Why girls want to be boys

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Summary

The mechanisms by which sex is genetically determined are bewilderingly diverse and appear to change rapidly during evolution.[1] What makes the sex-determining process so prone to perturbations? Two recent articles[2,3] explore theoretically the role of genetic conflict in sex determination evolution. Both studies use the idea that selection on sex-determining genes may act differently in parents and in offspring and they suggest that the resulting conflict can drive changes in sex-determining mechanisms. *BioEssays* 23:477–480, 2001.

Conflict over sex determination

Genetic conflict arises when different parts of the genome are selected in opposite directions and this concept is now widely accepted in evolutionary biology.[4] One type of conflict occurs between parents and offspring. For example, Trivers[5] proposed that, when the amount of resources needed to produce a son or daughter differs, parents and offspring may disagree over the sex ratio of the offspring. He showed theoretically that the sex ratio is less biased under offspring control. This implies that sex-determining genes in parents will be under different selection pressures than genes in offspring. Two recent articles by Werren and Hatcher[2] and Caubet and colleagues[3] show that such conflict between parental and offspring genes over the sex of an offspring can shape sex-determining mechanisms. The purposes of our article are to (1) draw further attention to the possible role of genetic conflict in sex determination evolution, (2) critically explore some of the implications of the models presented in both articles, and (3) consider how to test some of the predictions of the models.

The idea that genetic conflict can drive sex determination evolution has been proposed before.[6–8] Thus far, however, genetic conflict theory has largely been used for ad hoc explanations of the observed diversity in sex-determining mechanisms, whereas quantitative theoretical and empirical investigations of its potential evolutionary impact are still scarce. Sex-determining mechanisms appear to be particularly vulnerable to conflict because different genetic entities of the genome and the cytoplasm may gain disproportional transmission through either one of the two sexes. For example, cytoplasmic elements will be favoured to produce females because they are only transmitted through eggs (sperm does not contain cytoplasm) whereas the autosomes will generally be selected for equal numbers of males and females.

Studies on a few organisms that have been investigated in detail (e.g. *Drosophila melanogaster* and *Caenorhabditis elegans*) indicate that the sex-determining pathway consists of a cascade of male- and female-determining genes.[9] Some of these genes are expressed in the maternal parent (e.g. maternal sex products put into the egg, so called maternal-effects) and others in the developing zygote. Such a separation of parental and zygotic sex-determining genes could potentially lead to conflict because both categories differ in their mode of inheritance and expression.[8] Werren and Hatcher[2] derived optimal sex ratios for maternal-effect genes and zygotically expressed genes under partial inbreeding (sib mating) and subdivided population with local mating in temporary demes (local mate competition). They show that low levels of inbreeding (5%) or subdivision can result in a difference in optimal sex ratio for the mother and for the offspring. The optimal sex ratio for the mother turns out to be more female biased than for the offspring. Initially the mother sets a female-biased sex ratio to her advantage, but then, after the sex of each offspring has been determined, a gene that can revert a female into a male will be selected for. To do this the gene has to overrule the existing sex-determining mechanism. The question then becomes whether current sex-determining mechanisms resemble more the maternal or the offspring choice. This is a matter of who is in control: are these the parental genes because they can "act" first (i.e. already in the parent during oogenesis or fertilisation) or can the offspring genes overrule the "decision" of the parental genes (i.e. in the zygote during embryogenesis)?

Sex ratio conflict under inbreeding

Inbreeding has been shown to select for female-biased sex ratios by Hamilton in his Local Mate Competition model[10] and by Maynard Smith in his book "The Evolution of Sex".[11] Both authors have calculated optimal sex ratios for various conditions under maternal control. Werren and Hatcher for the first time use these models to calculate the optimal sex ratio under zygotic control. For both models, they show that the

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optimal sex ratio under offspring control will be less female biased than under maternal control.

When translated into genetic conflict terms, this means that parental and offspring genes disagree over the sex ratio. In other words, under maternal control some offspring end up with the "wrong" sex from the point of view of offspring genes, i.e. "some girls want to be boys". Thus, selection will act on zygotic sex-determining genes to become masculinising. In box 1, we use a numerical example to illustrate this conflict and, in box 2, we use an alternative approach to derive Werren and Hatcher's results.

Maynard Smith assumed that within a local mating population (= deme) a fixed fraction p of the matings is between brothers and sisters and a fraction $1 - p$ is random within the whole population. In Hamilton's model, n fertilised females lay eggs in a deme after which random mating occurs within the deme and the fertilised females disperse. For the common type in the population, the fraction sib mating p then equals $1/n$. A rare mutant plays against n-1 females of the common type in the host in which they are competing. The fraction sib mating depends on the two strategies involved and is not fixed. In both models, the resulting selection on sex ratio is the outcome of counteracting within and between group selection pressures, i.e. within population selection for a 50% sex ratio and between populations selection for 100% females. The net effect is a sex ratio somewhere intermediate between 0 and 50% males.

Although the models differ in their assumptions of population structure and inbreeding, as well as in some mathematical aspects regarding the stability of the ESS,[2] they yield the same prediction of the evolutionarily stable fraction sons (r). Under maternal control in the Maynard Smith model,

Box 1

Why would the optimal sex ratio from the mother's point of view differ from that from the offspring's point of view under inbreeding? If the sex ratio is female biased, a son will have a relatively high reproductive success compared to a daughter (one son mates with several daughters). This results in a selective advantage for a mutant gene that can transform a female into a male, because such a gene will be replicated more often (to more offspring) than a gene with no effect on the sex of its bearer. As an example, assume that a female produces 10 offspring, one son and nine daughters, which all mate among each other (100% sibmating) within a single patch (or host). This is the optimal sex ratio under maternal control considering that at least one son needs to be produced to mate with all her daughters. The son will have a reproductive success of 90 (each daughter produces again 10 offspring) and each of the daughters a reproductive success of 10. Any mutant masculinising zygotic gene that turns a female into a male will gain a reproductive advantage. Instead of having a female reproductive success of 10, as a male, this individual can mate with 4 sisters (assuming equal competition with its brother) and gain 40 offspring. A mutant autosomal gene that transfers a female into a male transmits 30 copies more to the next generation than a gene that leaves everything as it is (10 copies). The result is strong conflict between the maternal and zygotic sex-determining genes over sex determination when one sex is rare.

Box 2

An alternative way of looking at the results of Werren and Hatcher's population genetic model is to use an inclusive fitness approach. Inclusive fitness calculations take into account not only an individual's own fitness but also the fitness of relatives with whom they share part of their genes. Inclusive fitness therefore takes into account both individual and kin selection. Let S be the proportion of males (and 1–S the proportion of females) in the group where competition for mates takes place. Every son then enjoys a mating sucess of (1–S)/S. Thus, when a mother decides to produce an extra male instead of a female, she loses one unit of female fitness and gains (1–S)/S units of fitness. The same is true for an offspring that decides to become a male instead of a female: she loses one unit and gains (1–S)/S units. If competing males are not related, then it is simple: in equilibrium losses equal gains, giving (1-S)/S = 1 or S = 1/2. If competing males are related, however, then an extra male displaces another male that has relatedness R, say, to the individual in control of the sex ratio. Thus, the inclusive fitness effect is (1–S)/S–1–R(1–S)/S. Herein lies the conflict: the relatedness of mothers to displaced males (relative to her relatedness to her own male offspring) differs from the relatedness of offspring to displaced males. In fact, standard calculations for diploid organisms show that, for mother, we have R = 1/N, which is the average relatedness among all mothers in a patch, and for offspring R = 1(2N–1), which is the average relatedness among all offspring produced in a patch. They give the equilibria S = (N–1)/2N and S = (N–1)/(2N–1), respectively. Similar calculations can be made for haplodiploids and they reveal that the parent—offspring conflict is even slightly larger.

$r = (1 - p)/2$ and the same equation applies to the Hamilton model with $p = 1/n$. The equation derived by Werren and Hatcher under zygotic control, $r = (1 - p)/(2 - p)$, is also the same as for the Hamilton model with $p = 1/n$.

Given the similarity in predictions of the two models, it is tempting to apply these equations to a range of systems for which the fraction sib mating can be estimated. A small change in the assumptions, however, yields a different prediction for *r*. Sib mating may depend on the sex ratio. A single female surrounded by nine brothers must have a higher chance of being fertilised by one of her brothers than each of nine females with a single brother close by. Including this relation in the Maynard Smith model, changes the optimal seed sex ratio under maternal control[12] and probably also under offspring control. If we include male dispersal into the Hamilton model, the predicted values of *r* change.[13] The life history of the organism and what causes sib mating seem necessary ingredients of models that predict *r*. Werren and Hatcher have now added that there is not one evolutionarily stable value of *r* for a species. Mother and offspring each favour their own value and the realised value of *r* lies somewhere in between, depending on who has temporarily gained the upperhand in the conflict. This implies that there is not one simple relation between R and sib mating[13], like some authors assume[14] and that the life history of an organism has to be taken into account.

Evidence for conflict over sex determination

What is the evidence for the existence of parent–offspring conflict over sex determination? To answer this question, it helps to distinguish three subquestions: (1) who is in control of the sex of the offspring, (2) how is this control achieved, and (3) how can this control be overtaken by the other party? Werren and Hatcher mention parasitic wasps, bark beetles, parasitic nematodes, fungal gnats and plants as possible examples of organisms with frequent sib mating. The mating system of the plant *Silene latifolia* is well studied from a number of angles and may serve as an illustration here.

(1) In haplodiploid systems, where females have control over the fertilisation of their eggs, fertilised diploid eggs develop into daughters and unfertilised haploid eggs into sons. In diploids, the sex-determining mechanism is an important factor that limits the degree of sex ratio control by the mother. If the female is the heterogametic sex (WZ females and ZZ males), the window of opportunity for control may be larger than under male heterogamety. *Silene latifolia* has male heterogamety and female-biased populations. Seed sex ratio of different mothers is on average 0.41 and varies between 0.05 and 0.75.[15] This large variation in sex ratio may reflect different degrees of control of parents and offspring.

(2) Heterogametic females may in some way affect the relative production of W (male) and Z (female)-bearing follicles during oogenesis.[16] If the male is the heterogametic sex, females can only have control after oogenesis by selective fertilisation. This can be achieved by preferentially admitting an X-bearing (female) or Y-bearing (male) sperm or pollen to the egg or by selective abortion of one sex after fertilisation. In *Silene latifolia*, most variation in seed sex ratio is explained by the father used in a cross and this probably reflects meiotic drive.[17] However, the mother apparently has some control over the sex ratio of her offspring. This follows from the interaction between effects of maternal and paternal parent. It also follows from certation studies,[15] in which interactions were observed between maternal tissue and X- or Y- bearing pollen, which affected pollen germination, pollen tube growth and embryo maturation. Certation is the dependence of sex ratio of the seeds on pollination intensity; the fraction of sons is lower with abundant pollination than with sparse pollination.

(3) The third subquestion concerns the possible means of taking over control of sex determination by the other party. In the case of male heterogamety, it might be sufficient for the male gametes to hide their sexual identity. In the *Silene latifolia* example, any autosomal gene in the pollen that tampers with the discrimination system in the female parent will result in a less female-biased sex ratio and will be transmitted at a higher rate. Although theoretically plausible, it remains to be seen how strong this contest is of recognition and masking of the sexual identity of gametes.

Zygotic sex determiners with masculinising effects are also expected to evolve if the mother can impose a strong female bias on her offspring. In inbreeding haplodiploids such a sex determiner would turn a diploid female into a diploid male, which, in turn may produce triploid daughters. Because triploid females typically have reduced fertility, however, they may prevent the evolution of such sex determiners. Another theoretical possibility would be a gene that prevents or reduces the possibility of fertilisation, or the evolution of a Paternal Sex Ratio (PSR) element, such as found in *Nasonia vitripennis*.[18] PSR turns diploid (female) eggs into haploid males by destroying one set of chromosomes in the fertilised egg. The problem with this element is its "all or nothing" effect, i.e. when present, it turns all daughters into sons. Initially such an element will have a selective advantage, but in the long term it cannot exist in highly subdivided populations due to lack of female mates.[19] Thus, the scope for the evolution of masculinisers in haplodiploids may be narrow.

Masculinising genes may be more common in inbreeding diploid organisms. Under heterogametic sex determination, they would lead to individuals that have the "wrong" combination of gender and sex chromosomes, i.e. XX and WZ males under male and female heterogamety, respectively. Such progeny with "unexpected" gender have been reported from plants[20] and animals (e.g. XX males in the housefly, *Musca domestica*).[21] Another example that suggests that such masculinising agents could evolve is the smut fungus in *Silene*, which transforms genotypic females into phenotypic

males.[22] Bull and Charnov[21] already showed theoretically that such masculinising genes may, in turn, lead to changes in the heterogametic mechanism of sex determination. In their theoretical study of conflict over sex determination between cytoplasmic and nuclear genes, Caubet et al.[3] found a similar result. When they incorporated selection for the spread of autosomal masculinisers in response to cytoplasmic sex ratio distorters in their model, shifts from female heterogamety to male heterogamety were observed. The evolutionary outcome of the model was sensitive to specific parameter values, such as type and cost of repression and the population structure. Under some conditions, the intermediate multigenic sex-determining mechanism would be a stable polymorphism, again consistent with Bull and Charnov's results. These studies provide possible explanations for the multiple mechanisms of sex determination and the frequent shifts in the heterogametic sex observed in some groups.

Conclusion

There is a growing interest among evolutionary biologists to identify the selective forces that drive sex determination evolution. The topic is of particular interest because selection on sex-determining mechanisms need to be considered at different levels, including individual, chromosomal and gene selection. Genetic conflict theory may be a promising approach as shown by some recent theoretical investigations. Inbreeding may promote sex determination evolution through conflict between maternal and zygotic sex-determining genes. These studies highlight the need for better estimation of population structure parameters, as well as more knowledge of sex-determining mechanisms in a variety of organisms before general conclusions can be drawn about how natural selection shapes sex-determining mechanisms.

Acknowledgments

We thank Jacques van Alphen, Melanie Hatcher, Franjo Weissing, John Werren, and Adam Wilkins for stimulating discussions on sex determination evolution and valuable comments on the manuscript. LWB was supported by a fellowship of the Royal Netherlands Academy of Arts and Sciences.

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