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Meeting report

Tackling the diversity of sex determination

Claus Wedekind* and Rike B. Stelkens

Department of Ecology and Evolution, Biophore, University of Lausanne, 1015 Lausanne, Switzerland

*Author for correspondence (claus.wedekind@unil.ch).

A workshop on ‘The evolution of sex determination systems’ was held at a remote place in the Swiss Alps from 17 to 20 June 2009. It brought together theoreticians and empiricists, the latter ranging from molecular geneticists to evolutionary ecologists, all trying to understand key aspects of sex determination. The topics discussed included the evolutionary origins of sex determination, the diversity of sex determination mechanisms in different taxa, and the transition from genotypic to environmental sex determination and vice versa.

Keywords: sex genes; sex chromosomes; genomic conflict; zygotic drive; genetic degeneration

1. INTRODUCTION

The genetics, ecology and evolution of sex determination have always fascinated evolutionary biologists. Among the many important questions still puzzling researchers today is a very basic one: why is there such a diversity of sex determination mechanisms? Mammals and birds (and most dioecious plants) have only genotypic sex determination (GSD); that is, their sex is established at fertilization by genetic factors. Other vertebrates have environmental sex determination (ESD), which is also widespread in plants and other animals. In ESD, sex development is under the control of environmental cues (temperature, pH, social factors and so on) and is usually determined within a discrete period after conception. Many organisms, including many fish and amphibians, have a mixture of GSD and ESD, for example, when environmental sex reversal creates a mismatch between genotypic and phenotypic sex. (Such mismatches can have interesting consequences, for example, on the future demographics of a population.)

The following is another basic question that remains challenging: how do sex determination mechanisms evolve? Obviously, each sexually produced offspring has a father and mother, so we expect strong frequency-dependent selection on the production of sons and daughters. Meiotic separation of sex chromosomes ensures a 1:1 sex ratio, but ESD can lead to biased sex ratios. ESD may, however, be favoured over GSD under some sex-specific selection pressures, for example, if male fitness improves more with increasing size than female fitness and ESD allows males to grow larger than females (Bull 1983). These first thoughts set the stage, but cannot yet explain

the diversity of sex determination mechanisms we see in the wild.

2. FROM DATA TO THEORY AND BACK AGAIN

Separate sexes in plants have probably, and often recently, evolved many times. Deborah Charlesworth (University of Edinburgh) opened the meeting with an overview of the similarities and differences between plant and animal sex chromosomes. She reviewed genetic data on questions such as: (i) When did sex chromosomes evolve in different species? (ii) Why does this usually result in a loss of recombination? (iii) What are the consequences of the latter? It is now evident for several model systems that recombination ceased at different times on different parts of the sex chromosomes, that is, there is no single age of such chromosomes. Charlesworth also reviewed the argument that it needs at least two interacting sex determination genes on a chromosome, and selection for reduced recombination between these, to set off the evolution of sex chromosomes. Furthermore, sexually antagonistic genes may be added later to a system, leading to selection for reduced recombination in new regions. An important consequence of reduced recombination is genetic degeneration, that is, poorer gene function, loss of genes and sometimes the evolution of dosage compensation. It is not yet clear how much time is required for this process (Bergero & Charlesworth 2009).

In a second opening talk, theoretician Mark Kirkpatrick (University of Texas) reviewed ideas and models for evolutionary changes and turnover of sex chromosomes. In ‘homogametic transitions’, a pair of autosomes becomes a new pair of X and Y chromosomes replacing the old X and Y, whereas ‘heterogametic transitions’ change an XY system (with males heterogametic) to a ZW (with females heterogametic) or vice versa. Such transitions are feasible if Y or W are not considerably degenerated. They can be a result of random drift, pleiotropic effects favouring new sex determination alleles, selection on sex ratio, transmission distortion or sexually antagonistic selection. Kirkpatrick elaborated on the idea that an autosomal gene under sexually antagonistic selection can cause the spread of new sex determination genes linked to it, and that this is a likely cause for homo- or heterogametic transitions (van Doorn & Kirkpatrick 2007), which can in turn lead to the origin of new sex determination loci, the transposition of an ancestral sex determination gene to an autosome, or the maintenance of multiple sex determination factors in species that lack heteromorphic sex chromosomes.

Fishes generally seem to be excellent models in which to study changes in sex determination. Jean-Francois Baroiller (CIRAD, Montpellier) provided an overview of piscine sex determination mechanisms, which seem to vary continuously from different forms of GSD to different forms of ESD, including, for example, temperature-dependence (TSD) (Baroiller *et al.* in press). Additive genetic variation for reaction norms is sometimes found within a single species. Sex reversal is often possible and is routinely used in aquaculture to produce single-sex populations. Subsequent breeding and sex reversal can lead to YY females. These are viable in many species, suggesting that the

male-determining regions evolved too recently to undergo significant genetic degeneration. As a consequence, environmental sex reversal could be used in population management to control, for example, introduced exotic species (Cotton & Wedekind 2008). Delphine Galiana-Arnoux (Institut de Génomique Fonctionnelle, Lyon) described duplications, insertions, deletions and transposable elements in the sex determination region of the platyfish, and argued that there is no shared synteny to other fish sex chromosomes. Helena D'Cotta (CIRAD, Montpellier) reviewed molecular work aimed at discovering genes involved in the sex determination cascade in tilapia. In lizards, however, Martina Pokorná (Charles University, Prague) showed, using phylogenetic analysis, that transitions between different sex determination mechanisms are infrequent.

The significance of sexually antagonistic selection and genomic conflict was further elaborated in talks by William Rice (University of California) and Leo Beukeboom (University of Groningen). Beukeboom reviewed the genetic conflicts that are likely to influence the evolution of sex determination mechanisms and that emerge from conflicts between cytoplasm and nucleus, sex chromosomes, parents and offspring, and mothers and fathers (Werren & Beukeboom 1998). He supported some of his arguments with new simulations and suggested experiments on species with natural sex determination polymorphism, such as the house fly (*Musca domestica*). Rice explained in detail how a 'green beard effect', that is, a particular form of cooperation that is theoretically predicted, but has not often been demonstrated, can drive the evolution of sex chromosomes by sib competition for parental care. In this context, offspring sex is a tag (like a 'green beard'). Selection in the heterogametic sex can thus cause 'zygotic drive', a previously overlooked form of sexual genomic conflict that may be especially common in birds. Green-beard effects may occur if the opposite sex is more likely to be killed in sibicide, or if parental provisioning or epigenetic effects are sex specific. Genomic conflict may lead to chromosomes modifying gene expression on other chromosomes. Indeed, the *Drosophila melanogaster* Y has 12 known coding genes, but expression levels of hundreds of genes are affected by the Y (Lemos *et al.* 2008). Autosomes and new sex chromosomes are expected to evolve counterstrategies such as early inactivation of sex chromosomes during spermatogenesis. Such counterstrategies can ultimately lead to adaptations that reduce the fitness of the organism, for example, by disruption of sex-specific pathways, increased rate of spontaneous abortions or homosexuality (Rice *et al.* 2008).

Martin Hasselmann (University of Düsseldorf) presented details of the genetics of sex determination in the honeybee (*Apis mellifera*), a haploid-diploid system with complementary sex determination (heterozygotes develop into females, hemizygotes and homozygotes into males). He explained the regulatory interactions between the recently duplicated complementary sex determiner gene (*csd*), the feminizer gene (*fem*, the ancestrally conserved progenitor from which *csd* arose) and *Am-dsx* (a conserved sex-specific transcription factor). RNA interference-induced knockdowns

confirmed that *csd* affects sex through allelic combination, whereas *fem* induces sex-specific splicing, producing a functional protein only in females. Comparison between the sex determination pathways of *A. mellifera*, *Ceratitis capitata* and *D. melanogaster* suggests that the *fem/dsx* pathway is ancestral, and that rather simple evolutionary steps of gene duplication and neo-functionalization can yield radically different sex determination systems. Interestingly, the data from insects suggest that the plasticity of sex regulatory proteins may have facilitated the recruitment of upstream signals to take over sex determination function. Furthermore, a comparative analysis of *fem*- and *csd*-coding sequences from five bee species provides evidence for a recent origin of *csd* in the honeybee lineage, followed by positive selection at *csd* and accompanied by purifying selection at *fem* (Hasselmann *et al.* 2008). Hasselmann speculated that gene duplication and positive selection at *csd* may be consistent with selection for a novel sex determination pathway, resulting from deleterious mutations accumulating on the initial sex determination locus, due to recombination reduction and an erosion of gene function. These findings offer a potential explanation for the stunning diversity of genetic sex determination factors observed in insects.

Fredric Janzen (Iowa State University) identified the interplay between sex ratio selection and sex determination mechanisms as one of the most powerful drivers of population dynamics in species with ESD. The existence of organisms with multifactorial sex determination (such as GSD plus environmental effects) poses a problem for sex ratio theory, because it predicts the production of widely varying, unstable sex ratios. Janzen opined that if we are to understand the persistence of multifactorial systems and the seemingly infinite combinations of genotypic and environmental sex factors in nature, we need to tackle the issue from several angles. He recommended phylogenetic comparative methods, as well as field and laboratory experiments, that integrate different study areas and different levels of biological organization. As general explanations for the adaptive significance or persistence of ESD, Janzen listed phylogenetic inertia, group adaptation, inbreeding avoidance and sex-specific selection pressures (Janzen & Phillips 2006). He then reviewed some of the latest work on reptiles with TSD suggesting that the fitness of each sex is maximized by the incubation temperature producing that sex, as predicted by Charnov & Bull (1977). Janzen concluded that TSD is a classic case of phenotypic plasticity, that it is likely to have multiple evolutionary origins, and that it may be adaptive in turtles with seasonally shifting differential fitness for males and females. On a related note, Christine Grossen (University of Lausanne) explored the influence of stochastic effects and environmental variance on the spread of new sex determiners using an individual-based model with sex determination as an additive quantitative trait. The model gave three potential outcomes: population extinction, the evolution of ESD (and then new GSD) or a direct transition to another GSD system. Her analyses suggest that ESD and GSD are two extremes of a continuum.

Nicolas Perrin (University of Lausanne) asked the following question. Why do sex chromosomes not decay in lower vertebrates as they do in higher ones? Perrin suggested possible mechanisms that may have led to a low decay of Y chromosomes specifically in amphibia. The high evolutionary turnover rates of sex determination systems found in some species groups may partly explain the observations. But if this were the only reason, it would appear that >90 per cent of all amphibian species must have experienced a recent turnover. This seems unlikely, and we are left with another exciting problem that still needs to be solved.

3. POSSIBLE FUTURE DIRECTIONS

Fundamental organismic traits like sex determination mechanisms may rarely be amenable to experimental evolution. Many talks (including those that were not mentioned for lack of space) suggested that we can learn much about the evolution of sex determination from studying genetics and molecular pathways, using phylogenetic comparisons (e.g. to identify changes between sex determination mechanisms), as well as from extending theoretical analyses and combining them with field and laboratory studies on real populations. We may soon, for example, have a greater understanding of genetic degeneration and be able to estimate the divergence time between homologous X and Y sequences if we can identify specific genes involved in sex determination, and the genes linked to these. Models for the stable coexistence of ESD and GSD, as often observed in the wild, should be elaborated on and tested. There are further unanswered questions to be investigated. Why are some sex determination systems stable in some taxa but not in others? How did recombination between sex chromosomes cease in the heterogametic sex? What is the significance of genotype \times environment interactions, and are sexually antagonistic loci involved in transitions in sex determination systems? Can species with ESD adapt quickly enough to changing environments? Several promising systems have been identified for studying such questions and exciting breakthroughs can be expected within the next few years.

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