Large Y can only be interpreted from C-banded metaphases

Only 4 % of cytogenetically analysed amphibian species are reported to have structurally differentiated sex chromosomes. Remarkably, these few species exhibit a prevalence of larger Y and W chromosomes with various levels of heterochromatin accumulation. However, it should not be ignored that there are also species in which the Y and W chromosomes exhibit less amounts of constitutive heterochromatin than those present in the X and Z chromosomes.

Large Y and W chromosomes are exceedingly represented in fish lineages

Fishes exhibit the widest spectrum of sex-determining systems of all vertebrates ranging from different types of environmental sex determination to a variety of chromosomal sex-determining systems (Kobayashi et al. 2013; Volff et al. 2007).

Cytogenetic studies in the past have undoubtedly demonstrated that in the majority of gonochoristic fish species, the sex chromosomes are homomorphic and heteromorphic sex chromosomes have been encountered in roughly 10 % of species karyotyped (Devlin and Nagahama 2002). An extreme case of conserved identity between sex chromosomes is represented in the tiger pufferfish, *Fugu rubripes*, which has an XY sex determination system. Here the sex chromosomes differ by one non-synonymous substitution in the Amh-receptor II gene that is the sex-determining gene (Kamiya et al. 2012). No suppression of recombination around the male allele of this gene was found, which would have led to a structural differentiation of the X and Y. Remarkably, this situation is also found in two other species of *Takifugu*, which diverged more than 5 million years ago. Hence, over this period, suppression of recombination was not established and could not initiate the divergence of the Y chromosome from the X that is usually seen elsewhere.

In medaka, a male dominant sex determination system was described by classical genetic studies nearly 100 years ago (Aida 1921). More recent studies with molecular DNA probes revealed that, despite recombination suppression around the male-specific region on the Y (MSY), all markers were present on the X and Y with only minor sequence differences (Kondo et al. 2001). FISH probes derived from sex-linked markers identified the sex chromosome pair as the second largest in the karyotype (Matsuda et al. 2002; Nanda et al. 2002). The lack of morphological differentiation and low molecular differences were taken as evidence for a relatively young age of the medaka sex chromosomes. Indeed, it was shown that the Y chromosome of medaka is only 5 to 10 million years old (Kondo et al. 2004). Homomorphic sex chromosomes were also found in the platyfish *Xiphophorus maculatus*, where in different populations, Y, W and X chromosomes were

identified by sex-linked phenotypes (Kallman 1984) and molecular markers (Böhne et al. 2009; Zhou et al. 2010).

All salmonid species studied so far have a XX/XY sex chromosome system (Phillips 2013). As in many other fishes, the XY chromosomes in salmonids contain a small sex-specific region and a large pseudoautosomal region and only small structural differences between X and Y were reported in some trouts (Davidson et al. 2009). FISH mapping along with genetic mapping have already indicated that the sex chromosomes belong to different linkage groups (Woram et al. 2003). In rainbow trout, the male sex-determining gene sdY was identified and found to be a truncated version of a duplicate from the interferon response factor gene irf9 (Yano et al. 2012). Evidence was provided that sdy is also the Y-linked male-determining gene in other salmonids (Yano et al. 2013). Comparative analysis of the sex-determining region shared by three salmonids (rainbow trout, Chinook salmon and Atlantic salmon) revealed a minimal region to trigger masculinization. Interestingly, this region contains all elements necessary for transposition such as transposase and RNA-directed DNA polymerase (Faber-Hammond et al. 2015). Thus, sdY may have transposed between different linkage groups and thus became linked to different chromosomes that developed into a Y (Faber-Hammond et al. 2015; Lubieniecki et al. 2015).

A striking evidence for the low degree or even absence of genetic differentiation of sex chromosomes in fishes is that fully viable and fertile sex-reversed individuals can be obtained with ease. For instance, in medaka and tilapia, XX males occur spontaneously or can be obtained when embryos are incubated at higher temperatures (Baroiller et al. 2009; Sato et al. 2005; Shinomiya et al. 2010) and a plethora of studies have been published were treatment with hormones or endocrine disruptors produces all types of sex reversals, even YY females (Devlin and Nagahama 2002; Gutierrez and Teem 2006).

Several Neotropical species display various patterns of morphologically differentiated sex chromosomes, ranging from simple sex chromosome systems to multiple sex chromosomes (de Almeida Toledo and Foresti 2001). Differentiation of sex chromosomes in these species is largely achieved by heterochromatin accumulation (Cioffi et al. 2012). Karyotypes of species belonging to the genera *Characidium* (Crenuchidae) and *Triportheus* (Characidae) are fairly conserved and present identifiable sex chromosomes. In the genus *Triportheus*, several species with well-differentiated W chromosomes show variable extent of heterochromatin accumulation (Artoni et al. 2001). On the other hand, in many species of the genus *Characidium*, the Z and W chromosomes are of similar length. The dynamic transformation of sex chromosomes can be elegantly marked in different populations of the wolf fish species complex, *Hoplias malabaricus*, with seven karyomorphs showing undifferentiated or differentiated XX/XY sex chromosomes and neo-Y

sex chromosomes (Cioffi et al. 2011). A rare phenomenon with regard to sex chromosome differentiation is apparent in one population. Here, the Y chromosome appears smaller than the X, but its organization is unusual in the sense that the X chromosome has accumulated more heterochromatin than the Y chromosome. Similarly, in the glass knifefish, *Eigenmannia virescens*, which also displays an early stage of sex chromosome differentiation in some populations, heterochromatin accumulation appears to be confined to the X chromosome (de Almeida Toledo and Foresti 2001). This unusual accumulation of heterochromatin in the X chromosome is unexpected from the traditional evolutionary model of early XY/ZW differentiation in vertebrates, which predicts heterochromatization of the Y and W sex chromosome.

Strikingly, in many species with differentiated sex chromosomes, the Y or W chromosome of the heterogametic sex is larger than its X or Z counterpart (Table 5). This can range from a minor size difference that is noted only by most experienced specialists to extreme cases where the W or Y is the largest of the whole karyotype.

Some species of the genera *Parodon*, *Apareiodon* and *Saccodon* (Parodontidae) are known to have very large W chromosomes (Table 5) though the majority of species show simple ZZ/ZW sex chromosomes with smaller W chromosomes. In the canivete, *Parodon hilarii*, the W chromosome is the largest chromosome in the karyotype and highly heterochromatic (Vicente et al. 2003). In several species of *Apareiodon*, the W chromosomes are also larger than the Z chromosome (Table 5) but not completely heterochromatic and the euchromatic region of the W may be comparable to that on the Z (Bellafronte et al. 2012; Bellafronte et al. 2009), implying that the W chromosome in these species may be in an early stage of differentiation with a still large pseudoautosomal region. In the Neotropical genus *Leporinus* (Anostomidae), eight of the around 40 known species have female-specific heteromorphic sex chromosomes. In at least seven species, the W chromosome is enormously large compared to the Z owing to heterochromatin accumulation (Fig. 2a). A recent study using W chromosome-specific paints highlights the common origin of the differentiated sex chromosomes, and these W chromosome paints do not cross-react to the species with undifferentiated sex chromosomes (Parise-Maltempi et al. 2013).

In the Asian ricefish of the genus *Oryzias* all species have a well-defined genetic mode of sex determination but the sex chromosomes cannot be morphologically recognized except in one species, *Oryzias hubbsi*. This species has in contrast to the vast majority of species of *Oryzias*, which have a XX/XY system, acquired a ZZ/ZW system (Takehana et al. 2007). The W chromosome is larger than the Z due to an additional heterochromatic region at the terminal region, but most of part of the W chromosome appears to be euchromatic.

Stickleback fishes (Gasterosteidae) have provided important insights to sex chromosome evolution. This small teleost group shows remarkable sex chromosome diversity. Both three-spine and nine-spine sticklebacks have XX/XY sex chromosomes, but their Y chromosome organization is different. The Y chromosome in three-spine stickleback is smaller than the X and might have undergone pronounced degeneration, whereas in the nine-spine stickleback, the Y is larger than the X (Ross et al. 2009). On the other hand, the four-spine stickleback has a ZZ/ZW chromosome and the W chromosome is much larger than the Z (Ross et al. 2009).

The growth mechanism: what makes sex chromosomes grow?

Several investigations, in particular on fishes, provide some information on the question what makes sex chromosomes grow. A recent study investigated the distributions of transposable elements on the entire sex chromosomes compared to autosomes and in the genomic regions harbouring the sex determination loci of medaka, *Oryzias latipes*, platyfish, *X. maculatus*, guppy, *Poecilia reticulata*, tilapia, *Oreochromis niloticus*, the pufferfish, *Takifugu rubripes*, the Chinese tongue sole, *Cynoglossus semilaevis*, and three-spine stickleback, *Gasterosteus aculeatus* (Chalopin et al. 2015). In these fishes, where whole-genome sequence information is available, it is evident that transposons accumulate not only on Y or W sex determination segments but also on the corresponding regions of the X or Z. Furthermore, recent activity of some classes of transposable elements seems to be specific to these regions. This may indicate that the process of transposon accumulation on these young sex chromosomes is still ongoing. The focus on two closely related strains of medaka showed that the chromosomal region was relatively poor in transposons prior to the emergence of the new sex-determining gene. This gives support to the reasoning that young sex-determining regions sustained recent accumulations and amplifications of mobile elements. For instance, the less than 10-million-year-old Y of the three-spine stickleback has in the 3-Mb large region that contains the sex-determining gene 4.2 % of this region constituted by transposable elements, while this value is only 1 % on the corresponding region of the X (Peichel et al. 2004). The expansion of this compartment is mainly due to a massive increase in LINEs.

There are two species of fish, where extensive sequence information from heterogametic sex chromosomes is now available, namely from the medaka Y and Chinese tongue sole W. In medaka, the male sex-determining gene arose from duplication of an autosomal fragment that contains the *dmrt1* gene (Nanda et al. 2002). This fragment was inserted into another chromosome, which became the proto-Y (Fig. 1b). There, the new copy of *dmrt1*, named *dmrt1bY* (or *DMY*),

Table 5 Large Y (or W) chromosomes in heterogametic fish species

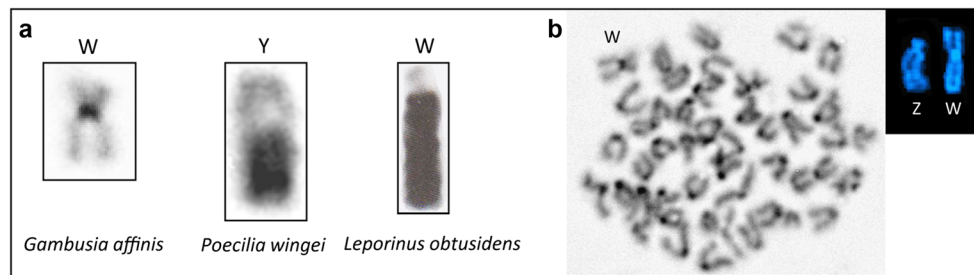| Species	Order	Sex chromosomes	Y/W chromosome size	Heterochromatin accumulation	References
Leporinus elongatus[a]	Characiformes	ZZ/ZW	W is the largest	Nearly heterochromatic	(Koehler et al. 1997)
Leporinus obtusidens	Characiformes	ZZ/ZW	W is the largest	Nearly heterochromatic	(Koehler et al. 1997)
Parodon hilarii	Characiformes	ZZ/ZW	W is the largest	Large part heterochromatic	(Vicente et al. 2003)
Semaprochilodus taeniurus	Characiformes	ZZ/ZW	W is larger than Z	Partial heterochromatic	(Terencio et al. 2013)
Apareiodon hasemani	Characiformes	ZZ/ZW	W is larger than Z	Partial heterochromatic	(Bellafronte et al. 2012)
Apareiodon ibitiensis	Characiformes	ZZ/ZW	W is larger than Z	Partial heterochromatic	(Bellafronte et al. 2009)
Apareiodon sp.	Characiformes	ZZ/ZW	W is larger than Z	Large part heterochromatic	(da Rosa et al. 2006)
Thoracocharax stellatus	Characiformes	ZZ/ZW	W is nearly equal to Z	Heterochromatic	(Venere et al. 2008)
Characidium lanei	Characiformes	ZZ/ZW	W is slightly larger than Z	Heterochromatic	(Noleto et al. 2009)
Parodon sp.	Characiformes	ZZ/ZW	W is larger than Z	Partial heterochromatic on p-arm	(Centofante et al. 2002)
Hoplias malabaricus	Characiformes	XX/XY [b]	Y equal to X	Only centromeric heterochromatin	(Cioffi and Bertollo 2010)
Gambusia affinis	Cyprinodontiformes	ZZ/ZW	W is the largest	Poor	present study, Fig. 2
Mastacembelus aculeatus	Perciformes	XX/XY	Y is larger than X	Large part heterochromatic	(Liu et al. 2002)
Dormitator maculatus	Perciformes	XX/XY	Y is equal to X	Partial heterochromatic on p-arm	(Oliveira and Toledo 2006)
Cynoglossus semilaevis	Pleuronectiformes	ZZ/ZW	W is the largest	Repetitive DNA sequences	(Chen et al. 2014)
Microlepidogaster leucofrenatus	Siluriformes	ZZ/ZW	W is larger than Z	Partial heterochromatic	(Andreata et al. 1992)
Ancistrus ranunculus	Siluriformes	ZZ/ZW	W is larger than Z	Large part heterochromatic	(Oliveira et al. 2007)
Ancistrus taunayi	Siluriformes	ZZ/ZW	W is larger than Z	Interstitial heterochromatic regions	(Konerat et al. 2015)
Steindachneridion sp.	Siluriformes	XX/XY	Y is the largest	Poor	(Swarca et al. 2006)
Pseudotocinclus tietensis	Siluriformes	XX/XY	Y is larger than X	Partial heterochromatic	(Andreata et al. 1992)
Apeltes quadracus	Gasterosteiformes	ZZ/ZW	W is the largest	NA	(Ross et al. 2009)
Pungitius pungitius	Gasterosteiformes	XX/XY	Y is the largest	NA	(Ross et al. 2009)
Oryzias hubbsi	Beloniformes	ZZ/ZW	W is larger than Z	Partial heterochromatic	(Takehana et al. 2007)
Poecilia wingei	Cyprinodontiformes	XX/XY	Y is larger than X	Partial heterochromatic	(Nanda et al. 2014)
Pterolebias hoignei	Cyprinodontiformes	XX/XY	Y is the largest chromosome	NA	(Elder et al. 1991)

NA not available

[a] Several more species are known to have large heterochromatic W chromosome in the genus *Leporinus*

[b] Population specific

evolved to become the master regulator of male development. As predicted from the evolutionary hypothesis on sex chromosome evolution, all co-duplicated genes degenerated. Concomitantly, other duplicated gene fragments from other regions of the genomes became inserted in the male-specific region on the Y (MSY) (Kondo et al. 2006). Comparison of the MSY to the autosomal region from which it was derived also uncovered a profound expansion in the copy number of repetitive DNA, most importantly of four distinct satellite sequences and various transposable elements. This resulted in the growth of the medaka MSY over its 5 to 10 million years of existence from 45 to 250 kb. The fivefold increase in size makes the Y in principle larger than the X, but it is still too small to become apparent as a visible difference in chromosome morphology. Suppression of recombination around the MSY can be detected over a region of 3.5 Mb (Takeda 2008; Wilson et al. 2014), but this resulted only in sparse and minor sequence differences between X and Y alleles and did still not contribute to a visible change in chromosome morphology.

In the Chinese half-smooth tongue sole, a draft sequence of the W has been produced (Chen et al. 2014). Different from the medaka Y where the MSY is tiny and the pseudoautosomal region spans most of the chromosome, the tongue sole W has only 22 protein-coding genes in an approximately 650-kb region where cross-over occurs at a similar rate as on autosomes. The rest of the chromosome shows

Fig. 2 Unusually large sex chromosomes of fishes. **a** Divergent organization of large heterogametic Y and W sex chromosomes in three different fish species. **b** C-banded metaphase and DAPI staining of the exceptionally large W chromosome of the Western mosquitofish. Note that except the centromeric region, the large W chromosome is not heterochromatic

strongly reduced up to absent recombination and has the expected features of a degenerating sex chromosome. Only about one third of the original 1000 protein-coding genes are still present and appear to be intact. A 10 times higher content of pseudogenes and transposable elements than on the Z and autosomes makes the W considerably larger than its homogametic counterpart and even the largest chromosome of the whole complement. The age of the W was determined to be around 30 million years. Although two thirds of the genes were already lost over this period, this decrease in DNA content has obviously been overcompensated by accumulation of repetitive DNA and transposable elements.

From several fish species, molecular cytogenetic findings confirm such an accumulation process of repetitive sequences. In the platyfish (*X. maculatus*), the region around the sex-determining locus has been shown to be enriched for transposons (Chalopin et al. 2015; Volff et al. 2003). In particular, a local expansion of the XIR LTR-like transposon in the subtelomeric region of the Y occurred, which can be documented by FISH analysis (Nanda et al. 2000). Such a structure is not seen on the X. But again like in medaka, the transposon expansion on the Y is too small to result in heteromorphy of sex chromosomes in this species.

Guppies have an XY sex determination mechanism and show a very pronounced Y chromosome polymorphism, which manifests in different-sized Ys, ranging from the same size as the X to being the largest chromosome of the complement. This size polymorphism is explained by expansion of a block of constitutive heterochromatin specifically on the Y (Nanda et al. 2014). In one particular species, the Endler guppy, *Poecilia wingei*, the Y chromosome is enormously large arising from the heterochromatin accumulation at the distal end of the chromosome (Fig. 2a). It must be emphasized that in most cases, heterochromatin accumulation is viewed as a mechanism explaining Y chromosome degeneration, but in *P. wingei*, the heterochromatin accumulation hardly affected the large pseudoautosomal region. The Y chromosomes of different guppy strains show accumulation of different microsatellite repeats (Nanda et al. 1990; Nanda et al. 2014) which was taken as an indication that the size polymorphism of the

heterochromatin block may be due to the expansion of different repetitive sequences.

In the redfin prochilodus, *Semiprochilodus taeniatus*, the W is the largest chromosome. It presents with broad areas of constitutive heterochromatin at the two terminal regions but also at pericentromeric and interstitial locations. FISH with probes for the Rex 1 transposon indicated that invasion and local expansion of this element were responsible for accumulation of heterochromatin of the W (Terencio et al. 2012). Furthermore, in the large heterochromatic W chromosomes of several *Leporinus* species, accumulation of Rex transposable elements is detected (Splendore de Borba et al. 2013).

In the mosquitofish, *Gambusia affinis,* the W chromosome is the largest chromosome of the complement. In contrast to the large W of *Leporinus* or the large Y chromosome of *P. wingei*, surprisingly it does not stain in conventional C-banding for additional heterochromatin except for the centromeric region. Also DAPI staining did not reveal specific features for the W, which may indicate that this unique large W chromosome has not undergone degeneration (Fig. 2). This does not contradict the reasoning that the large size of fish sex chromosomes is connected to TEs because in fishes, many transposons are transcribed and still active (Huang et al. 2012) and thus would not be necessarily heterochromatic.

Discussion

The Y and W chromosomes of vertebrates come with an astonishing structural plasticity ranging from tiny, dot-like and cytogenetically almost invisible ones to complete homomorphy with the X or Z, and to cases where they are gigantic and the largest chromosome of the whole complement. This variety reflects the evolutionary trajectory of sex chromosome development. From the common theories that predict that once a sex-determining gene has established itself on a proto-sex chromosome recombination is suppressed around this gene, a one-way street process of degeneration, diminution, gene loss and heterochromatization has to be expected. Those Ys and Ws that are heterochromatic and smaller

than the X or Z down to the dot-like-sized ones certainly fit and are generally regarded to be of old age and to represent the endpoint of the degeneration process. This is supported by many examples from mammals and birds.

The homomorphy of many sex chromosomes is in most cases easily explained, when they are of proven young age, because then the process of decay did not go on long enough to leave its traces on the morphology and in many cases also not to a considerable extent on the level of genomic structures. Recent molecular analysis in fishes, e.g. medaka and fugu, confirm this.

An alternative hypothesis has been proposed based on studies on the homomorphic sex chromosomes of hylid frogs, where occasional cross-over between the sex chromosomes in sex-reversed individuals would lead to homogenization of both chromosomes and explain results obtained with sex chromosome specific molecular markers (Perrin 2009).

When homomorphic sex chromosomes appear in one lineage but highly degenerated ones in a parallel lineage where both are derived from a common ancestor, a reasonable explanation is a different and lineage-specific speed of the degeneration process. Such a situation is for instance found in the palaeognathous and neognathous birds.

The unexpected ones are, however, the Y and W chromosomes, which are larger than their homogametic counterparts and those which are euchromatic. To explain their existence, we propose first to categorize them as the result of secondary or primary sex chromosome growth.

A clear case of secondary growth is found in the laboratory mouse. Here it is evident from the sequencing of the whole Y that those sequences which make it larger have been added more recently to a shared common small piece with the other mammalian Ys (Soh et al. 2014). Typically, such examples of secondary growth would locate at derived positions in a phylogenetic tree, where most, and in particular the more basal species, would show the more widespread small Y type. Secondary growth would be a phenomenon to occur in groups with old sex chromosomes, but it rarely concedes the Y chromosome to exceed the size of X chromosome.

As primary growth we regard those instances, where young Ys and Ws are larger than their X or Z counterpart. We hypothesize that in the initial phase of sex chromosome evolution, the repression of recombination will favour accumulation of transposons and expansion or repetitive sequences. This is a rapid and effective mechanism to make the emerging Ys and Ws different from the other chromosomes and thus even further prevents crossovers. This process that is well documented in several young fish sex chromosomes (e.g. in medaka) will then lead to a stage where the addition of material becomes visible as a larger chromosome in the karyotype. Only in a further phase of their evolution the degeneration process and gene loss initiates the shrinking of the chromosome to the well-known small size of the mammalian and avian sex chromosomes. It should be noted that the proposed dynamics of sex chromosome morphology makes them pass a second time through a stage where both are of the same size and thus appear homomorphic.

Three different organization profiles of these large Y and W organization can be delineated Firstly, both the large Ys and Ws are nearly heterochromatic (e.g. *Leporinus*) that may emphasize the enormous amplification of repetitive sequences. Expansion of microsatellite arrays is known to occur in young Y chromosomes of plants (Kejnovský et al. 2013). However, this pattern of organization does not bear much importance, as it does not affect the recombination suppression. Secondly, both the large Ys and Ws are partially heterochromatic (e.g. guppy, *O. hubbsi*) that may signify the early stage of sex chromosome differentiation, as well as recombination within the large pseudoautosomal region. Interestingly, both highly differentiated Y and W chromosomes in old sex chromosome systems, as encountered in mammals and birds, show extreme contraction of their length, and they even loose most of the heterochromatin. This means that different levels of degeneration can affect both young and old sex chromosome. In the Chinese tongue sole, gene loss has occurred to a relatively high level in the early phase of W evolution (Chen et al. 2014), and also in plants, genetic degeneration has been documented to occur soon after suppression of recombination between the Y and X (Hough et al. 2014). Lastly, a more impressive organization is that the Y or W chromosomes are larger than their counterparts (X or Z), but they are nearly euchromatic (e.g. in *G. affinis*) elucidating a possible regular recombination between the sex chromosomes, unless interrupted through accumulating non-synonymous SNPs. One potential complication in this pattern of organization concerns the underlying basis of Y or W chromosome expansion without heterochromatin accumulation. It is suggested that occasionally the X or Z chromosome may undergo some level of degeneration without involving heterochromatin. Alternatively, taking the example of the large euchromatic Y in mouse (Soh et al. 2014), one may envisage expansion of amplicons in the heterochromatin free large Y or W chromosomes.

The emerging information from sequencing of still a very limited number of vertebrate sex chromosomes and the wealth of information from decades of cytogenetic investigations employing the classical staining and molecular methods of FISH and chromosome paintings have opened novel and exiting views on the amazing variety of sex chromosome structures and the dynamics of their evolution. Due to their often highly repetitive structure and genetic degeneration, sequencing of sex chromosomes still presents a major challenge and often an insurmountable problem. Nevertheless, we can hope to see in the near future sex chromosomal sequence information not only from the handful of model organisms but also from vertebrates that stand out by an unusual sex chromosome and/or genetic sex determination system.

Compliance with ethical standards

Ethics and animal welfare statement The manuscript or parts of it have not been submitted elsewhere. No data or images have been manipulated to support our conclusions. All presented data are our own; work of other authors is cited with correct references. All authors have given their consent to submit the final version. All co-authors have contributed sufficiently to the manuscript and therefore share collective responsibility and accountability for the results.

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no competing interests.

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