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The Hopeful Monster Finds a Mate and Founds a New Species

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Abstract

Saltation (fundamental changes in a species in a single-generation) has been argued to be incompatible with evolution and Darwinism. Indeed, the mental image of a "hopeful monster" looking unsuccessfully for a mate has been used to ridicule the concept put forward by Richard Goldschmidt in 1940. Nonetheless, over the last decade it has become well known that simple, common pericentric inversions of chromosomes (which may have no effect on morphology) drastically decrease the fertility of affected individuals when mated with individuals with normal centromere parity. But, mating between individuals with the same (inverted) parity appears to lead to formation of a population with homozygous inverted parity chromosomes, which has normal fertility. In this paper, it is argued that these populations with homogeneous (pericentromeric) inversions represent nascent new species within larger populations of the parent species. Examples involving mice, horses and even humans are presented. The phenotypes of these nascent species are almost indistinguishable from the normal population and they only diverge from the general population through stochastic variation and selection during periods of ecological change.

Introduction

Evolution involves a two-step process: (1) variation in genetics that are reflected in the phenotype and (2) preferential selection for survival and reproduction based on the phenotype. "Natural selection" relates to the selection resulting from competition among individuals in some ecological setting. Charles Darwin (1809-1882) and Alfred Russel Wallace (1823-1913) both recognized the role of natural selection in determining the phenotype of surviving species in 1858. Unfortunately, Darwin entitled his book *On The Origin of Species by Means of Natural Selection, or The Preservation of Favoured Races in the Struggle for Life*, which is better known as *The Origin of Species*. The implication of Darwin's title is that natural selection creates species. Although natural selection drives changes in morphology (e.g., as in the peppered moth example), it does not seem to be the driving forces producing new *biological species* (as defined by Theodore Dobzhansky (1900-1975) and Ernst Mayr (1903-2005) who proposed that a biological species is composed of all those individuals that can successfully interbreed regardless of geography or morphology). For example, Darwin's fabled finches have been identified as separate species based on morphology (e.g., *G. fortis* and *G. scandens*), but they are capable of interbreeding with one another [1-3]. There are also several examples of ring species where quite different morphologies, separated for long periods of time, are mutually fertile [4]. These ideas have recently been refined by Baker and Bradley [5].

Reproductive Saltation is Inescapable

Richard Goldschmidt (1878-1958) proposed that speciation occurred as the result of a major mutation (i.e., saltation) that created what would be recognized by the existing species as a monster (teratogenesis), but which would have unique features that allow the new species to proceed. This idea flew in the face of Darwinian gradualism and was ridiculed because it seemed that a pair of similar monsters would never appear simultaneously (i.e., the problem of the hopeful monster finding a mate). The people who laughed at Goldschmidt (and perhaps Goldschmidt himself) were apparently thinking only in terms of gross mutations that made major changes in phenotype. Phenotype, however, is almost irrelevant to determination of biological species [1, 3, 6, 7]. No matter how you twist or parse the idea, at some point, the essential act in creation of a new species must break the chain of mutual fertility. In one or a very few generations, the new species (that cannot breed

reliably with the existing species) must form. This is a special case of saltation and it appears to be inescapable for the formation of new biological species.

Origin of the Hopeful Monsters and Species

The answer to the hopeful monster paradox appears to be very simple. We now know that pericentric inversions are common and that closely related species frequently display pericentric inversions [8-15]. These inversions do not generally have much impact on phenotype of the individual unless they disrupt specific coding or non-coding genes [16-19]. For small inversions (i.e., pericentromeric double strand breaks) the most likely impacts are to the pericentromeric repeats, which give rise to various developmental abnormalities [17, 20-30]. I have offered a hypothesis for why this is so [31], but it is not relevant here.

Here, the important feature is what happens during reproduction. Long centromeric inversions (greater than 30% of the chromosome length) in one parent are capable of achieving a quasi-normal parity with the normal chromosome of the other parent through formation of inversion loops [16, 32]. These genomic gymnastics are accompanied by various adverse impacts on karyotype and genomic stability, but can be successful. The short (pericentric) inversions, however, do not permit such compensation and lead to low fertility *when mated with an individual of normal chromosomal parity* [19, 25, 27, 32-34]. However, when mated with another heterozygous individual, who inherited the same inversion (a relative: sibling, parent or cousin [23, 24, 28, 29, 35, 36]) there is no reason to believe that the couple could not display near normal fertility. For example, related species with uniform (homozygous) distribution of pericentric inversions within their populations (e.g., chimpanzees and humans) are both fertile [8, 10-15, 37-39]. Such inbreeding (e.g., proto-humans with proto-humans and proto-chimps with proto-chimps) would soon produce a population of homozygous inverted parity individuals [40-42] that cannot breed with the normal members of the population, but are fertile within their group. In this situation, reproductive isolation has been achieved in the midst of the normal population. This is a well known fact [43]. The hypothesis that I am advancing here is that this group of individuals (that look just like the original species) are in fact a *nascent new species* and that examples have been reported in the literature. Specifically, the individuals with inversions (particularly pericentromeric inversion) represent Goldschmidt's hopeful monsters and finding a fertile mate is actually not very difficult.

Obviously, while the nascent new species is subjected to the same ecological conditions as the parent species population (i.e., they are assumed to be comingled), they have different stochastic events in variation and selection. In the absence of any change in the environment, the original species and the nascent new species would presumably both oscillate around the same (optimized) phenotype (evolutionary stasis) [44-50]. But, if the ecology changes, the stochastic variation and selection processes will tend to make the morphology of the species separate. For example, a retrovirus infection [31, 48, 51-59] might affect the small (nascent new species) population and a portion of the parent population inducing new repeat elements into the genomes. The large parental population (that is only partially affected by the virus) will tend to redistribute genes to minimize the effects of the retrovirus infection and will tend to stay near the previously established optimum phenotype (i.e., phenotype stasis in comingled species) [60, 61]. On the other hand, the small nascent species will tend to evolve toward a new optimum more rapidly. Overall, the rate of change of the new species will depend upon the strength of the environmental influence and the rate of variation. Evolution might appear to be gradual or punctuated in the fossil record [31]. The important point is that the speciation event was not dependent on gradual changes, nor was it dependent on geographic separation. Please note that geographic separation *per se* is neither necessary nor sufficient to cause biological speciation, but it may give rise to phenotypically different groups in the same species that are easily mistaken for separate species [1, 3-6, 62].

Nascent New Species

It should be possible to demonstrate the existence of nascent new species in laboratory animals. To this end, a review of the literature was conducted focusing on mice. It has been found that pericentric inversions in the mouse reduce fertility as observed in humans [63]. Unfortunately, no data were found for homozygous pericentric inversions in mice. However, there are data for a short inversion in the long arm of chromosome 6 of the C3H/HeJ mouse [64]. This inversion is believed to have occurred before 1970 and was well inbred by the time it was discovered (2006). Mice with the homozygous inversion have normal phenotypes and have been used in many published experiments. These experiments include a few where hybrids of C3H/HeJ mice with other strains were used. Generally, there is

no discussion of the success rate of the hybridizations in these publications. However, a very interesting experiment was carried out looking at the fragmentation of two-cell blastomeres of C3H/HeJ mice (presumably containing the homozygous inversion) crossed with other strains of mice [65]. Blastomeres produced by C3H/HeJ males with C3H/HeJ females developed normally as would be expected since the chromosomes all had the same parity. But, crosses of (putative homozygous inverted) C3H/HeJ males with (putative normal parity) C57BL/6 females resulted in a high incidence of fragmentation at the two-cell stage. The C57BL/6 females crossed normally with males from other strains (i.e., C57BL/6, DBA/2, AKR/J, or SJL) as one would expect. On the other hand, female C3H/HeJ mice crossed with C57BL/6 males show a high frequency of fragmentation of the two-cell blastomeres. In the F1 generation, female "C3H/HeJ X C57BL/6" mice showed a high level of blastomere fragmentation with males of either strain. At the time these experiments were done, the authors [65] were unaware of the inversion in C3H/HeJ mice, but the results are consistent with the idea that the inversion was usually lethal (even though it is not a pericentric inversion) [64]. There are also examples of infertility in mice related to inheritance of chromosomes with conflicting centromeric heterochromatin C-band polymorphisms [66]. Overall, the C3H/HeJ mice appear to meet the criteria of a biological species and not belong to the species that the other strains of mice are part of [5].

There is an analogous situation in horses with a paracentric inversion in ECA3 chromosomes that produces the unusual "Tobiano pattern" of white markings [67, 68]. This inversion and unrelated mutations that also produce white animals (e.g., horses and mice) affect the *c-Kit* gene. Some of the *c-Kit* mutations are lethal so that *c-kit* mutants often only survive as heterozygotes. In contrast, horses with heterozygous or homozygous Tobiano alleles are healthy and have the same phenotype [68]. As a matter of fact, heterozygous Tobiano horses make up less than 21% of the animals [69]. The fact that greater than 79% of Tobiano horses are homozygous is attributed to the genetically unbalanced zygotes required to produce heterozygote adults. These problems with fertility appear to be related to inappropriate (out-of-phase) chromosomal separation sequence during meta-anaphase [70, 71]. Here also, the Tobiano horses appear to meet the criteria for a biological species, although some hybrids with normal horses occasionally survive [5].

What about Humans?

It is noted that humans and chimpanzees have very similar protein-coding genes and proteins and similar gross phenotypes [72] but these species are separated by nine pericentromeric inversions and a fusion involving human chromosome 2 [15, 73, 74]. For these inversions to be uniform in one species and missing in the related species, either: (i) the inversion occurred at the point of speciation, (ii) the inversion was eliminated from members of the parent species, or (iii) the inversion spread rapidly through the new species. It seems most likely that the observed (species-specific) inversions occurred at the point of speciation. Indeed, the point made here is that the inversions were most likely the cause of speciation.

It is also noted that pericentric inversions and related rearrangements are frequently discovered in the human population [30, 75-77]. Some of these are *de novo* and some are inherited from parents [23, 78]. The case of human chromosome 9 is particularly relevant. In the human population, inversions in chromosome 9 (which often do not affect phenotype) are so common (about 1% [79]) that they are considered a normal variation [11, 17, 19, 27, 34]. There are documented cases [40-42, 77] where inbred groups of humans may represent nascent new species. When the inversions disrupt the pericentromeric heterochromatin (e.g., 9p11q13) significant developmental abnormalities are usually observed [31] but there are clearly some cases where humans with homozygous chromosome 9 inversions appear normal [80] and some have produced numerous offspring [42].

The example discussed by Vine et al. [42] is particularly relevant to this discussion. They observed a chromosome 9 pericentric inversion in 7 out of 10 members of an inbred family. Two individuals with homozygous inversions were discovered and one of these had fathered many children (most of whom were heterozygous). These people lived in a village that was established over 3000 years ago and had a current population of 3,000 people. Interestingly, the early human population is believed to have involved approximately 10,000 individuals [72].

The Hopeful Monster Finds a Mate

If we consider animals with chromosomal inversions (particularly the common pericentromeric inversions) to be Goldschmidt's hopeful monsters, there are two plausible ways for them to find mates. First, inbreeding within a family group (e.g., tribe or clan)

appears to be the most certain. Although humans have a taboo against inbreeding this is a relatively recent concept (even Darwin married his first cousin) [81] and other higher animals (including primates) don't seem to avoid inbreeding.

Second, even in the absence of mating within families, with a frequency of chromosome 9 inversions of 1% in the general population of humans, the probability of individuals with some sort of "chromosome 9 inversion" mating is about 1 in 10,000. A perfect match of inversion break-points may not be required for quasi-homozygous chromosome 9 inverted individuals to survive. Thus, even within the general out-breeding population, cases will likely arise where there is mutual fertility within the inverted group that isolated them genetically from the normal parity group. Proximity, familiarity and reproductive necessity will tend to keep these groups together. But, their importance is not that they are individually likely to progress to a new species (those odds are very low). But since they are distributed worldwide as a dynamic, but constant element of the population; if and when some event that isolates a portion of the population and places demands on it occurs, some inverted group is likely to be present and able to evolve quickly to take advantage of the situation. Natural selection will eventually make it the predominant group.

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