Sex Determination

L Ross, University of Edinburgh, Edinburgh, UK
H Blackmon, University of Minnesota, Saint Paul, MN, USA

Glossary

Anisogamy   Form of sexual reproduction where the gametes differ in size or structure. The most familiar type of anisogamy is oogamy where females produce a large non-motile egg and males produce small motile sperm.

Dosage-dependent sex determination   Sex determination system where the transcription level of certain genes determines whether an individual develops as female or male.

Gonochoristic   Having only one of the two possible sexes in any individual organism. In contrast to hermaphroditic where any single individual can function as both male and female.

Hermaphrodites   Individuals capable of producing both oocytes and spermatocytes, either as (1) 'simultaneous hermaphrodites' producing both types of gametes at the same time, or as (2) 'sequential hermaphrodites' which can only produce one type of gamete at a given time, but switch sex at some point during their lifetime.

Heterogametic   Individual that produces gametes with different sex chromosome complements.

Master switch   Gene that acts as the initial trigger of female or male development. Sometimes also referred to as feminizers (causing female development) or masculinizers (causing male development).

Mating types   A mechanism that determines the compatibility of individuals in a population to reproduce with one another. Mating types are common in fungi, and the number of different mating types in a population may range from two to many hundreds.

Sex chromosome (X and Y, Z and W)   In heterogametic sex determination system, the pair of chromosomes that are responsible for sex determination. In male heterogametic species the male will have an XY complement and females an XX complement. In female heterogametic species the male will have a ZZ complement and females a ZW complement.

Sex determination cascade   A process where the transcription of a specific allele or the transcription level of a gene regulates a series of genes downstream culminating in the genes that are responsible for the development of an individual as either female or male.

The prevailing view of reproduction is that of a female and male mating to produce offspring. This is indeed the case in most animals, some plants and even some unicellular organisms. But does reproduction always work this way? How did the sexes originate? And how is an individual's sex determined? These simple but fundamental questions are key to our understanding of evolution across the tree of life.

A Brief History of the Sexes

Sexual reproduction is an ancient feature of eukaryote life, yet the sexes as we currently recognize them are relative latecomers in the evolution of sex (Beukeboom and Perrin, 2014). The ability to reproduce through sex (fusion of haploid gametes) evolved in the common ancestor of all eukaryotes, but did not involve separate sexes; each individual was able to exchange genetic material with any other of the same species, as is still the case in many modern-day unicellular eukaryotes (Lahr et al., 2011). However, throughout the course of evolution this changed in certain organisms: some, for example many fungi, evolved tens or even hundreds of 'mating types,' where certain genotypes become incompatible with others (Perrin, 2012). In others 'anisogamy' evolved: here individuals produce not one but two different types of gametes, a large type – 'oocytes' in low frequency and a more prevalent smaller type – 'spermatocytes.' Anisogamy is thought to evolve because an individual with limited resources has two options to maximize
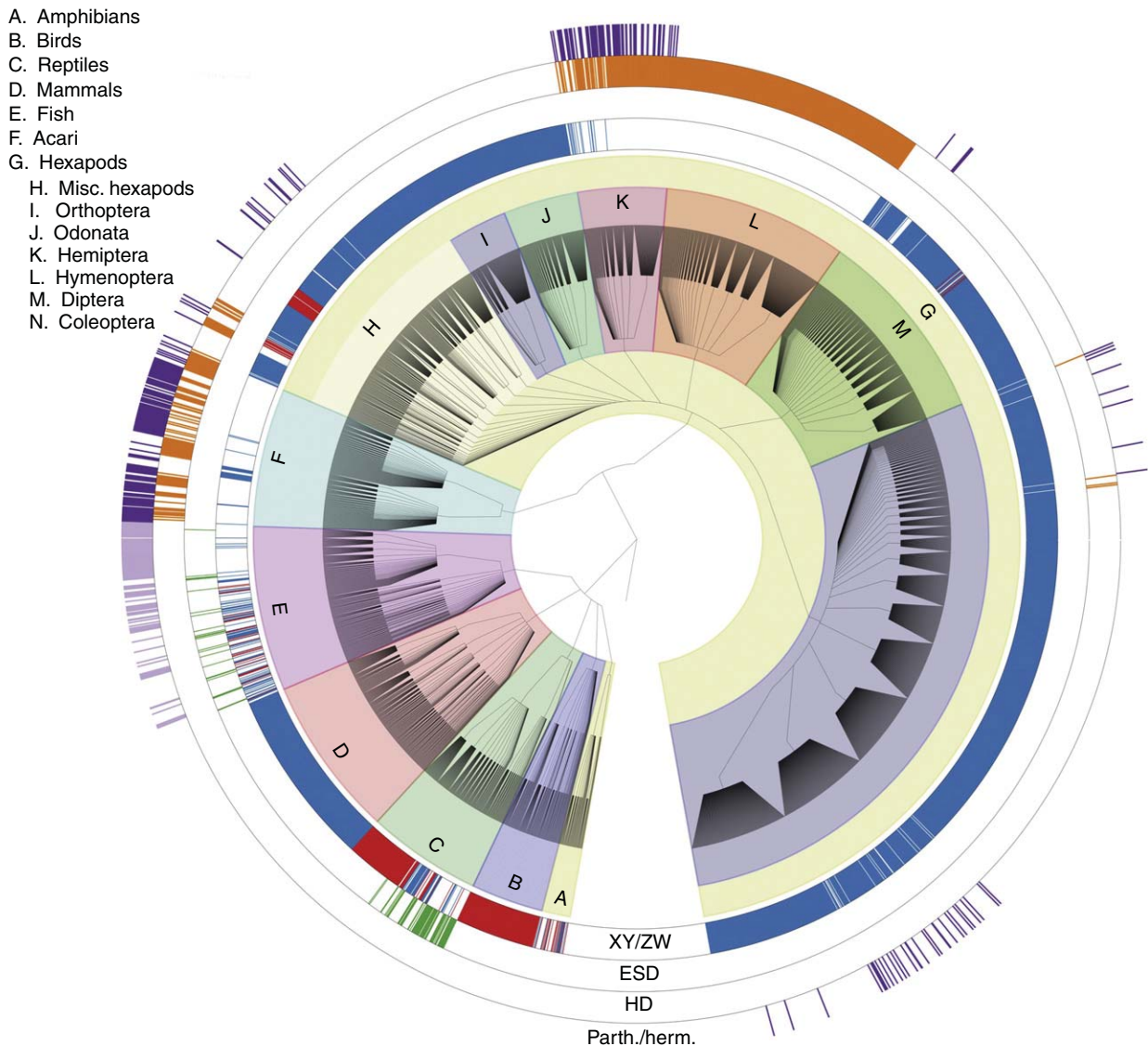
their reproductive success: either by maximizing the number of gametes they produce, or by maximizing the survival probability of each of their gametes (Parker et al., 1972). In many cases an individual can produce both these types simultaneously and either self-fertilize or mate with others to exchange gametes ('hermaphroditism'), yet some – for example, most animals and some plants – specialized on producing one or the other, giving rise to the sexes as we currently recognize them (Jarne and Auld, 2006; Bawa, 1980).

How Sex Is Determined?

But how is an individual's sex determined? The answer to this question is far more complex than you might think. Sex-determining mechanisms are surprisingly diverse and evolutionary biologists have only just started to understand what causes this variation (Beukeboom and Perrin, 2014). Here we will start by describing some of this variation and how it is distributed across different organisms. We only focus on sex determination in species with true separate sexes, not those with mating types, and primarily focus on sex determination in multicellular organisms.

Genetic Sex Determination

Perhaps the most familiar sex determination systems are those that employ 'heterogametic' sex determination where a species

A. Amphibians
B. Birds
C. Reptiles
D. Mammals
E. Fish
F. Acari
G. Hexapods
 H. Misc. hexapods
 I. Orthoptera
 J. Odonata
 K. Hemiptera
 L. Hymenoptera
 M. Diptera
 N. Coleoptera

XY/ZW
ESD
HD
Parth./herm.

Figure 1 The phylogenetic distribution of sex-determining systems across animals. The tree structure is based on taxonomy and each tip represents all species in genus. The underlying data consist of 13 700 records representing 3886 genera from the tree of sex database. The XY/ZW ring is colored blue for XY and red for ZW taxa. The environmental sex determination (ESD) and haplodiploidy (HD) rings indicate the presence or absence of environmental and haplodiploid sex determination systems, respectively. The Parth./Herm. ring is colored dark purple for parthenogenic taxa and light purple for hermaphroditic taxa. Data reproduced from the Tree of Sex Consortium, 2014. Tree of Sex: A database of sexual systems. *Scientific Data*, 1.

has two alternative versions of a sex-determining region. Whether an individual is homozygous or heterozygous for this region will determine if it develops as a female or male. The sex-determining region can be a single gene, a portion of a chromosome, or even an entire chromosome; regardless, the chromosome that carries the sex-determining region is called the 'sex chromosome.' Heterogametic sex determination systems can be divided by whether the female or male is heterogametic.

In many species, including humans, the male is heterogametic and carries an X and Y sex chromosome while females are homogametic and carry two copies of the X chromosome. XY sex determination is the most common form of

heterogametic sex determination and is found in amphibians, non-avian reptiles, mammals, and many invertebrates (Figure 1). In other groups it is the female that is heterogametic and the female possesses a Z and W chromosome while males carry two copies of the Z chromosome. ZW sex determination is found in birds, some amphibians and non-avian reptiles, and several groups of invertebrates most notably the butterflies (Figure 1). In both of these systems, the sex chromosome found in only one sex (Y or W) often degenerates and contains few genes in comparison to the X or Z chromosome. The taxonomically widespread observation of XO and ZO sex determination systems indicates that these sex-limited chromosome can be completely lost creating systems where the

heterogametic sex has one copy of the sex chromosome and the homogametic sex has two copies (The Tree of Sex Consortium, 2014). Finally, in some bryophytes and algae only the gametophytes (haploid life stage) have separate sexes and sex is determined by which version of the sex chromosome they carry. The gametophyte develops as a female if it carries a U sex chromosome and develops as a male if it carries a V sex chromosome. While sporophytes (diploid life stage) carry both sex chromosomes and do not have separate sexes (Bull, 1983).

In some fish, plants, and copepods there are multiple genes that can act as the 'master switch' for sex determination. In these polygenic sex determination systems there are more than two distinct versions of the sex chromosomes. For instance in the platyfish *Xiphophorus maculatus* which was ancestrally XY there are three types of sex chromosomes X, X*, and Y, where X* is a version of the X chromosome that carries a dominant feminizing mutation. This creates a system where there are multiple types of females, including the normal XX females, but also X*X and X*X* and even X*Y females, with the dominant female determining mutation (Volff and Schartl, 2001).

Generally the genotype of the offspring determines their sex. Yet a few species exhibit monogenic sex determination where the mother's genotype determines whether she will produce broods of all female or male offspring. One such example is the sciarid fly *Sciara coprophila*, where the sex of offspring produced by a female depends on the presence or absence of an inversion (X') on one of her X chromosomes (Sánchez, 2010).

Environmental Sex Determination

In many unicellular and some multicellular species, males and females have identical genomes and their sex is determined by environmental factors. Environmental sex determination (ESD) is common among unicellular eukaryotes (Beukeboom and Perrin, 2014). Among multicellular organism ESD is found primarily among non-avian reptiles, amphibians, and some fish (Bachtrog *et al.*, 2014). Temperature appears to be the most common determinant of sex under ESD. However, there are other factors too, like social environment. Many fish are sequential hermaphrodites, where they start their life as one sex, but change sex later in development. In the anemone fish (*Amphiprion akallopisos*), which live in social groups with one dominant breeding pair as well a several subordinate males, sex change occurs when the dominant female dies and the largest male in the group becomes the dominant female (Fricke and Fricke, 1977). ESD systems are more often evolutionary labile than genetic sex determination (GSD): closely related species differ in their sex-determining mechanism and shifts can include changes in the threshold temperature or transitions between ESD and GSD. In some cases there is even variation within species: the lizard *Bassiana duperreyi* determines sex through GSD (XX-XY) but at low temperatures some of the XX females develop as males (Shine *et al.*, 2002).

Other Sex Determining Mechanisms

Among invertebrates the most common alternative sex determining mechanism is haplodiploidy (HD; Normark, 2003;

Bull, 1983). Here, males develop from unfertilized eggs and have only a single copy of each gene ('haploid'), while females develop from fertilized eggs and have two copies of each gene ('diploid'). In haplodiploid organisms sex determination is therefore dependent on the fertilization of eggs, which is often thought to be under the control of mothers (Beukeboom and Perrin, 2014). HD has evolved repeatedly across insects, mites, nematodes, and rotifers and has been estimated to occur in around 12% of all animals (Normark, 2003; Jarne and Auld, 2006; The Tree of Sex Consortium, 2014). Another alternative reproductive system that shows similarity with HD is Paternal Genome Elimination (PGE) (Bull, 1983; Burt and Trivers, 2009). Here, both sexes develop from fertilized eggs, yet in males all genes inherited from the father are lost at some point during development. PGE occurs in thousands of species across insects, springtails, and mites. The loss of paternal genes occurs either early in development such that these males are haploid throughout development, or later such that males retain their father's genes in all cells but their sperm (Normark, 2003; Gardner and Ross, 2014). As both sexes develop from fertilized eggs, fertilization cannot serve as the trigger for sex determination, and it is currently unclear what sex-determining factor does. Both HD and PGE tend to occur in closely related species and are only found in terrestrial invertebrates. They are conspicuously absent from tetrapods, plants, and marine invertebrates (Normark, 2003; Normark and Ross, 2014).

Finally there are cytoplasmic sex determination systems where either an intracellular bacterial parasite (e.g., *Wolbachia*) or the genotype of the mitochondria determines the sex of offspring (Beukeboom and Perrin, 2014). Such cytoplasmic elements are only transmitted to the next generation by females and as such have an interest in manipulating the sex determination of their host.

Evolution of Different Sex Determining Systems

The variability of sex-determining mechanisms among eukaryotes is startling. But what evolutionary forces are responsible for transitions between different sex determination systems? Moreover, why are certain groups of plants and animals exceptionally variable in the way they determine sex?

Some of the difference in sex determination can simply be explained by the fact that they evolved independently. For example, separate sexes evolved independently in plants and in animals, so any similarities in sex-determining mechanisms – for example, differentiated sex chromosomes – are examples of convergent evolution (Beukeboom and Perrin, 2014). However, not all diversity is the result of the independent evolution of separate sexes: for example, insects – one of the most diverse group of animals in terms of their sex determination – ancestrally have separate sexes (Normark, 2003). So which evolutionary forces cause this variation? And what sex-determining systems are favored under different conditions?

Sex Ratio Selection

The first important selective force is sex ratio selection, in other words, what is the optimal offspring sex ratio an individual

can produce? In most sexually reproducing organisms the answer is an equal proportion of sons and daughters. The reason for this is that if one sex is more common than the other, the rarer sex has a higher fitness and will increase in frequency until equality arises (Fisher, 1930). Selection for balanced sex ratios is probably a primary explanation for why GSD is so prevalent across life – it is the only SD mechanism that guarantees an equal proportion of males and females (Beukeboom and Perrin, 2014). If this is the case, how can alternative SD systems evolve? One reason is that the sex ratio of an individual's offspring is selectively neutral as long as the population sex ratio is unbiased. So, mutations that alter offspring sex or local fluctuations in temperature under ESD are not selected against until they become so prevalent that they change population sex ratios. In fact ESD can be favorable if the environmental cue that determines sex differentially affects the fitness of males and females. Under that scenario selection favors sex-determining mechanisms that match each sex to its best environment (Bull, 1983). Finally there are conditions under which balanced sex ratios are selected against: for example, when related males compete for matings with their sisters a female-biased sex ratio is preferred (Hamilton, 1967). This would select for SD systems that allow mothers to bias their sex ratio. Several authors have suggested that HD and PGE might have evolved because of such sex ratio selection (Bull, 1983; Beukeboom and Perrin, 2014; Burt and Trivers, 2009; Gardner and Ross, 2014).

Sexual Conflict

The two sexes are defined by their difference in gamete size, however sexual dimorphism generally extends to other traits including differences in morphology and behavior. Sexual conflict occurs when the sexes have different fitness optima for such traits. One form of sexual conflict that is thought to be especially important in the evolution of sex determination systems is sexual antagonistic selection, which occurs anytime that a gene has multiple alleles that have different fitness in males and females. The presence of sexual antagonistic selection increases the probability of a transitions in the sex-determining gene, sex determination method, or sex chromosome pair (Van Doorn and Kirkpatrick, 2007). For instance, in an XY system, if a masculinizing mutation occurs near an autosomal allele that is associated with higher fitness in males, then this may give rise to a new Y chromosome that may fix in the population.

Endosymbiotic Bacteria

A large number invertebrates harbor bacteria that live inside their cells (Buchner, 1965). In some cases these bacteria are mutualists and essential for the survival of their host, often thought they are parasites that evolved ways to increase their frequency without providing any benefits. Many (in particular those in the genera Wolbachia and Cardinium) do so by manipulating their hosts into producing more female offspring. This benefits the bacteria because only females, not males transmit them to their offspring. By far the best example comes from the woodlice Armadillidium vulgare. In those

individuals that are uninfected sex is determined genetically by a ZZ/ZW system, but infection with Wolbachia lead to the feminization of ZZ males into functional females, or one of two types of intersexes: (1) individuals with female physiology but some external characteristics of males, or (2) individuals that are physiologically male but are sterile (Juchault et al., 1992).

Evolution of Sex Chromosomes

The canonical view of sex chromosome evolution begins with autosomes that gain a sex-determining gene (Westergaard, 1958). Upon the evolution of a sex-determining gene, the Y chromosome is expected to begin a process of degeneration because of its reduced population size (between one male and one female, there is only one copy of a Y chromosome and 3 copies of X chromosomes) and reduced recombination that sometimes evolves between the X and Y chromosomes; both factors reduce the effective population size of the Y chromosome and reduces efficacy of selection, which, in turn, can lead to its degeneration. Selection to reduce recombination may be a byproduct of sexual antagonism (SA), where different SA alleles provide higher fitness in males and females; for example, reduced recombination between the sex-determining region and a SA locus can lead to associations between a male-benefit (female-detriment) allele and the Y chromosome, and thereby restrict the allele's benefits to males and not expose females to its costs. Cessation of recombination often occurs through inversions that isolate increasingly large stretches of the Y chromosome (Charlesworth et al., 2005). In chromosomal regions where recombination is suppressed genes are quickly lost until only a core set of genes essential to the male fertility and viability remain (Bachtrog, 2008) (Figure 2). Suppression of recombination between the X and Y chromosome of humans occurred in 5 steps over 200–300 million years (Hughes et al., 2012). This process only affects the sex-limited chromosome; the X is still able to recombine in a normal fashion in females; this process of degeneration is expected to be largely the same in ZW systems, applying to the W chromosome. Sex chromosomes that have gone through this process are described as heteromorphic and the sex-limited chromosome as degenerate. However, not all organisms follow this pattern; for instance the emu as well as some amphibians and fish appear to maintain homomorphic sex chromosomes for long periods. It is likely that different explanations for the retention of homomorphic sex chromosomes apply to these groups. In the case of the emu sex specific gene regulation may allow the resolution of SA (but see Charlesworth et al. (2014) for an alternative explanation). In contrast very low levels of intermittent recombination may be responsible for the lack of degeneration seen in amphibians (Perrin, 2009; Vicoso et al., 2013).

While heteromorphic sex chromosomes are usually quite stable, homomorphic sex chromosome often exhibit rapid changes in which chromosomal pair determine sex, and even between XY and ZW systems. The simplest type of turnover involves the translocation of the sex-determining gene onto an autosome creating a new sex chromosome pair. However, masculinizing or feminizing mutations of genes on autosome can create new sex chromosomes or cause transitions between
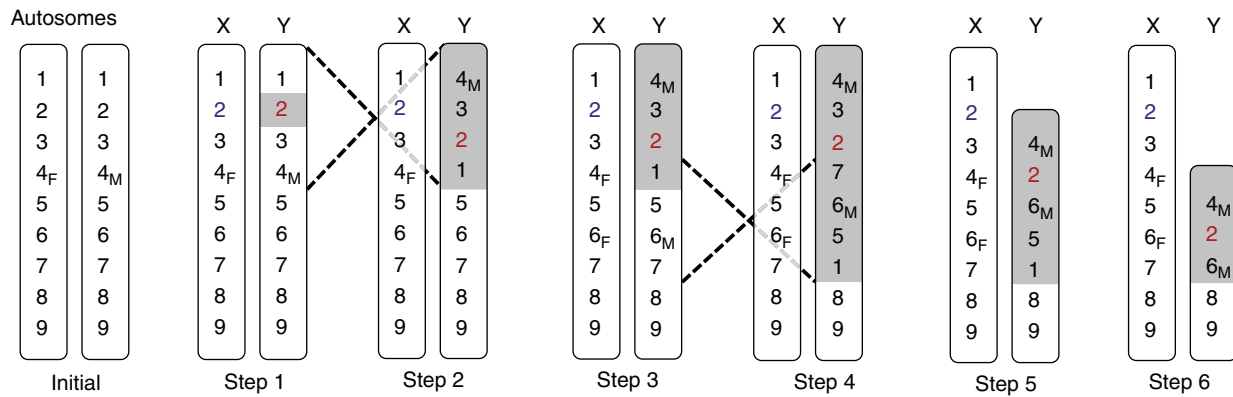
Initial: No sex chromosomes are present; sex is determined by environmental conditions.

Step 1: A masculinizing mutation occurs at gene 2 creating an XY sex determination system.

Step 2: Sexual antagonistic selection favors an inversion of genes 1 to 4 on the Y chromosome. This keeps the allele of gene 4 that is best for males with the male sex determining region, and expands the portion of the Y chromosome that cannot recombine.

Step 3: A new mutation at gene 6 creates sexual antagonistic selection at this gene.

Step 4: Sexual antagonistic selection favors an inversion of genes 1, 5, 6, and 7 on the Y chromosome further reducing the amount of the Y chromosome that can recombine.

Step 5-6: The region of the Y chromosome that cannot recombine begins to lose genes that are not essential to male fitness.

Figure 2 The process of sex chromosome differentiation. The progression from undifferentiated autosomes to heteromorphic sex chromosomes. The sex-determining locus is gene 2. The female allele is in blue and the male allele is in red. Alleles that have different fitness in males and females are indicated with a subscript where M indicates an allele with high fitness in males and F high fitness in females. The gray shading indicates the region that is non-recombining.

XY and ZW systems. Masculinizing mutations can change the 'master switch' in XY systems or transitions from ZW to XY. Likewise, feminizing mutations can change the master switch in ZW systems or transitions from XY to ZW. Whether these translocation, feminizing mutations, or masculinizing mutations fix in a population is likely determined by presence of SA (Van Doorn and Kirkpatrick, 2007). For instance if a feminizing mutation occurs near a gene with an allele that is associated with higher fitness in females (but lower in males) then the new sex-determining region is more likely to fix in the population.

Sex Ratio Distorters

GSD typically leads to equal sex ratios as a result of meiosis, where each copy of a gene (e.g., the sex-determining locus on a mammalian Y chromosome) has a 50% of being present in a particular gamete. This is not always the case though: we now know of genes that can 'cheat' the fair raffle of meiosis to ensure they are included in the gametes at a higher rate. These 'meiotic drive alleles' can thus rapidly spread through populations and if they are located on autosomes, they have little effect. However if located on a sex chromosome they can have profound effects, often threatening to wipe out populations through the demise of one of the sexes. Such 'sex ratio distorters' can therefore select for the evolution of new sex-determining loci that can override the ancestral locus linked to the driver, thereby restoring an equal sex ratio. The occurrence of autosomal feminizers and masculiners able to override the normal XY sex determination in house flies (*Musca domestica*) have been hypothesized to result through this mechanism, though there is as yet no direct evidence of driving sex chromosomes resulting in novel SD loci.

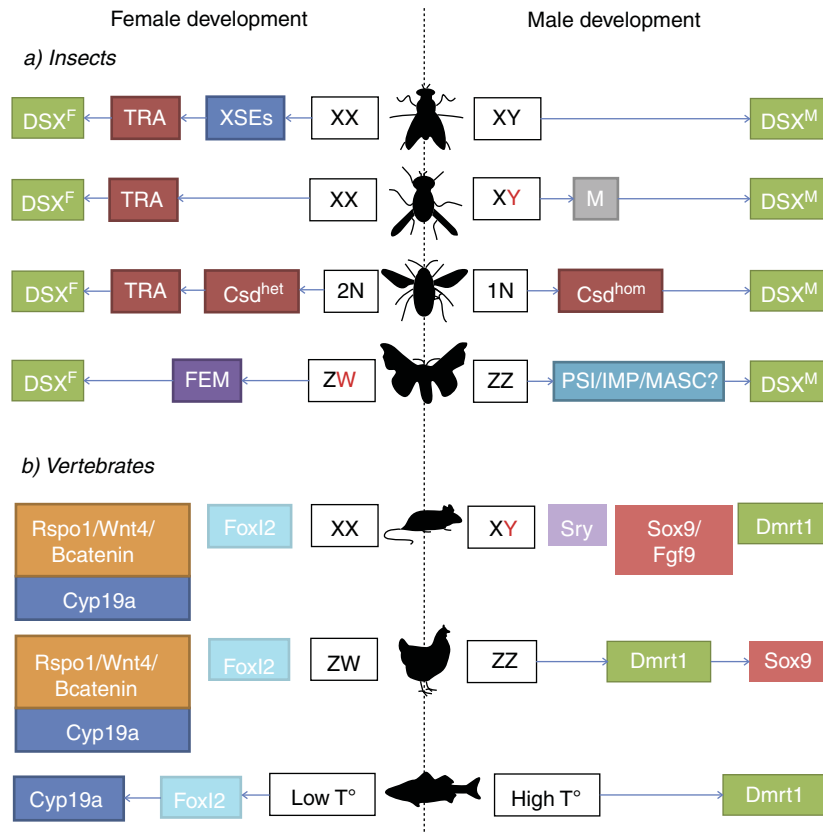## Molecular Mechanism of Sex Determination

Over the last few decades scientists have unraveled the molecular mechanisms of sex determination for a number of model organisms. This research has lead to some general insights: First of all, the underlying molecular mechanisms can vary dramatically between species that on the surface appear to have very similar sex determination systems (Bachtrog *et al.*, 2014). On the other hand, however, some of the same genes are involved in sex determination across all metazoan and shared among species with very different sex-determining systems (Beukeboom and Perrin, 2014; Smith *et al.*, 1999). Genes involved in sex determination can generally be divided into those that determine the initial switch (the master switch) and those further downstream in the 'sex determination cascade,' which are responsible for organizing and maintaining sexual differentiation. A general pattern that has emerged from genetic studies is that those 'master switch' genes show high turnover between closely related species while those genes further down the cascade tend to be more conserved (Beukeboom and Perrin, 2014). The reason for this pattern is not fully understood, though they might arise from the fact that mutations in the switch genes tend to result in a change in sex ratio, while mutations further down the cascade will lead to more detrimental effects, for example the production of sterile intersex offspring. The sex-determining switch can be a large chromosomal region, a single gene, or even a single nucleotide polymorphism. It can act either by its presence or absence or by the amount of gene product that is present ('dosage' above or below a threshold).

Here we briefly review the molecular sex-determining mechanism of a number of model organisms and how these examples allow us to make inference across the tree of life.

Insects

Most of what we know about the molecular mechanism of sex determination in insects comes from studies on fruitflies in the genus *Drosophila*. *Drosophila* have an XY sex determination system. Sex is determined by a 'dosage-dependent sex determination' factor on the X chromosome (XSEs, see **Figure 3**): those individuals with two copies of the X chromosome develop as females while those with just one copy develop as males. Expression of the X-linked XSEs above the dosage threshold promotes the transcription of another gene called transformer (TRA), which in turn causes the alternative splicing of the gene double sex (DSX) (**Figure 3**; Maine *et al.*, 1985). Double sex is responsible for organizing sexual differentiation across all insects studied to date, while the other genes are more taxonomically restricted. Other flies that seemingly have the same sex determination system as *Drosophila* (XY) do not determine sex through dosage but through a dominant Y-link gene (M) that blocks the transcription of transformer and leads to the male-specific splice form of DSX (**Figure 3**). Unlike most insects butterflies determine sex through a female-heterogametic sex determination system (either ZW or Z0). The molecular mechanisms of sex

determination in butterflies has been studied primarily in the silkworm (*Bombyx mori*, **Figure 3**) and like other insects, DSX determines sexual differentiation. However, unlike other insects the master switch is not a protein, instead, a small non-coding RNA molecule located on the W chromosome and acts as a dominant 'feminizer' (Kiuchi *et al.*, 2014). Finally in many insects sex is determined through HD where males develop from unfertilized haploid eggs (Normark, 2003). The mechanisms by which sex determination is accomplished under HD are as yet only known for bees, ants, and wasps (Hymenoptera) (Schmieder *et al.*, 2012). Perhaps surprisingly much of the sex-determining cascade is identical to that found in *Drosophila* (**Figure 3**; Beukeboom and Perrin, 2014). In bees the master switch is the complementary sex determiner gene (CSD). Many different alleles at this locus segregate in a population and those individuals with two different alleles ('heterozygous' individuals) develop as females, while those with just one, either because they are haploid or because they have two copies of the same allele, develop as males (Beukeboom and Perrin, 2014). Although CSD is found across hundreds of hymenoptera, it is absent from some parasitoid wasps and there is no evidence for CSD in any of the other haplodiploid groups of insects or mites.

Figure 3 The molecular pathways of sex determination in a range of model organisms. The top half of the panel depicts examples of a number of well-studied insect model with different sex-determining pathways (from top to bottom: the common fruit fly: *Drosophila melanogaster*, the Mediterranean fruit fly: *Ceratitis capitata*, the buff-tailed bumblebee: *Bombus terrestris*, and the silkworm: *Bombyx mori*), while the bottom half shows such examples for vertebrates (from top to bottom: *Mus musculus*, *Gallus gallus domesticus*, and *Dicentrarchus labrax*). The solid white box indicates the 'master switch,' while the other colored boxes depict sex-determining genes further down in the cascade. Genes with a shared evolutionary history are depicted in the same color. Based on various references (Beukeboom and Perrin, 2014; Schmieder *et al.*, 2012; Kiuchi *et al.*, 2014).

Vertebrates

Across vertebrates sexual differentiation is regulated by Dmrt1 (Smith et al., 1999), which simultaneously turns on male development, while suppressing female development (**Figure 3**). Dmrt1 is a transcription factor that belongs to the same gene family as *doublesex*, but it is its presence or absence, not its alternative splicing, that causes sex differentiation (Beukeboom and Perrin, 2014). While Dmrt1 is pivotal for vertebrate sex determination, it does not usually act as the primary master switch, which – like in insects – is much more variable across species. In mammals the master switch is a dominant masculinizing gene called Sry that is located on the Y chromosome (**Figure 3**; Foster and Graves, 1994). The identity of the master switch in birds remains controversial, though most evidence points to Dmrt1 fulfilling this role (Smith et al., 2009; Beukeboom and Perrin, 2014). Dmrt1 in birds is Z-linked and the dosage of Dmrt1 is thought to directly determine male development. (**Figure 3**) In vertebrates with ESD, like some reptiles and fish, much of the downstream sex determination cascade is similar to that of species with genetic sex determination. Temperature-dependent sex determination is often mediated by the temperature-dependent expression of aromatase (Cyp19a), an enzyme that is involved in the synthesis of estrogens. Finally in some vertebrates, especially telost fish, sex is not controlled by a single master regulator but is instead a quantitative threshold trait with either a male or female outcome, which is determined by multiple regions in the genome (Bachtrog et al., 2014).

Flowering Plants

Among flowering plants, separate sexes (dioecy) are rare (about 6% of species (Renner and Ricklefs, 1995)), and have evolved relatively recently from hermaphroditic ancestors. The transition from hermaphroditism to separate sexes is generally thought to involve two separate mutations: one suppressing male function and one suppressing female function. Indeed sex is determined by two separate genes in papaya, one of the few plants for which the sex-determining cascade has been deciphered. Like most dioecious plants papaya has a male heterogametic (XY) sex determination system and sex is determined by an X-linked feminizer and a Y-linked masculinizer (Beukeboom and Perrin, 2014).

Why Are Some Groups so Variable?

From an evolutionary viewpoint, one of the most intriguing questions is why some groups of plants and animals (e.g., reptiles, fish) are exceptionally variable in the sex-determining systems, while others display hardly any variation (e.g., birds, mammals). One possibility is that certain SD systems are more labile than others. Generally, GSD is thought to be more stable than environmental SD. For example in reptiles transitions from ESD to GSD occur frequently, but there are no clear examples of transitions the other way. And even among GSD systems, those with highly differentiated sex chromosome (XY, ZW), are thought to be more stable than those where the sex chromosomes are monomorphic, or those that have lost one

of the sex chromosomes (X0 or Z0). Finally, HD is thought to serve as an 'evolutionary trap'; no haplodiploid lineage has re-evolved an SD system with diploid males (Bull, 1983).

Outstanding Questions

Some aspects of sex determination – such as the evolution of sex chromosomes and the molecular mechanism of sex determination in model organism – are now well understood. However many unresolved questions remain. Many of these involve the large-scale phylogenetic distribution of different sex determination systems. For example, why is male heterogamety more common than female heterogamety? Why does HD only occur in certain groups of invertebrates? Why do sex-limited chromosome degenerate in some groups but not others? Finally an important challenge is to understand how a species' sex determination mechanism can impact other aspects of their biology and evolution, such as rates of speciation (Orr, 1997), and the evolution of male ornaments (Kirkpatrick and Hall, 2004). Solving these challenging questions will require the concerted effort of scientist from a wide range of disciplines as well as a broad taxonomic outlook.

> *See also*: Sex and Recombination in Snails. Sex Chromosome Evolution: Birth, Maturation, Decay, and Rebirth. Sex, Evolution and Maintenance of. Sexual Dimorphism

References

Bachtrog, D., 2008. The temporal dynamics of processes underlying Y chromosome degeneration. Genetics 179, 1513–1525.

Bachtrog, D., Mank, J.E., Peichel, C.L., et al., 2014. Sex determination: Why so many ways of doing it? PLoS Biology 12, e1001899.

Bawa, K.S., 1980. Evolution of dioecy in flowering plants. Annual Review of Ecology and Systematics 11, 15–39.

Beukeboom, L., Perrin, N., 2014. The Evolution of Sex Determination. Oxford: Oxford University Press.

Buchner, P., 1965. Endosymbiosis of Animals with Plant Microorganisms. New York: Interscience Publisher.

Bull, J.J., 1983. The Evolution of Sex Determining Mechanisms. Menlo Park, CA: Benjamin/Cummings Publishing Company.

Burt, A., Trivers, R., 2009. Genes in Conflict: The Biology of Selfish Genetic Elements. Cambridge: Harvard University Press.

Charlesworth, B., Jordan, C.Y., Charlesworth, D., 2014. The evolutionary dynamics of sexually antagonistic mutations in pseudoautosomal regions of sex chromosomes. Evolution 68 (5), 1339–1350.

Charlesworth, D., Charlesworth, B., Marais, G., 2005. Steps in the evolution of heteromorphic sex chromosomes. Heredity 95, 118–128.

Fisher, R.A., 1930. The Genetical Theory of Natural Selection. Oxford: Clarendon Press.

Foster, J.W., Graves, J.A., 1994. An SRY-related sequence on the marsupial X chromosome: Implications for the evolution of the mammalian testis-determining gene. Proceedings of the National Academy of Sciences 91, 1927–1931.

Fricke, H., Fricke, S., 1977. Monogamy and sex change by aggressive dominance in coral reef fish. Nature 266, 830–832.

Gardner, A., Ross, L., 2014. Mating ecology explains patterns of genome elimination. Ecology Letters 17 (12), 1602–1612.

Hamilton, W.D., 1967. Extraordinary sex ratios. Science 156, 477–488.

Hughes, J.F., Skaletsky, H., Brown, L.G., et al., 2012. Strict evolutionary conservation followed rapid gene loss on human and rhesus Y chromosomes. Nature 483, 82–86.

Jarne, P., Auld, J.R., 2006. Animals mix it up too: The distribution of self-fertilization among hermaphroditic animals. Evolution 60, 1816–1824.

Juchault, P., Rigaud, T., Mocquard, J.P., 1992. Evolution of sex-determining mechanisms in a wild population of Armadillidium vulgare Latr.(Crustacea, Isopoda): Competition between two feminizing parasitic sex factors. Heredity 69, 382–390.

Kirkpatrick, M., Hall, D.W., 2004. Sexual selection and sex linkage. Evolution 58, 683–691.

Kiuchi, T., Koga, H., Kawamoto, M., et al., 2014. A single female-specific piRNA is the primary determiner of sex in the silkworm. Nature 509, 633–636.

Lahr, D.J.G., Parfrey, L.W., Mitchell, E.A.D., Katz, L.A., Lara, E., 2011. The chastity of amoebae: Re-evaluating evidence for sex in amoeboid organisms. Proceedings of the Royal Society B: Biological Sciences 278, 2081–2090.

Maine, E.M., Salz, H.K., Cline, T.W., Schedl, P., 1985. The Sex-lethal gene of Drosophila: DNA alterations associated with sex-specific lethal mutations. Cell 43, 521–529.

Normark, B.B., 2003. The evolution of alternative genetic systems in insects. Annual Review of Entomology 48, 397–423.

Normark, B.B., Ross, L., 2014. Genetic conflict, kin and the origins of novel genetic systems. Philosophical Transactions of the Royal Society B: Biological Sciences 369, 20130364.

Orr, H.A., 1997. Haldane's rule. Annual review of ecology and systematics 28, 195–218.

Parker, G.A., Baker, R.R., Smith, V.G.F., 1972. The origin and evolution of gamete dimorphism and the male—female phenomenon. Journal of Theoretical Biology 36, 529–553.

Perrin, N., 2009. Sex reversal: A fountain of youth for sex chromosomes? Evolution 63, 3043–3049.

Perrin, N., 2012. What uses are mating types? The "developmental switch" model. Evolution 66, 947–956.

Renner, S.S., Ricklefs, R.E., 1995. Dioecy and its correlates in the flowering plants. American Journal of Botany 82, 596–606.

Sánchez, L., 2010. Sciara as an experimental model for studies on the evolutionary relationships between the zygotic, maternal and environmental primary signals for sexual development. Journal of Genetics 89, 325–331.

Schmieder, S., Colinet, D., Poirié, M., 2012. Tracing back the nascence of a new sex-determination pathway to the ancestor of bees and ants. Nature Communications 3, 895.

Shine, R., Elphick, M.J., Donnellan, S., 2002. Co-occurrence of multiple, supposedly incompatible modes of sex determination in a lizard population. Ecology Letters 5, 486–489.

Smith, C.A., McClive, P.J., Western, P.S., Reed, K.J., Sinclair, A.H., 1999. Evolution: Conservation of a sex-determining gene. Nature 402, 601–602.

Smith, C.A., Roeszler, K.N., Ohnesorg, T., et al., 2009. The avian Z-linked gene DMRT1 is required for male sex determination in the chicken. Nature 461, 267–271.

The Tree of Sex Consortium, 2014. Tree of Sex: A database of sexual systems. Scientific Data, 1.

Van Doorn, G., Kirkpatrick, M., 2007. Turnover of sex chromosomes induced by sexual conflict. Nature 449, 909–912.

Vicoso, B., Kaiser, V.B., Bachtrog, D., 2013. Sex-biased gene expression at homomorphic sex chromosomes in emus and its implication for sex chromosome evolution. Proceedings of the National Academy of Sciences of the United States of America 110, 6453–6458.

Volff, J.N., Schartl, M., 2001. Variability of genetic sex determination in poeciliid fishes. Genetica 111, 101–110.

Westergaard, M., 1958. The mechanism of sex determination in dioecious flowering plants. Advances in Genetics 9, 217–281.