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The convoluted evolution of snail chirality

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Abstract The direction that a snail (Mollusca: Gastropoda) coils, whether dextral (right-handed) or sinistral (left-handed), originates in early development but is most easily observed in the shell form of the adult. Here, we review recent progress in understanding snail chirality from genetic, developmental and ecological perspectives. In the few species that have been characterized, chirality is determined by a single genetic locus with delayed inheritance, which means that the genotype is expressed in the mother's offspring. Although research lags behind the studies of asymmetry in the mouse and nematode, attempts to isolate the loci involved in snail chirality have begun, with the final aim of understanding how the axis of left–right asymmetry is established. In nature, most snail taxa (>90%) are dextral, but sinistrality is known from mutant individuals, populations within dextral species, entirely sinistral species, genera and even families. Ordinarily, it is expected that strong frequency-dependent selection should act against the establishment of new chiral types because the chiral minority have difficulty finding a suitable mating partner (their genitalia are on the ‘wrong’ side). Mixed populations should therefore not persist. Intriguingly, however, a very few land snail species, notably the subgenus *Amphidromus* sensu stricto, not only appear to mate randomly between different chiral types, but also have a stable, within-population chiral dimorphism, which suggests the involvement of a balancing factor. At the other end of the spectrum, in many species, different chiral types are unable to mate and so could be reproductively isolated from one another. However, while empirical data, models and simulations have indicated that chiral reversal must

sometimes occur, it is rarely likely to lead to so-called ‘single-gene’ speciation. Nevertheless, chiral reversal could still be a contributing factor to speciation (or to divergence after speciation) when reproductive character displacement is involved. Understanding the establishment of chirality, the preponderance of dextral species and the rare instances of stable dimorphism is an important target for future research. Since the genetics of chirality have been studied in only a few pulmonate species, we also urge that more taxa, especially those from the sea, should be investigated.

Introduction

A coiled or spiral form has evolved in various groups of shelled organisms with an elongated shape, such as Foraminifera and the larval stages of caddis flies (Trichoptera). The organisms best known for their coiled form, however, are probably the Mollusca, especially the gastropod snails.

Although some of the external body parts of a snail, such as the head and foot, appear outwardly to be bilaterally symmetric, the manner in which the shell coils reflects a complex and highly asymmetric internal body structure, which originates from the earliest embryonic cell divisions. Development is further complicated during ontogeny by a torsion in which the visceral mass rotates by 180°, bringing the anus, genital opening and some other organs to an anterior position. Like all other helices, the body asymmetry of snails (and slugs) is chiral or ‘handed’. This means that it could come in two distinct forms that are each other's mirror image (Fig. 1). If the spiral twists clockwise when viewed from the shell apex, then it is right-handed or dextral (D); if it twists anticlockwise, it is left-handed or sinistral (S).

Although studies on snail coiling started in the early days of both embryology and genetics [10, 16], our understanding has only really begun to progress in the past few decades. A *Nature* paper by Vermeij [86] and a widely read popular science article by Gould [33] raised awareness

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Fig. 1 A sinistral (*left*) and a dextral (*right*) shell of the chirally dimorphic *A. inversus* from Southeast Asia (shell height approximately 4 cm)

of the evolutionary implications of snail chirality. A few years later, a seminal paper by Gittenberger [30] sparked a vigorous debate on the possibility that ‘single-gene’ speciation could occur due to a change in coiling direction. This then triggered several studies that used computer models to simulate whether this process was likely to occur in reality. These, in turn, appear to have set in motion empirical studies of reverse-coiled and mixed (dimorphic) populations. Latterly, our understanding of the developmental genetics of molluscan asymmetry has progressed, perhaps inspired by studies of asymmetry in other organisms [8, 9, 12].

Although snail chirality might be regarded as a topic of only parochial interest, it has important implications for the study of evolution, genetics and development. First of all, coil reversal in snails could be a route to reproductive isolation, and thus new species. Second, modeling of the population genetics of coiling alleles should have applications to the evolutionary biology of the many other genes with delayed inheritance. Finally, snail coiling could be a model with which to compare the developmental genetics of asymmetric structures in other animals, including ourselves [37]. In support of this, understanding chirality was recently cited as one of the remaining ‘big questions’ [46].

The aim of this review is to detail advances in the biology of snail chirality. Asami [2] concluded a similar review with five unanswered questions:

- Is dextrality always recessive in ordinarily sinistral species or groups?
- How has the dominance of sinistrality evolved?
- Are snails with unusual chirality subjected to structural distortion in general?
- Why is sinistrality rare in the sea?
- Why is shell shape associated with the pattern of mating behaviour?

Twelve years on, and over a hundred years since the first embryological studies [16], most of these questions remain unanswered, and several new and urgent ones have gained

prominence. Here, we deal with these issues by examining six main aspects of chiral reversal: (1) taxonomic and ecological distribution; (2) developmental genetics; (3) effect on mating behaviour; (4) persistence of chiral dimorphism; (5) speciation; and (6) reproductive character displacement. Rather than providing definitive answers, our review portrays a fascinating field of research that is bound to expand in the coming years.

The taxonomic distribution of sinistrality in snails

The vast majority of the approximately 70,000 living gastropod species are dextral, although the exact proportions are undetermined. Van Batenburg and Gittenberger [85] state, on the basis of data in Robertson [72], that the proportion is ‘far more than 90%’; Asami [2] goes even higher and estimates it to be more than 99%. Despite the overall rarity of sinistrality, however, variants are present at all taxonomic levels. Rare sinistral individuals are sometimes encountered in dextral gastropod species (e.g. in *Helix pomatia*: [55]) and vice versa [66] and are popular collector’s items, to the extent that forged specimens are sometimes offered for sale (Fig. 2; [26]). Less frequently, entirely sinistral populations have been reported [30], although some of these may have been misinterpreted. For example, the 2,000 sinistral *Cepaea nemoralis* from Holocene deposits in the UK probably refer to individual mutants among millions of dextral individuals, rather than a single contemporaneous population [80]. Sinistral species exist as either lone species within a dextral genus (e.g. *Busycon perversum*: [89]) or as groups of related sinistral species within a dextral genus (e.g. in *Diplommatina*: [68]). Finally, some genera and families are almost entirely sinistral (e.g. *Dyakia*: [47]; Clausiliidae: [62]).

Even without the benefit of recent molecular phylogenies (e.g. Wade et al. [87]), it is beyond doubt that reversal of chirality has occurred independently and frequently throughout the evolution of gastropods [4]. However, individual cases still have to be approached with some caution because chirality is occasionally defined by the coiling direction alone, without reference to the internal body asymmetry. In circumstances where the shell grows ‘upward’ rather than ‘downward’, shell coiling direction is reversed, but the body asymmetry is as normal. The condition is known as hyperstrophy [86]. There is even a ‘sinistroid’ genus, *Opisthostoma*, in which coiling direction appears to reverse during shell growth (Fig. 3; [7, 31]).

Stable intraspecific dimorphism for coiling direction is much rarer than sinistrality itself and appears to be associated with the mating position and the shape of the shell. Another pattern is that sinistral species tend to be more prevalent in groups with ‘high-spired’ shells than in groups with ‘low-spired’ shells [2, 4, 30, 56]. Since there are several other tendencies in the distribution of coil reversal, we discuss possible causes for these patterns later. Because it is impossible to understand snail chirality without reference to genetics, we first give an overview of the inheritance of asymmetry.

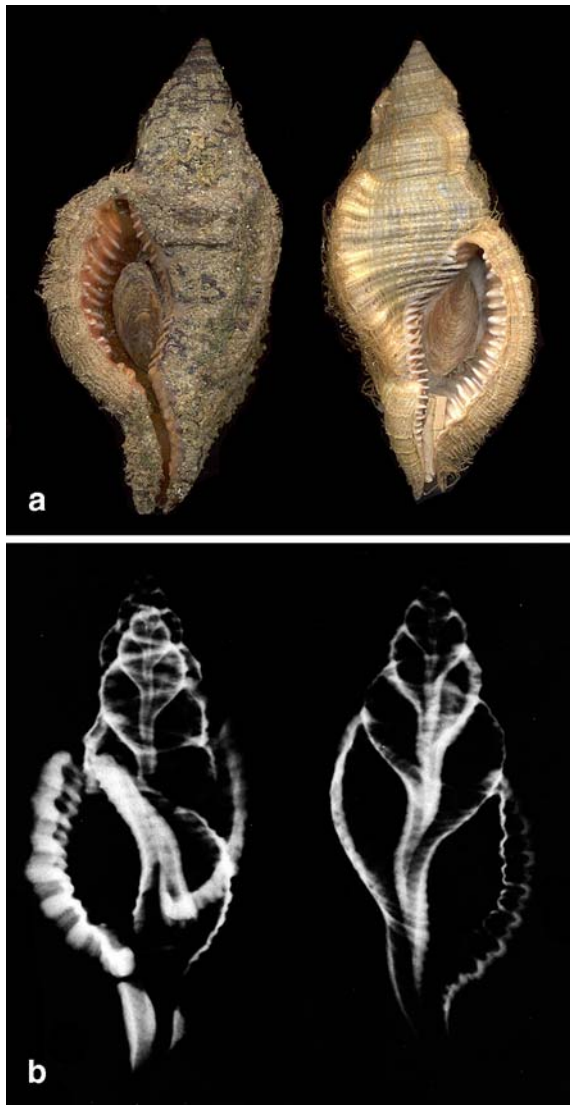


Fig. 2 a A normal specimen of *Cymatium pileare* (right) and a forged sinistral specimen (left) from the Philippines. The X-ray image of the same specimens (b) shows how fragments of the spire and an upside-down aperture have been used to create the forgery. Photos: H. G. Lee and W. Frank

Genetics and development of chirality

The study of the inheritance of asymmetry in snails had an important role in the early history of Mendelism. In the 1920s, Boycott and Diver [10] observed that shell coiling in the pond snail *Lymnaea peregra* was a hereditary character, although the patterns of variation in the offspring were difficult to understand, requiring a complicated model to fit the data. In a now famous example of predictive thinking, Sturtevant [79] prophesied that the apparently aberrant patterns of inheritance were because the expression of the gene is delayed by a generation. When the crucial experiments were carried out, Sturtevant's 'inspired guess' proved to be correct [11, 23]. The chromosomal locus that determines asymmetry acts via a maternal effect,



Fig. 3 The 'sinistroid' shell of *Opisthostoma lituus* from Borneo (shell height approximately 2 mm). Artist: J. J. Vermeulen

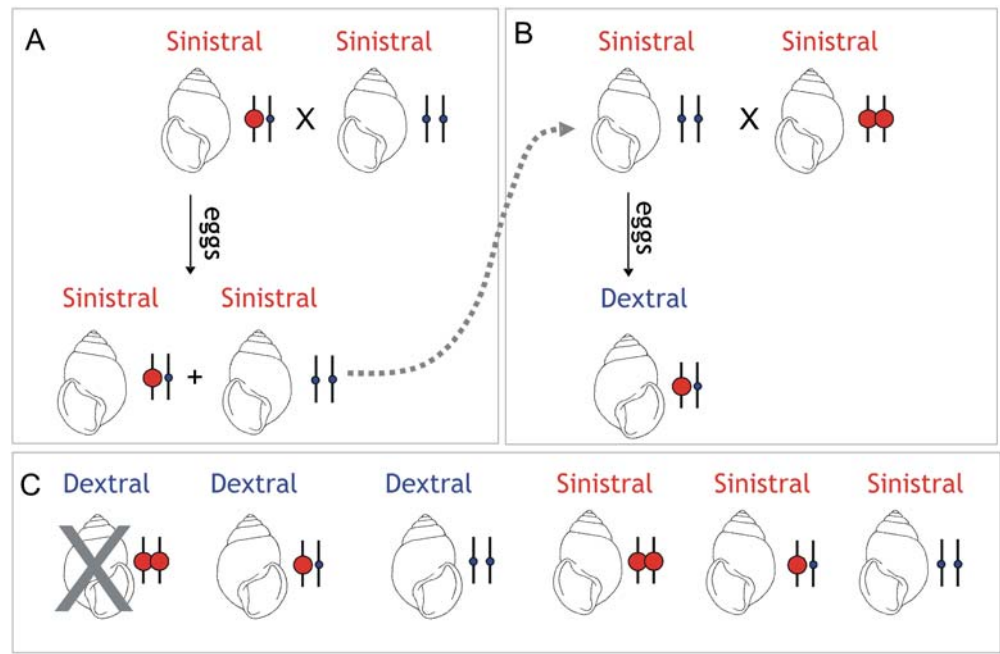
so the direction of coiling in the offspring is dictated by the genotype of their mother (Fig. 4).

In the snails that have been investigated, dominance is variable: dextral is dominant in *L. peregra*, *Lymnaea stagnalis*, *Bradybaena similaris* and *Partula mirabilis* that have been crossed with *Partula olympialtohiveana* [10, 27, 60, 77, 79, 81], but sinistral is dominant in *Partula suturalis* and *Laciniaria (Balea)* [21, 59].

In the ensuing years, the same pattern of delayed inheritance has been shown to occur in all the snails that have been examined, although the total number is still rather few. It has also been established that rare reversed individuals can sometimes arise from accidents during development, which might explain some of the sporadic cases that have been discovered in otherwise invariant species (e.g. Bantock et al. [5]). To date, *Lymnaea* has remained the most popular genus in which to investigate the genetics and embryology of the establishment of asymmetry, not least because its husbandry is relatively simple and because it has translucent eggs that lack a hard shell. There are now also some hundreds of *Lymnaea* genes in the genetic databases, which could be used to identify candidate genes or for linkage mapping [18]. *Lymnaea* is also relatively closely related to *Biomphalaria glabrata*, which is scheduled to be the first mollusc to have its genome sequenced.

Recently, steps towards understanding the establishment of asymmetry have been made by Kuroda et al. in Japan and Gittenberger et al. in the Netherlands. The strategy of the former has been to cross dextral and sinistral strains, then follow the inheritance of candidate gene markers to see if they co-segregate with the asymmetry locus (no promising contenders have been reported so far; see Harada et al. [35], Hosoiri et al. [38]). The Kuroda group has also used microscopy to investigate the very early stages of the establishment of asymmetry; contrary to prior belief, the early cytoskeletal dynamics of dextral and sinistral snails are not mirror images of one another [77].

Fig. 4 Inheritance of coiling direction: the genotype of a mother snail is not expressed until the next generation, i.e. in the offspring. For the purposes of illustration, we assume that sinistral alleles (*large red circles*) are dominant over dextral alleles (*small blue circles*). For simplicity, the offspring of only one hermaphroditic partner is shown. **a** Due to the maternal effect, all outcrossed offspring of a heterozygous mother will be sinistral, regardless of their genotype. **b** An outcrossed sinistral homozygous recessive mother (DD) will produce all dextral offspring. **c** Only five combinations of genotype and phenotype can exist: dextral individuals that are SS homozygotes are impossible since the mother must have carried the dominant S allele



In contrast, the strategy of the Gittenberger group was to select six candidate asymmetry genes from nematodes and chicken, reasoning that they would probably be conserved in snails [37]. Interestingly, five of the six genes were unequally expressed in sinistral and dextral lines of *L. stagnalis*, with the most prominent differences in the reproductive tissue. Although these results are not unexpected, they indicate that some of the early development genes in snails are in common with the same genes in nematodes and chickens, even though the overall modes of development are different (development is spiralian in molluscs, 'idiosyncratic' in nematodes and radial in deuterostomes; Valentine [83]). However, the precise role of these genes in establishing snail asymmetry remains undetermined because Hierck et al. [37] did not control for genetic differences between strains. As an aside, it is presently unknown if the inheritance of asymmetry in other Spiralia (e.g. Annelida and Platyhelminthes) is the same as in molluscs.

Although there have been several investigations into the genetics of asymmetry in *Lymnaea* [10, 11, 22, 23, 35, 38, 79], and some embryological studies [16, 77], there have been few attempts to integrate the genetic data with the embryology. The exceptions are Freeman and Lundelius [27] and Asami [2]. The former gave evidence that the maternal effect of the asymmetry gene is determined by a factor that the mother deposits in the unfertilized egg. When egg cytoplasm from dextral *L. peregra* was injected into eggs from a sinistral mother, the receiving eggs developed dextrally. In contrast, the reciprocal experiment did not change the asymmetry, presumably because in recessive sinistral homozygote mothers, the factor is lacking, or mutated, so it does not function [27]. It has generally been assumed that the factor is an RNA, which is then transcribed into a protein in the egg (hence the attempts by Harada et al. [35] to isolate candidate genes by

differential screening), but conceivably, it could also be a mature protein or other signalling molecule.

One intriguing feature of asymmetry is that homozygous recessive *L. peregra* sometimes give birth to broods that contain a few percent of the opposite coiling direction, some of which then give birth to further snails of that coiling direction. As at least a proportion of the new dextrals in *L. peregra* seem to have, in some way, 'reconstituted' a fully functional and stably inherited dextral gene [11, 22, 27], this is a peculiar result. If asymmetry is determined by a single gene of maternal effect, then a homozygous mother should never give birth to mixed broods. The observation also may be a general one because there is some evidence for mixed broods in other snails: *Laciniaria (Balea)* and *L. stagnalis* occasionally produce sinistrals and dextrals within the same clutch ([21]; Gittenberger, personal communication). In *Partula*, mixed broods are infrequent but seem to be associated with sites where there is evidence of interspecies hybridization [45]. In *L. stagnalis* and *P. suturalis*, it is not known if the effect is heritable, but in the latter, the genetic context is important in generating the mixed broods, just as in *L. peregra* [22, 45].

To attempt to explain the phenomenon of mixed broods in *L. peregra*, Diver and Andersson-Kottö [22] proposed that a series of modifiers are able to 'convert' the recessive sinistral allele so that it produces dextral phenotype. In contrast, Freeman and Lundelius [27] proposed that the asymmetry locus is made up of more than one gene, and so is effectively a 'supergene'. This latter explanation makes sense because other developmental genes, such as the homeobox cluster, tend to group together on the same chromosome. However, the explanation is also rather complicated because both meiotic and mitotic crossovers were required to recreate the wild-type dextral supergene in the correct proportions [27].

In light of recent developments, we would like to add a final, albeit unlikely, explanation for mixed broods. Lolle et al. [52] have shown that in *Arabidopsis* plants that are mutant for *HOTHEAD*, gene sequences are inherited in a non-Mendelian manner. Offspring are, in some way, able to stably reintegrate a gene that was not present in their parents, although the template that is used to restore the original DNA sequence is unknown. The results in *Arabidopsis* bring to mind the mixed brood studies in *L. peregra*: perhaps the snail gene in the egg that determines asymmetry in developing pond snails can also be inherited in a similar unorthodox manner.

Another important but neglected issue is the function of the asymmetry gene during later development. As mentioned earlier, Shibazaki et al. [77] have recently shown that early dextral and sinistral embryos of *L. stagnalis* are not exact mirror images of one another. While this is a novel observation, it has been known for some time that in other species, adult shells are not always exact mirror images, which means that the asymmetry locus has a pleiotropic effect [34, 43]. In the land snail *Cerion*, sinistrals are rare, and it is unknown whether they arise due to accidents of development or due to a mutation in the asymmetry gene. Gould et al. [34] showed that the final whorls of the shell and size and orientation of the aperture are extreme in sinistral *Cerion*. Similarly, sinistral *P. suturalis* shells tend to be shorter and squatter than dextral shells [34, 43, 45]. As the direction of coiling and shell shape are disconnected (the coiling direction is determined by the mother's genotype, whereas the shape of the shell is controlled by the genotype of the snail itself), this means that the asymmetry gene product has a pleiotropic effect beyond the establishment of asymmetry. Observations of a similar nature have been made recently in *Bradybaena* and *Achatinella* [3]. Pleiotropic effects have also been noted for many genes implicated in the deuterostome left–right asymmetry [54].

Except for the problem of mixed broods, the mutant gene in snails causes a complete switch in asymmetry, owing to the maternal effect, in contrast to other animals where most mutations randomize asymmetry (e.g. *iv*; see McManus [54]). In the mouse, it has been argued that in a mutant, the molecular gradient that ultimately determines asymmetry is absent, so that stochastic differences decide the asymmetry. The *inv* mutation is exceptional because of the way it is believed to act: it affects ciliary function, so a gradient is created in the opposite direction, and all embryos have reversed asymmetry [54, 64]. It seems possible that the mutation could also act in an analogous manner in snails. However, if the distribution of the determining molecule is a mirror image in an egg from a mutant mother, then this limits the methods that can be used to isolate the gene. Finally, the manner in which the gene functions will also affect the dominance relations between different alleles. Asami [2] pointed out that if sinistral is dominant (as in *P. suturalis*), then the mutation is not likely to be the inactivation of a dextral allele. Moreover, if asymmetry is due to a molecular gradient, then a dominant sinistral allele might evolve if its effect is to reverse the gradient. Another

means to achieve sinistral dominance might be if a sinistral allele has a product that binds more strongly to a receptor site than a dextral allele.

Although *Lymnaea* is probably the best taxon in which to investigate the establishment of chirality, we would like to correct the impression that sinistral individuals are relatively common (e.g. see Wandelt and Nagy [88]). Although they are known as fossils from several paleontological strata [69], most populations ordinarily do not contain sinistrals, or else do so at a very low rate. Those that do contain a low proportion of sinistrals were described many years ago and have subsequently been lost: of the original sites in the UK that contained sinistral *Lymnaea*, many were filled in, polluted or else the snails are extinct. Perhaps as a consequence, only one strain of *L. stagnalis* is currently in circulation. The wild stock was collected by Gerhard Falkner in the Danube valley and was sent to the Gittenberger laboratory [37]. Subsequently, sinistrals from the same strain were used by the Kuroda Laboratory for their experiments [35, 38, 77]. Similarly, the *L. peregra* strain used by Freeman and Lundelius [27] is no longer in Texas, but was donated recently to the Kuroda Laboratory. If the research on sinistral *Lymnaea* is going to progress, then it would be wise to broaden the range of available cultures since they may all contain independent mutations of chirality loci.

Interchiral copulation

Any discussion on the evolutionary genetics of chirality hinges on the degree of reproductive success of mating between individuals with opposite coiling direction (interchiral mating), relative to that between individuals with the same coiling direction (intrachiral mating). For convenience, we will use a parameter α to refer to the degree of interchiral mating isolation ($\alpha=1$, no interchiral mating; $\alpha=0$, random mating; see also Davison et al. [19]).

A dextral individual has its genital opening on the right-hand side of the body, and a sinistral on the left-hand side. While the helical fibres of the sperm may be unaffected (as in *L. peregra*; [76]), coiled structures of the genitalia themselves are also reversed in individuals of opposite chirality (e.g. the coiled penis in *B. similaris*—Asami et al. [4]; the spiral shape of the flagellum in *Amphidromus*—Schilthuizen, unpublished data). Lipton and Murray [51] and Asami et al. [4] have indicated that even the choreography of mating behaviour is mirror-imaged between dextral and sinistral individuals of *P. suturalis* and *B. similaris*, respectively.

It has therefore been known for some time that the asymmetry can create insurmountable barriers to interchiral copulation in certain species. Meisenheimer [55] confined a sinistral and a dextral individual of *H. pomatia* in a container and observed that ‘for days and weeks the animals fatigue each other in courtship, without achieving a final copulation’. Likewise, Hesse [36] recorded that interchiral copulation is impossible in *H. pomatia* as well as in *Helix aspersa*, and Janssen [41] reported the same for

a third helicid, *Arianta arbustorum*, after several months of attempts. Finally, Ueshima and Asami [81] stated that two *Euhadra* (Bradybaenidae) chiral morphs failed in interchiral copulation despite frequent attempts. Even in chiral slugs, interchiral mating can be hindered [70].

A quantitative study was carried out by Asami et al. [4], who described two sets of no-choice tests in the bradybaenid *B. similaris*. In the first set, one virgin sinistral, taken from the wild, was presented with three consecutive dextral virgin partners and observed for 2 weeks per pair. All attempted interchiral copulations failed ($\alpha=1$). Although a few one-way penis insertions were seen, in these, the spermatophore came out with the penis. In the second set of experiments, laboratory-reared sinistrals and dextrals were paired as 23 DS (i.e. dextral \times sinistral), 22 DD and 16 SS pairs for 1 week. Almost all intrachiral pairs copulated successfully and reciprocally (18 of 22 DD pairs, 15 of 16 SS pairs), whereas only 4 of the 23 DS pairs achieved one-way copulation, again without the spermatophore being retained. In contrast, in intrachiral pairs, penis insertion (and presumably spermatophore transfer) was unsuccessful in just 10% of the attempts. Subsequently, it has been shown that interchiral pairs of *B. similaris* produce few or no fertile eggs, most of which are probably due to selfing [81].

These studies suggest that interchiral copulation may be near impossible. However, Asami [2] and Asami et al. [4] pointed out a previously unnoted dichotomy in the mating behaviour of land snails. Whereas low-spined groups like *Helix*, *Arianta*, *Bradybaena* and *Euhadra* mostly mate in a ‘face-to-face’ position, the majority of high-spined snails mate by ‘shell mounting’, with the shells aligned in parallel. It is in members of this latter group that interchiral mating appears to be less inhibited.

Among such high-spined snails, the most detailed data on interchiral mating and fertilization success are available for *P. suturalis*. Murray and Clarke [58, 59] reported that interchiral copulation was observed between captive individuals, and they also refer to unpublished field data of assortative mating by coiling direction [14, 60]. However, the only published, quantitative data in *Partula* are from laboratory experiments by Johnson [42]. He created pairs of virgin or sperm-depleted individuals (26 DS, 14 DD and 20 SS pairs) and, over 3 months, observed them during regular intervals. About half of the intrachiral pairs were seen to mate successfully (6 of 14 DD pairs and 9 of 20 SS pairs). Of the interchiral pairs, however, only 12% (3 of 26) mated successfully, although the frequency of courtship was the same for all categories ($\alpha\sim 0.74$). Asami et al. [4] studied Johnson’s data and concluded that successful penis insertions were about as frequent as unsuccessful ones in intrachiral pairs. However, they were ten times as rare as successful ones in interchiral matings. Johnson [42] reported that, over the year following copulation, interchiral pairs had a 28% lower reproductive output compared with intrachiral pairs. He also noted that in populations with a low frequency of sinistrals, sinistrals have 41% lower fecundity compared with the dextrals.

Anecdotal reports on copulation in other groups of high-spined snails also suggest that α is usually >0 but <1 . Degner [21] reported five interchiral copulations in the clausiliid *Laciniaria (Balea) biplicata*. Nordsieck [63] mixed equal proportions of dextral and sinistral individuals of several species of the clausiliid *Alopiia* and reported that out of ‘about 20’ observed copulations, 3 involved interchiral pairs and were apparently ‘normal.’ (In contrast to these observations, however, Giokas et al. (unpublished data) report that in the clausiliid *Albinaria*, allospecific copulation attempts were successful in intrachiral species pairs, but unsuccessful in interchiral pairs.) Freeman and Lundelius [27] observed successful interchiral mating in the similarly high-spined *L. peregra*.

There is one intriguing exception to the general pattern of reduced interchiral mating success. Schilthuizen et al. (unpublished data) observed 65 mating pairs of the high-spined camaenid *Amphidromus inversus* in the field (20 SS, 33 DS and 12 DD) and found that the numbers of interchiral and intrachiral pairs were as expected under random mating ($\alpha=0$). This genus is unusual among high-spined snails in mating in a face-to-face fashion (Fig. 5), which ordinarily means that interchiral copulation is impossible (see below for further discussion regarding *Amphidromus*).

The data so far indicate that, in general, low-spined, reciprocally face-to-face mating snails suffer severe impediments to interchiral copulation, whereas these impediments are, to an extent, relaxed in high-spined, shell-mounting, non-reciprocally mating species [2, 19]. It is unknown which of the factors (shell shape, mating position and degree of reciprocity) is the more important one; the correlations are difficult to untangle since most have arisen due to shared ancestry [20, 87]. At present, the data on interchiral reproductive success involve only



Fig. 5 An interchiral copulation in *A. inversus*. Actual shell height approximately 4 cm. Photo: B. J. Scott

stylommatophoran land snails. Similar data from terrestrial Neritopsina or Caenogastropoda, or externally fertilizing marine snails, are lacking.

Coil dimorphism

Given the ordinarily reduced interchiral mating success ($\alpha > 0$), individuals (of a non-selfing species) that have a coiling direction opposite to that of the majority of the population will experience difficulty in finding a mate. As a consequence of this selection, dimorphism in a single population is not a stable situation, and populations will tend to be driven to monomorphism for the commonest morph [85], usually determined by the dominant allele [44, 53]. The field data necessary to evaluate whether morphs coexist are available for only a few taxa. Asami et al. [4] mentioned 13 genera in which such dimorphism occurs. However, in many of these, it is either restricted to local populations (e.g. in *Lymnaea*) or is a cline between a dextral and a sinistral population (e.g. *P. suturalis*; Johnson [42]). True dimorphism is very rare indeed and may be restricted to just a few groups (possible candidates are *Achatinella*, *Amphidromus*, *Auriculella*, *Corona*, *Liguus* and *Partulina*; Asami, personal communication).

Probably the best known of these groups is the tree snail *Amphidromus* sensu stricto (Camaenidae). Thirty-six species are currently included in this subgenus, of which 28 are dimorphic, 4 dextral, and 1 sinistral; coiling direction is unknown for the remaining 3 species (data assembled from Laidlaw and Solem [48, 50, 67]; Maassen, personal communication; Asami, personal communication). Observations on several dimorphic *Amphidromus* species from Malaysia and Singapore (Craze et al., unpublished data) suggest that dextrals and sinistrals normally occur in roughly equal proportions within local populations.

Even though recent data on mating in *A. inversus* (see above) suggest that there is random mating among dextral and sinistral individuals ($\alpha = 0$), the widespread dimorphism, which appears to be present even in very small populations (Panha, personal communication), suggests that a balancing factor must maintain it [4, 30]. Although the cause is currently unknown, several explanations may be imagined, both extrinsic and intrinsic.

In the first category, the positive frequency-dependent selection against the rarer morph could be counteracted by a negative frequency-dependent selection, mediated by an environmental factor. Predators may set their search image or their routine way of prey handling by the most common morph, and this negative frequency dependence may maintain both morphs in the population. This explanation is not completely implausible, as both handedness and preferences for one morph among chirally diverse prey have been observed in various molluscivores (e.g. Ng and Tan [61]; Inoda et al. [40]). The problem though is that this explanation is not likely to be simultaneously applicable to the almost 30 species inhabiting a variety of habitats in a region spanning a large part of South and Southeast Asia.

An alternative explanation might be if *Amphidromus* has an extreme population structure, so that individual morphs are maintained in separate tree-sized subpopulations. However, Schilthuizen et al. [75] found random dispersion of dextral and sinistral individuals of *A. inversus* down to the smallest spatial scale, with no indication of morph clustering, indicating that population structure cannot explain the persistence of both types on its own.

In the second category, the dimorphism could be maintained because there is a low but significant excess of interchiral mating ($\alpha < 0$), or interchiral pairs tend to produce more offspring. Hitchhiking (as suggested by Laidlaw and Solem [48]) can be excluded because recombination will tend to dissociate the chirality gene and the selected gene [19]. However, heterosis remains a possibility, but it would have to be associated with the chirality gene itself [48].

Speciation

Although the obstacles to interchiral mating in snails had been known for some time, the suggestion that chirality might play a role in speciation did not achieve prominence until the late 1980s. Gittenberger [29] originally posed the hypothesis that snail chirality can drive sympatric speciation, and Alexandrov and Sergievsky [1] published the same idea independently, but a full speciation model was only developed 10 years later. Then, Gittenberger [30] presented a scenario in which a recessive S-allele drifts to a relatively high frequency in a small, dextral population. Eventually, dextral SS homozygotes produce clutches of sinistrally coiled offspring, owing to the delayed inheritance. Intrachiral mating among the sinistrals could then result in the loss of the D-allele from the sinistral part of the population, so the two types would be reproductively isolated and therefore different species.

Although the model appears straightforward, it has proved to be controversial for several reasons. First, it was explicitly presented as a sympatric model: the new, reproductively isolated morph arises from within the ancestral population, which, in the 1980s, was still widely considered to be an unlikely scenario for speciation [28]. Second, it is a 'single-gene' speciation model [65], whereas speciation is expected normally to require at least two genes that accumulate incompatibilities independently (the so-called Dobzhansky–Muller model of reproductive isolation, developed by Bateson [6], Dobzhansky [24] and Muller [57]).

Two factors might relax the conditions in land snails to enable sympatric single-gene speciation [30, 65]. First, demes in land snails could be very small, of the order of tens of individuals (see, for example, Schilthuizen and Lombaerts [74]), which might allow the new allele to drift to high frequencies in spite of frequency-dependent selection. Second, the delayed inheritance might allow frequencies of the new allele to rise in a small population because all broods from the same mother will have the same coil.

However, the delayed inheritance could also mean that gene flow may continue between the dextral and sinistral subpopulations, even if different chiral types are unable to mate ($\alpha=1$).

These complexities make the outcome of the model hard to predict without the help of computer simulations. Johnson et al. [44] were the first to carry out such simulations. Motivated chiefly by the perceived improbability of sympatric modes of speciation, they used field data from *P. suturalis*, a species with stable coil dimorphism, to select the necessary parameters. They then simulated a single dimorphic population, in which a very low frequency of the sinistral allele was present in the dextral subpopulation and vice versa. In the absence of positive frequency-dependent selection, $\alpha=1$, and an infinite population size, the population reached an equilibrium in which a large proportion of the dextral allele was present in the sinistral subpopulation and vice versa. To examine the effect of frequency-dependent selection, they then modeled a linear arrangement of demes connected in a stepping-stone population structure. They found that with positive frequency-dependent selection, an initial cline in morph frequencies will tend to move in favour of the genetically dominant allele, except under very narrow conditions of selection and migration (see Mallet [53] for a similar result). Hence, Johnson et al. [44] concluded that ‘chirality is particularly unlikely to serve as the basis for sympatric speciation’, especially in *Partula*.

In a separate reaction to Gittenberger [30], Orr [65] emphasized the small population size and fragmented population structure of many land snail species. He modeled isolated demes of 8–20 either gonochoristic or hermaphroditic individuals (the latter allowed 5% selfing) and specified that a single mutation was sufficient to change chirality. He found that with $\alpha=1$, delayed inheritance increased the likelihood of fixation of the new allele by an order of magnitude compared with normal, zygotic inheritance. For the smallest demes, the chance of fixation was 2–4%. It was also rapid, taking roughly $2N_e$ generations (where N_e is the effective population size). Although it might be imagined that selfing could also promote single-gene speciation, it did not make an appreciable difference in Orr’s model. He concluded that if snail populations are as subdivided as is often assumed, then single-gene speciation should be fairly common because genetic drift will lead inevitably to the fixation of alleles in small populations, adding that Johnson et al. [44] might have reached the same conclusion had the populations in the simulations been of finite size.

A much larger simulation study was subsequently carried out by Van Batenburg and Gittenberger [85]. Among other things, they explored the influence of N_e , α and genetic dominance. They found that the fixation probability of a mutant allele would be highest if N_e values were small, the mutant allele was dominant and the number of introduced mutants was high. However, overall fixation probabilities were low compared with the simulations by Orr [65]. For example, fixation probability was just 2% for

a deme of 16 individuals into which four heterozygotes were introduced, each carrying one copy of the dominant allele, and $\alpha=0.75$.

In a more recent simulation study, Stone and Björklund [78] paid particular attention to α by allowing it to evolve on the basis of loci for shell shape (ranging from ‘stout’ to ‘slender’). They also incorporated a more complex population structure by simultaneously simulating five randomly placed demes within a 20×20 unit grid with distance-dependent migration among the demes and incorporating conchological variation among and within demes as a starting condition for the simulations. All demes were dextral, but a single recessive sinistral mutant allele was introduced into each deme at the start of a simulation run.

The results from a large number of 100-generation runs showed frequent coil reversal (20% of all runs) and a strong influence of migration in shaping the coil and shell differentiation among the demes. Unfortunately, the biological details of the model may not be very realistic, so the relevance may be limited. Shell shape is more likely to be affected by stabilizing selection [13, 32], so that it cannot evolve freely under the pressures of interchiral mating. Nonetheless, the model may yet provide a good basis for more realistic simulations once further details of chirally dimorphic systems become available.

Overall, the simulation studies indicate that populations fixed for an alternative coiling allele may occasionally become established. They differ instead in the degree in which they argue that it is possible. The crucial parameter to highlight is α . The simulations by Van Batenburg and Gittenberger [85] show that fixation of a new chiral morph is most likely when α is relatively low because the inhibiting role of positive frequency-dependent selection is reduced. The evidence therefore supports the hypothesis of Gittenberger [30], Asami [2] and Asami et al. [4] that chiral reversal (which, in these groups, does not equate with speciation) is more likely to occur in high-spired species.

In contrast, the best candidate snails for single-gene speciation must be low-spired species in which reverse-coiled individuals are completely unable to mate ($\alpha=1$). If dextral individuals are all DD homozygotes and sinistral individuals are all SS homozygotes, then gene flow between them ceases. Recently, Ueshima and Asami [81] have used evidence from a mitochondrial DNA phylogeny to propose that *Euhadra* species from Japan may have evolved by single-gene speciation. They found that a dextral species *Euhadra (senckenbergiana) aomoriensis* is nested within a clade of sinistral *Euhadra quaesita*. Their explanation was that a chiral mutation must have taken place in *E. quaesita*, so that newly arising dextral individuals were unable to mate with normal *E. quaesita* and were thus reproductively isolated from them. Instead, using a larger mtDNA dataset, Davison et al. [19] argued that another and equally plausible interpretation of the phylogeny is that the mitochondrial genes have introgressed between species. The confounding factor is that while it is the maternal inheritance of the chirality gene that

could promote single-gene speciation, it also causes gene flow to remain possible between different morphs even if they are unable to mate.

To clarify the conditions under which single-gene speciation or gene flow might occur, Davison et al. [19] developed a mathematical model. They found that two equilibrium conditions are possible. In the first, gene flow remains substantial between morphs, even with $\alpha=1$, because of the delayed inheritance. In the second, where all dextral individuals are DD homozygotes and all sinistral ones are SS homozygotes, reproductive isolation is present. This second equilibrium is, however, unstable and will revert to the first equilibrium (gene flow) if intrachiral matings occasionally produce offspring with the opposite chirality. A further possibility was that selection could operate against hybrids between chiral morphs because genetic differences leading to postmating isolation might be held in disequilibrium with the chiral gene itself, preventing introgression. However, evidence from the model suggested that disequilibrium is unlikely to build up in sympatry, but if two different morphs met after a period of allopatry, then the populations could fall into an equilibrium where gene flow is reduced, and so maintain the initial association. Nonetheless, even in this extreme circumstance, the model showed that for all but very strong assortment ($\alpha \gg 0.99$), there should still be high gene flow between morphs.

Determining whether single-gene speciation has occurred in *Euhadra* will depend on determining the phylogeny at several nuclear loci. More generally, the results from the model suggest that speciation that is associated with chiral change will tend to involve other factors, such as ecological selection or the accumulation of additional reproductive incompatibilities in allopatry. While it is beyond doubt that chiral change may be a contributing factor in snail speciation events, a convincing case of true single-gene speciation has yet to surface.

In conclusion, we wish to emphasize that, even though simulations show the high likelihood of the appearance of reverse-coiled populations, full reproductive isolation is unlikely. Although a degree of gene flow may not be a problem for some models of speciation, because selection on linked genes can overcome the genetic 'leakage' [15], the situation is different for the coiling gene because the phenotype is decoupled from the corresponding genotype. Other genes will thus be prevented from co-segregating with the phenotype that permits the reproductive isolation. Hence, any optimism for single-gene speciation by coil reversal may not be warranted by the population genetics involved.

Reproductive character displacement

Even though a change in coiling direction may not be a crucial factor in snail speciation, it could act as a mechanism to reduce mating between closely related species. A convincing example of such reproductive character displacement is known from *P. suturalis*. Although both

dextral and sinistral species of *Partula* occur on the island of Moorea, the only commonly dimorphic species is *P. suturalis*. The central and southern parts of the island have dextral populations of this species, whereas sinistral populations live in the northeastern and northwestern portions of Moorea [17]. Narrow (400–1,600 m wide) zones of dimorphism occur between these blocks. Clarke and Murray [14] noted that in the west, the transition zone, at a distance of 100–400 m, runs parallel to the edge of the distribution area of the sinistral *Partula mooreana*, which is closely related to *P. suturalis*.

Clarke and Murray [14] argued that the populations of *P. suturalis* have become fixed for the dextral allele in response to selection against hybridization with the sinistral *P. mooreana*. The fact that the transition zone begins only a few hundred metres away from the edge of *P. mooreana*'s range is presumed to be the result of positive frequency-dependent selection within the dimorphic area, which will steepen the cline on both sides. The hypothesis was strengthened by Murray and Clarke [60], who gave evidence for reduced *P. suturalis* × *P. mooreana* hybrid fitness. They also showed that the eastern monomorphic sinistral *P. suturalis* coexists with dextral *Partula aurantia*, and dextral *P. suturalis* with sinistral *P. olympia/tohiveana*; therefore, a similar process of reproductive character displacement may have taken place there.

The same explanation could apply to many instances of species co-occurring with related species of opposite coiling direction. These include cases in *Euhadra* [19, 81], *Isabellaria* [82], *Alopi*a (Szekeres, personal communication) and *Diplommatina* [68]. It may also be an explanation for the apparent trend for sinistral species to be linked to insular habitats (Lee, personal communication), as many related species will coexist there.

Although coil-related reproductive character displacement was first suggested some years ago, the process lacked theoretical support. A model within Davison et al. [19] was used recently to show that a new morph would be at an advantage even when rare, if at least a third of all matings were otherwise with another species. Moreover, if the new allele is dominant, then it will tend to increase because of 'dominance drive' [44, 53]. In these circumstances, a new allele could be fixed rapidly and begin to spread out from the region in which the ancestral morph was abundant. However, since dextral is recessive in *P. suturalis*, then dominance drive would tend to act *against* the establishment of a new dextral morph.

Conclusion

Asami [2] concluded his review on genetic variation and evolution of coiling chirality in snails with several questions (see above). The first three of these (Is dextrality always recessive in ordinarily sinistral species or groups? How has the dominance of sinistrality evolved? Are snails with unusual chirality subjected to structural distortion in general?) relate to the genetics and development of coiling. Although in this review we describe how the dominance

and recessiveness of both dextrality and sinistrality appear to vary among taxa, it is clear that a meaningful discussion will only be possible once the details of the genetic basis have been uncovered. We therefore eagerly await the promising developments from the work on *Lymnaea*. Once the gene(s) have been characterized, their expression can be followed through ontogeny, and this may explain if and why developmental defects occur in individuals with a reversed chirality. Once the nature of the expression pathway is known, dominance and recessivity may also be better understood. We therefore hope that the insight gained from *Lymnaea* will deepen in the coming years. At the same time, data on the genetics of coiling need to be broadened across more than the few taxa for which they are presently available. This means investigating not just more pulmonate species, but also other snail and slug taxa. The Pulmonata, although species-rich, are only one clade in the wide phylogenetic diversity of the Gastropoda. As far as we are aware, studies into the genetics of coiling have never been carried out in the terrestrial Neritopsina and Caenogastropoda or in any of the many groups of marine gastropods.

This brings us to Asami's fourth question, the presumed rarity of sinistrality in the sea [2]. Judging from the number of shell dealers that offer sinistral specimens for sale, incidental sinistrality among marine snail taxa may be more common than presumed. (A quick Google search on the Internet yielded hundreds of Web sites of shell clubs, traders and collectors mentioning the find or sale of sinistral 'monstrosities'.) Some reports of small but persistent sinistral populations are available as well [25, 49, 84]. On the other hand, entirely sinistral species indeed appear to be rarer than on land. However, exact data seem to be lacking: as mentioned above, even the proportion of sinistral gastropod species is unknown to the nearest order of magnitude. Though tedious and time consuming, a detailed and exhaustive survey of literature and shell collectors' knowledge is required to answer this question. If sinistral marine species indeed are rare, then why would this be? As many have external fertilization, frequency-dependent selection against rare types should be lacking in these groups. In contrast, however, their broadcast spawning and planktonic stages should mean that they lack population structure and hence no small, isolated populations for sinistral alleles to build up in [86]. Reproductive character displacement may also be ineffective.

The evolutionary ecology of snail coiling (speciation, coil dimorphism and reproductive character displacement) remains a fascinating subject. The prevailing consensus on speciation is that it is generally caused by simultaneous, multifarious, divergent selection on many loci [15, 71]. Together with instantaneous speciation by allopolyploidy and by cytoplasmic incompatibility microbes [39, 73], single-gene speciation by chiral reversal would be an interesting exception. While the field data and theoretical considerations so far do not make us confident that the process occurs in nature, the model is of sufficient

relevance for speciation theory to warrant further research. Perhaps long-term laboratory experiments may aid, as they have in *Drosophila* speciation genetics [15]. Unfortunately, the practical impediments to working with snails in the laboratory (including long generation times and sometimes sensitive husbandry) remain formidable.

A better case can be made for chiral reversal as a factor contributing to divergence after speciation (reproductive character displacement). Theory shows that coiling reversal will be selected if it prevents wasting gametes or time on mating with non-conspecifics. Viewing reverse-coiled populations or species in this light rather than as cases of single-gene speciation may be fruitful. Finally, species or populations in which coil dimorphism is stably maintained present what we consider one of the most tantalizing puzzles. We hope that further research on the dimorphic subgenus *Amphidromus* will reveal what aspect of its environment, genetics or reproduction permits it to go against all theory of snail chirality so far developed.

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