Sex-specific genetic structure: new trends for dioecious parasites

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In dioecious parasite species, genetic structure can differ between sexes, as recently demonstrated for the digenetic trematode *Schistosoma mansoni* and the ectoparasitic tick *Ixodes ricinus*. This article presents some of the methods that allow detecting such a pattern in natural populations. The proximate and ultimate factors that potentially generate a sex-specific genetic structure are discussed, as are evolutionary and epidemiological consequences for dioecious parasites and vectors.

Successful transmission of parasites from one generation to the next involves three sequential steps: (1) establishment of infection; (2) development and reproduction in or on the host; and (3) dispersal of propagules to new infection sites [1]. Characteristics of these steps can differ among species, leading to differences in their respective POPULATION GENETIC STRUCTURE (see Glossary) [2,3]. Differences in traits related to transmission can also be expected between two populations of the same species (e.g. if the host species or environments are different among populations), and even between distinct groups within the same population, shaping thus a group-specific population structure. Males and females, in dioecious species, represent good candidates for such groups.

Sexes are often submitted to different selection pressures and, as a consequence, display variable life history traits (see, for example, Ref. [4]). Some of these traits can substantially affect the distribution of genetic variability and lead to sex differences in population genetic structure. This possibility is very well documented in some vertebrates where differences in juvenile dispersal rate between males and females were shown to generate a sex-specific genetic structure in adult populations (see Refs [5–7] for details about conditions where sex-specific genetic structure is expected to occur under sex-biased dispersal patterns).

Numerous parasite species are dioecious. This is the case for some Trematoda (e.g. *Schistosoma mansoni*, the cause of intestinal human schistosomiasis), the majority of Nematoda [e.g. *Ascaris lumbricoides* (human ascaris), *Onchocerca volvulus* (river blindness)], all Acanthocephala [e.g. *Onicola canis* (thorny-headed worm of dogs and cats)] and Acaria (e.g. ticks). Some of these parasites could present sex differences in transmission patterns (establishment, development, dispersal) (see Ref. [8] for *S. mansoni*) and, thus, potentially display a sex-specific genetic structure, as already demonstrated for two very different parasite species: *S. mansoni*, a water-dependent endoparasite [9], and *Ixodes ricinus*, a terrestrial ectoparasite [10]. In both cases, male allele frequencies observed from microsatellite markers were significantly more similar among samples than were female-allele frequencies.

How to detect sex-specific genetic structure?

The genetic structure is sex-specific when the distribution of the genetic variability observed from neutral AUTOSOMAL GENETIC MARKERS differs between males and females. Therefore, a comparison between classical parameters (e.g. Wright's *F*-statistics [11]) (Box 1) describing how alleles are distributed within and among males and females is a way to detect a sex-specific genetic structure. Complementary approaches, based on recently described individual 'assignment indices', are also able to detect this phenomenon [6,7] (Box 1).

Glossary

Allelopathy : Production of toxic chemicals to suppress the growth and/or survivorship of local competitors.
Altruism : Refers to actions of one individual that increase the survival and reproduction of another individual, the recipient of altruism, and decrease the survival and reproduction of the altruist.
Arms race : In host–parasite systems, an arms race designates the fact that hosts evolve defenses against parasites, and parasites evolve countermeasures to overcome them.
Autosomal genetic marker : A gene located on an autosome (not on a sex chromosome).
Genetic differentiation : Two populations are genetically differentiated when they present different allele frequencies at the considered loci.
Inbreeding : Refers to the process of mating with a relative.
Local competition : Designates competition among relatives of the same sex for a limiting resource (e.g. mating partners or breeding sites).
Philopatry : Refers to individuals that stay or return to their natal site or group to breed.
Population genetic structure : Defined as the total genetic diversity and its distribution within and among populations.
Proximate factors : Characterize the physiological and behavioural mechanisms involved in an adaptation; describe how an adaptation operates by opposition to ultimate factors.
Ultimate factors : Correspond to the evolutionary factors that determine the direction of evolution of a particular trait; describe 'why' an adaptation should arise.

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http://parasites.trends.com 1471-4922/03/$ - see front matter doi:10.1016/S1471-4922(03)00037-0

Box 1. Parameters to compare male and female population genetic structure obtained with autosomal markers

For each parameter presented below, expectations are given for the case where males and females display differential dispersal rates. The dispersing sex is designated 'D' and the philopatric one 'P'. All the parameters described here are available in the software Fstat V. 2.9.3 (updated from Ref. [32]), which can be downloaded for free from: http://www.unil.ch/izea/softwares/fstat.html

Locus-based parameters

- F_{is} measures the discrepancy within samples between the observed and the expected heterozygosity under Hardy–Weinberg expectations [11] $\{F_{is}(D) > F_{is}(P)\}$.
- F_{st} measures the extent of genetic differentiation between samples [11] $\{F_{st}(D) < F_{st}(P)\}$.
- **Relatedness** (r) measures the average relatedness within samples when compared with the whole population [33]. It is connected to F_{st} through the relation $r = 2F_{st}/(1 + F_{it})\{r(D) < r(P)\}$. Note that F_{it} (the discrepancy between the observed and expected heterozygosity under Hardy–Weinberg expectations in the overall population) is linked to F_{st} and F_{is} by the formula: $(1 - F_{it}) = (1 - F_{is})(1 - F_{st})$.

Individual-based parameters: assignment indices

An individual assignment index (*AI*) corresponds to the expected frequency of its multilocus genotype within the population where it was collected [34]. A rough comparison in *AI* between individuals sampled in different populations is rendered inaccurate when those populations differ in genetic diversity. Thus, *AI* is corrected (*AIc*) by subtracting from its value the average probability computed among all individuals sampled in the population. Two indices can be used to detect sex-specific genetic structure: the mean (m*AIc*) and the variance (v*AIc*) of the corrected assignment index [7] {m*AIc* (D) < m*AIc* (P)}; {v*AIc* (D) > v*AIc* (P)}.

The respective power of these different statistics is highly dependent on sampling, dispersal rate, intensity of the dispersal bias and population structure (see Ref. [7] for details).

The comparison between male and female biparentally inherited markers (e.g. microsatellites) generally relies on a particular sampling scheme of individuals among subpopulations. Indeed, alleles are randomly transmitted to both sexes (i.e. no difference is ever expected between male and female genetic structure in newborn offspring). In other words, sex-specific genetic structure must be recreated each generation. It is thus crucial to sample those individuals that survive the step where males and females differ from one another; otherwise, the ability to detect sex-specific genetic structure is reduced [6,7]. Detecting that crucial step where sex-specific genetic structure is recreated at each generation requires sampling individuals within cohorts and then comparing results from one cohort to the next.

Another way to infer sex-specific genetic structure comes from the comparison between markers with different mode of inheritance (e.g. uniparentally versus biparentally inherited markers) [6]. The justification of this approach is that, for uniparentally inherited markers [e.g. mitochondrial DNA (mtDNA) or Y-linked markers], one sex does not transmit them to its offspring. By contrast, for biparental markers, both sexes contribute to the genetic diversity of the progeny. In this respect, differences in the level of genetic structure between the two kinds of markers can be expected under certain conditions. For example, for species in which females are philopatric and males disperse, GENETIC DIFFERENTIATION between populations is expected to be higher when estimated using maternally inherited markers (e.g. mtDNA markers) than using biparental markers. However, such methods still raise many statistical and practical problems, and so need to be interpreted cautiously [6]. Indeed, differences in population differentiation between markers could also result from differences in their respective mutation rates, effective sizes and recombination rates (for review, see Ref. [6]).

Potential proximate factors

Sex-specific genetic structure is a pattern recurrently found in free-living organisms and particularly in vertebrates. Encountered in mammals [5,12], birds [13,14], reptiles [15] or fishes [16], it is generally due to sex differences in juvenile dispersal. Male mammals often disperse more than females [17], thus leading to a more uniform allele distribution among sub-populations in males than in females. Conversely, the opposite pattern is generally found in birds where females disperse more than males [18,19].

Parasite dispersal from one host or population to another occurs: (1) during free-living stages; (2) as passively carried by a host; or (3) through an active manipulation by the parasite of its host behaviour [20]. All these dispersal routes raise a possibility for a sex difference in migration, hence in population genetic structure. Sex-specific dispersal abilities in free-living stages of a parasite species are possible. Cases where immature male and female parasites differ in their preference among hosts with different mobility might also lead to sex-specific genetic structure. This phenomenon was assumed to explain the genetic patterns observed in *I. ricinus* [10]. Finally, we can speculate that a sex difference in host manipulation, where parasites induce host dispersal to achieve their own dispersal, should conduct to similar patterns.

Sex-specific genetic structure can also arise as a consequence of sex- and genotype-specific selection processes occurring during recruitment or establishment phases. Competitive exclusion between individuals of one sex could be one of these processes. For example, we suppose that individuals of one sex could have evolved mechanisms (e.g. ALLELOPATHY) to prevent the installation of either related or unrelated individuals. Indeed, Brown and Grenfell [21] demonstrated, with simulation models, the theoretical feasibility for established adult schistosomes to manipulate adaptively their host immune system to enhance the exclusion of larval competitors. Moreover, because of within-sex competition, they argued that induced immune responses might well turn out to be sex-specific, whether immunity targets kin or non-kin competitors. The resulting truncation of the genetic diversity of one sex would thus generate a sex-specific genetic structure. This hypothesis remains to be tested, but it is noteworthy that Prugnolle and collaborators [9] effectively observed a sex-specific genetic structure in *S. mansoni* that cannot easily be explained by sex dispersal differences *per se*.

Whatever the PROXIMATE FACTORS involved (sex-biased dispersal or competitive exclusion processes), a sex-specific

genetic structure is not a stable state in time because in offspring the difference between males and females does not exist anymore, given that they inherit randomly chosen alleles from their parents. Therefore, it is important to note that a sex-specific genetic structure is stable across generations only if the proximate factors operate recurrently at each generation.

Potential ultimate factors

Dispersal rate ultimately evolves as a compromise between costs (e.g. difficulty to find proper new sites, mortality during migration, non-acquaintance to foreign territories or mates), and benefits (e.g. avoidance of INBREEDING and/or kin competition) [22]. Sex-biased dispersal is thus expected as soon as the cost–benefit balance differs between sexes [23]. As such, if sex-biased dispersal prevents strong inbreeding in any case, other ULTIMATE FACTORS potentially interfere [23].

A sex difference in the intensity and/or susceptibility to LOCAL COMPETITION for mates or for resources is one of these factors [24]: the sex submitted the most to local competition would disperse the most. So, a male-biased dispersal could have been selected for in dioecious parasites in which male–male local mate competition is supposed to be strong (see, for example, Ref. [25]).

An alternative would be a sex difference in the susceptibility to dispersal costs [18]: the sex that benefits the most from its familiarity to its natal territory would disperse the least. This arises when philopatric individuals make better use of local resources (translated into higher fecundity) or have a greater probability to mate than immigrants of the same sex. Some parasitoids could be good candidates for this scenario in that finding a suitable host appears to be a formidable task [26]. When hosts are gregarious and confined to certain patches of the environment, it could indeed be advantageous for females to stay in the patch where they emerged (i.e. to evolve toward stronger PHILOPATRY than males). Co-operation and reciprocal ALTRUISM could also provide stronger philopatry benefits to one sex than to the other one when territory owners are less aggressive towards related than towards unrelated intruders (e.g. Ref. [27]; see, however, Ref. [28]). Here, local settlement is facilitated by acquaintance not with territory, but with relatives of the same sex. This mechanism was possibly assumed to explain why, within hosts, *S. mansoni* females are more related to one another than are males [9]. To confirm this hypothesis, it would be necessary to test whether settled *S. mansoni* females could disfavor the settlement of unrelated female competitors. Some parasitoid females are also known to defend hosts or sites containing hosts against conspecific females [26]. In such systems, aggressiveness could then be negatively correlated with relatedness, leading to the evolution of female philopatry.

Evolutionary and epidemiological implications

The evolutionary potential of a species is dependent on the extent and pattern of its genetic variations [29]. This seems particularly important for parasites that have to adapt continuously to their environment changes driven by their hosts along the permanent ARMS RACE that characterizes host–parasite interactions (see, for example, Ref. [30]). Sex-specific genetic structure, hence genetic differentiation between males and females within reproductive units, necessarily increases (if adults mate randomly) offspring heterozygosity relative to Hardy–Weinberg expectations [31]. This is likely to provide a parasite advantage in the arms race against the host by promoting the effects of two fundamental consequences of sex: (1) segregation; and (2) recombination. Such predictions underline the relevance to look for this pattern in dioecious parasite species.

Such a pattern might also profoundly modify the perception we have on the epidemiology of the concerned parasite: sex-specific genetic structure reflects sex differences in transmission (establishment, development, dispersal) or in host–parasite interactions. In this case, the epidemiology and the ecology of the parasite species considered should be analyzed by considering males and females separately. The same considerations relate also to vectors and associated pathogens. Indeed, if the vector displays sex-biased dispersal, we might suppose that some mechanisms will evolve in the transmitted parasite to prefer the sex that displays the most appropriate dispersal pattern. Thus, endemic stability and epidemic risk will not be dependent on the same sex.

Conclusion

Further research on parasites should now consider the possibility of sex-specific genetic structure, as well as the biological mechanisms that are likely to create this pattern. Indeed, we think that sex differences in genetic structure are likely to be widespread in parasites for three reasons. First, this pattern has repeatedly been detected in free-living organisms [6]. Second, it was detected in the two parasite species that were studied so far [9,10]. Third, the immunological interactions that characterize the host–parasite system are likely to reinforce this pattern. Methods and theoretical concepts described above should allow the determination of its genesis, importance and distribution among parasite species.

Acknowledgements

We thank François Renaud, Nicolas Perrin, Philippe Jarne and Patrice David for very useful discussions. Many thanks for the comments of four anonymous referees. This work has received financial support from the CNRS (PNDBE) and the MENRT (PRFMMIP n° 95).

References

1 Ennos, R. (1992) Ecological Genetics of Parasitism. In *Genes in Ecology* (Berry, R. *et al.*, eds), pp. 255–280, Blakewell Scientific Publication
2 Nadler, S.A. (1995) Microevolution and the genetic structure of parasite populations. *J. Parasitol.* 81, 395–403
3 Anderson, T.J.C. *et al.* (1998) Population biology of parasitic nematodes: applications of genetic markers. *Adv. Parasitol.* 41, 219–283
4 Badyaev, A.V. (2002) Growing apart: an ontogenetic perspective on the evolution of sexual size dimorphism. *Trends Ecol. Evol.* 17, 369–378
5 Favre, L. *et al.* (1997) Female-biased dispersal in the monogamous mammal *Crocidura russula*: evidence from field data and microsatellites patterns. *Proc. R. Soc. London B Biol. Sci.* 264, 127–132
6 Prugnolle, F. and De Meeûs, T. (2002) Inferring sex-biased dispersal from population genetic tools: a review. *Heredity* 88, 161–165
7 Goudet, J. *et al.* (2002) Test for sex-biased dispersal using bi-parentally inherited genetic markers. *Mol. Ecol.* 11, 1103–1114

8 Boissier, J. *et al.* (1999) A review of performance and pathogenicity of male and female *Schistosoma mansoni* during the life cycle. *Parasitology* 119, 447–454
9 Prugnolle, F. *et al.* (2002) Sex-specific genetic structure in *Schistosoma mansoni*: evolutionary and epidemiological implications. *Mol. Ecol.* 11, 1231–1238
10 De Meeûs, T. *et al.* (2002) Sex biased genetic structure in the vector of Lyme disease *Ixodes Ricinus*. *Evolution* 56, 1802–1807
11 Hartl, D.L. and Clark, A.G. (1997) *Principles of Population Genetics*, Sinauer Associates
12 Mossman, C.A. and Waser, P.M. (1999) Genetic detection of sex-biased dispersal. *Mol. Ecol.* 8, 1063–1067
13 Gibbs, H.L. *et al.* (2000) Limited differentiation in microsatellite DNA variation among northern populations of the yellow warbler: evidence for male-biased gene flow? *Mol. Ecol.* 9, 2137–2147
14 Piertney, S.B. *et al.* (1998) Local genetic structure in red grouse (*Lagopus lagopus scoticus*): evidence from microsatellite DNA markers. *Mol. Ecol.* 7, 1645–1654
15 Karl, S.A. *et al.* (1992) Global population genetic-structure and male-mediated gene flow in the green turtle (*Chelonia mydas*): RFLP analyses of anonymous nuclear loci. *Genetics* 131, 163–173
16 Knight, M.E. *et al.* (1999) Evidence for male-biased dispersal in lake Malawi cichlids from microsatellites. *Mol. Ecol.* 8, 1521–1527
17 Dobson, F.S. (1982) Competition for mates and predominant juvenile male dispersal in mammals. *Anim. Behav.* 30, 1183–1192
18 Greenwood, P.J. (1980) Mating systems, philopatry and dispersal in birds and mammals. *Anim. Behav.* 28, 1140–1162
19 Clarke, A.L. *et al.* (1997) Sex biases in avian dispersal: a reappraisal. *Oikos* 79, 429–438
20 Boulinier, T. *et al.* (2001) Dispersal and Parasitism. In *Dispersal* (Clobert, J. *et al.*, eds), pp. 169–179, Oxford University Press
21 Brown, S.P. and Grenfell, B.T. (2001) An unlikely partnership: parasites, concomitant immunity and host defence. *Proc. R. Soc. London B Biol. Sci.* 268, 2543–2549
22 Gandon, S. and Michalakis, Y. (2001) Multiple Causes of the Evolution of Dispersal. In *Dispersal* (Clobert, J. *et al.*, eds), pp. 155–167, Oxford University Press
23 Pusey, A.E. (1986) Sex-biased dispersal and inbreeding avoidance in birds and mammals. *Trends Ecol. Evol.* 2, 295–297
24 Perrin, N. and Mazalov, V. (2000) Local competition, inbreeding, and the evolution of sex-biased dispersal. *Am. Nat.* 155, 116–127
25 Sasal, P. *et al.* (2000) Sexual competition in an acantocephalan parasite of fish. *Parasitology* 120, 65–69
26 Godfray, H.C.J. (1994) *Parasitoids: Behavioural and Evolutionary Ecology*, Princeton University Press
27 Perrin, N. and Goudet, J. (2001) Inbreeding, Kinship, and the Evolution of Natal Dispersal. In *Dispersal* (Clobert, J. *et al.*, eds), pp. 123–142, Oxford University Press
28 West, S.A. *et al.* (2002) Cooperation and competition between relatives. *Science* 296, 72–75
29 West, S.A. *et al.* (1999) A pluralist approach to sex and recombination. *J. Evol. Biol.* 12, 1003–1012
30 Bremermann, H.J. (1980) Sex and polymorphism as strategies in host-pathogen interactions. *J. Theor. Biol.* 87, 671–702
31 Prout, T. (1981) A note on the island model with sex dependent migration. *Theor. Appl. Genet.* 59, 327–332
32 Goudet, J. (1995) Fstat (vers. 1.2). A computer program to calculate F-statistics. *J. Hered.* 86, 485–486
33 Hamilton, W.D. (1971) Selection of Selfish and Altruistic Behaviour in some Extreme Models. In *Man and Beast: Comparative Social Behaviour* (Eisenberg, J.F. and Dillon, W.S., eds) pp. 57–91, Smithsonian Institute Press
34 Paetkau, D. *et al.* (1995) Microsatellite analysis of population structure in Canadian polar bears. *Mol. Ecol.* 4, 347–354