Genetic variation in small populations

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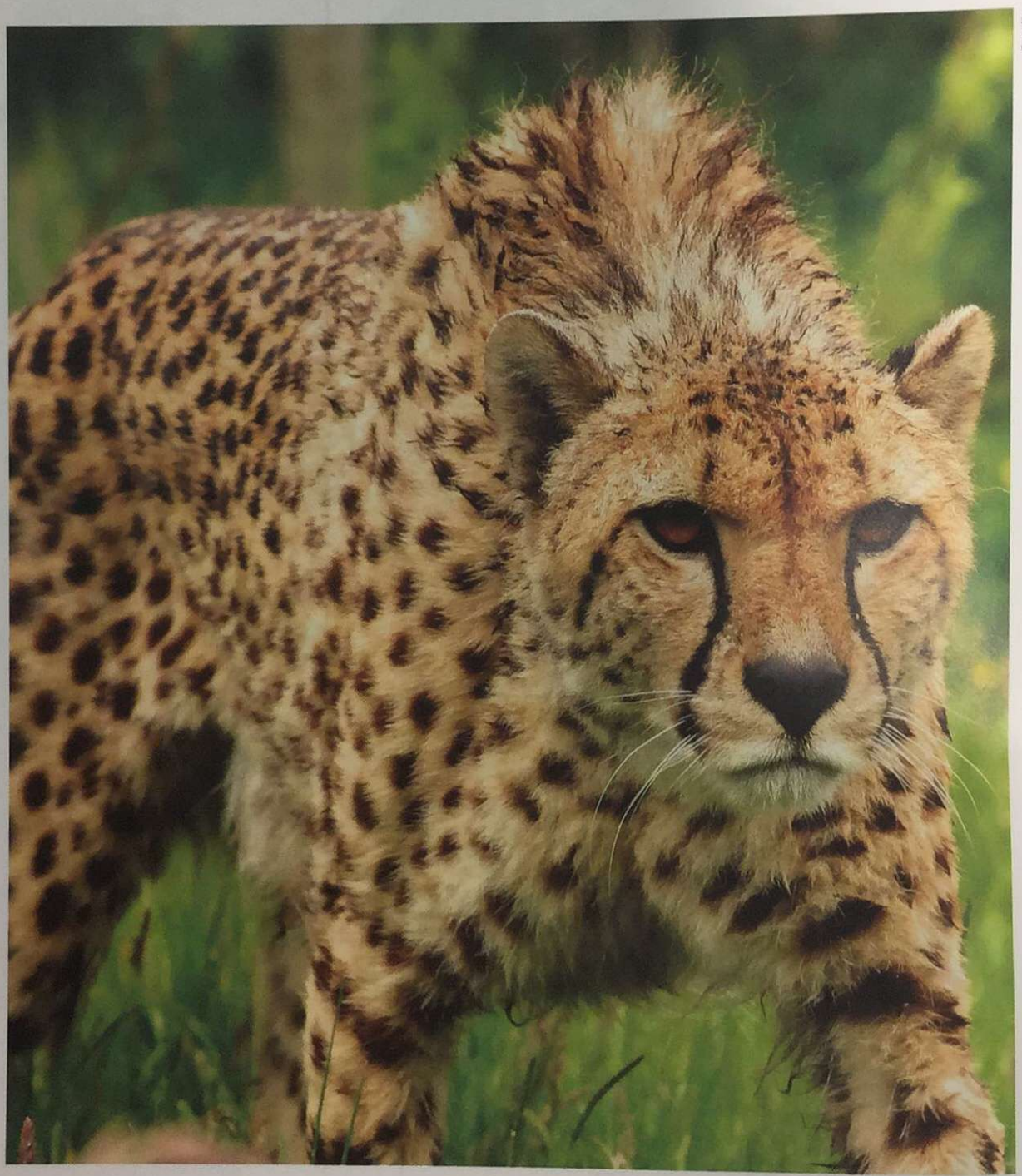
The amount of genetic variation in a population tells us something about that population's evolutionary history. Populations that have arisen from just a few individuals may have genetic variation that differs widely from their parent population. Why is this, how can we investigate such populations and what are the practical uses for such information?



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Key words

Founder effect
Genetic bottleneck (population bottleneck)
Genetic variation
Alleles
Inbreeding
Mutation

It seems reasonable to expect big populations to have more genetic variation than small ones. But that is not necessarily the case. For example, there is more genetic variation in the world's 300000 chimpanzees than there is among 7 billion humans. This reflects recent human evolutionary history, as we are undergoing rapid population expansion from perhaps only 10000 individuals 70000 years ago. In contrast, chimpanzee populations may have stayed steady or decreased over the same period of time.

Recent advances in DNA sequencing technology allow us to measure genetic variation at a level that has not been possible previously. This gives us great insight into the evolutionary history and population structure of a wide variety of organisms. DNA technology has also been used in the quest to find genes that cause specific human genetic disease (see Biological Sciences Review, Vol. 24, No. 3, pp. 34–38).

Evolution

When we consider Darwin's theory of evolution by natural selection (see Biological Sciences Review, Vol. 25, No. 2, pp. 38–41), we often think of it in terms of 'survival of the fittest'. An understanding of genetics enables us to explain the mechanism underpinning evolution. Mutations in DNA generate variation, and natural selection acts on this variation so that the most advantageous genetic variants survive.

However, selection is not the only important aspect of evolution. Chance also plays a major role. This is particularly true in small populations, where we see what statisticians call a 'sampling effect' (see Box 1). Random processes have relatively little consequence for large populations, but can have a profound influence on genetic variation in small populations. There are really only two ways by which small populations can arise from large populations — genetic bottlenecks and founder effect, and we will consider each in turn.

Box 1 Sampling effects

The best way to understand genetic bottlenecks and founder effect is to consider a simulation. Assume you start with a population of 100 individuals. Suppose that within this population there are five different colour phenotypes all at equal frequencies. So you have 20 of colour A, 20 of colour B and so on. You can now simulate a genetic bottleneck by randomly killing 90 individuals, or create a founder population by randomly selecting ten individuals. Do this several times and allow the individuals to breed. What happens to the frequency of each colour in the new populations? Are all colours always retained or do some disappear? If some disappear, how often? If you vary the number of survivors or founders, does this make any difference?

Genetic bottlenecks

Genetic bottlenecks happen when a large population crashes due to a catastrophic event, so that only a relatively small number of individuals survive (see Box 2). Catastrophes may happen suddenly, such as by volcanic eruptions, tsunami or famine, or over much longer periods of time, such as climate

Box 2 Genetic bottleneck versus founder effect

In a genetic bottleneck (see Figure A) the large original population has red and blue individuals (1). If the population goes through a genetic bottleneck (population crash (2 a, b and c)) the relative frequencies of red and blue individuals may change quite dramatically, even when the population recovers to something approaching its original size (3 a, b and c). In founder effect (see Figure B) a few individuals from an original population of red and blue individuals (1) migrate and start a new population (2 a, b and c) where the frequencies of red and blue individuals may differ significantly, by chance, from the original population. Note that in founder effect the original population survives, whereas in a genetic bottleneck it does not.

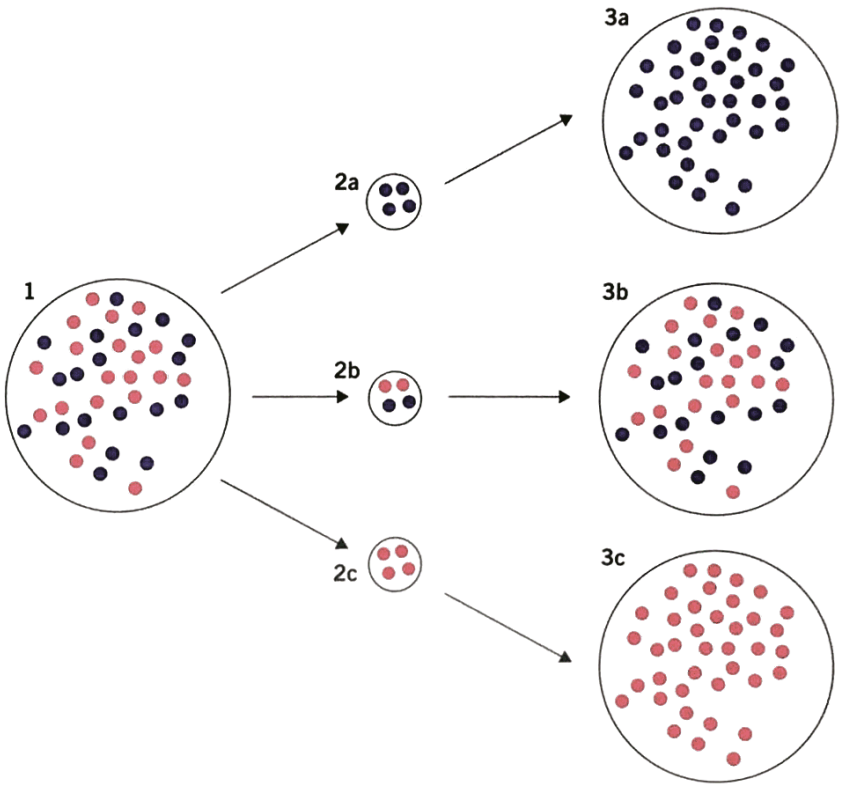

Figure A The effect of a genetic bottleneck.

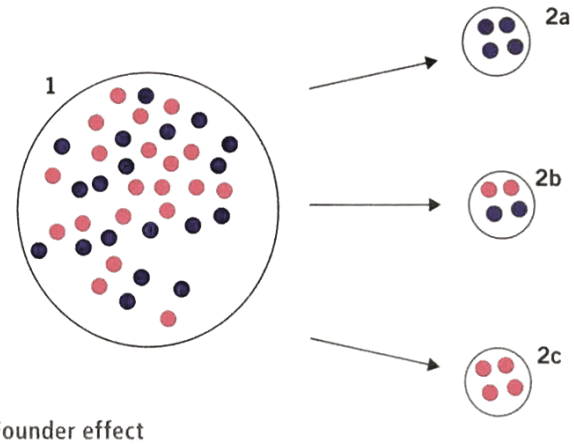

Figure B Founder effect

Overhunting of bison by humans in the nineteenth century caused a genetic bottleneck. Although numbers of bison have recovered, their genetic variation is low.

change. Whatever the cause, the effect on the population size may be profound. Environmental catastrophes kill individuals in the host population at random, so those that survive do so primarily by chance. Alternatively, a population may crash due to infectious disease, where selection will favour individuals with specific genetic variants of their immune system. Whatever the cause, genetic bottlenecks always reduce the amount of variation in a population.

Cheetahs are perhaps the best-documented example of a natural genetic bottleneck. The world's 14 000 or so cheetahs have remarkably low genetic variability. This probably reflects a prolonged period of inbreeding following a population crash in the last ice age, 10 000–15 000 years ago. Cheetahs are so similar that skin grafts between apparently unrelated individuals are only rarely rejected. Having so little genetic variation in their immune system means the entire cheetah population is potentially vulnerable to a single infection.

DNA evidence also supports the idea that our human ancestors underwent a series of genetic bottlenecks. These were probably associated with severe climate change linked to successive ice ages and perhaps environmental catastrophes such as the Toba Megaeruption — a huge volcanic event in Indonesia around 70 000 years ago.

Man-made bottlenecks

Our ancestors caused many recent genetic bottlenecks, such as the one that affected American bison. Prior to the arrival of Christopher Columbus in 1492, the bison population of North America is estimated to have been over 60 million. Four hundred years later, over-hunting had reduced this population to just 750 individuals. There are now around 400 000 bison, but these animals still have the genetic variation expected in 750 individuals. So, like cheetahs, the world's entire inbred bison population is potentially susceptible to a single catastrophic infection.

Northern elephant seals lead an even more perilous existence. Hunting caused their population to fall to just 30 individuals by the 1890s. While their numbers have now recovered to hundreds of thousands, the story is complicated by the fact that the dominant bull male mates with nearly all the females — perhaps as many as 100 — in his colony. So few males pass their genes to the next generation, making an already inbred species even more so.

Founder effect

'Founder effect' was first described by Ernst Mayr in 1942. He described it as 'The establishment of a new population by a few original founders (in an extreme case, by a single fertilised female) which carry only

a small fraction of the total genetic variation of the parental population.' The simplest example is when a small number of individuals colonise an island previously uninhabited by their species (see Box 2). As these few colonising individuals carry a fraction of the genetic variation from their parental population, all future generations of the newly colonised island will be derived from this subset of variation.

The great colonisers of the modern world are humans and no human population is more isolated and better documented than that of the South Atlantic island of Tristan da Cunha (see Figure 1). The first permanent settlement comprised eight men and seven women who arrived on the island in the early 1800s. DNA testing confirms that nearly all the 250 current inhabitants are descended from these 15 Europeans.

So how does the Tristan da Cuhna population differ from its European ancestors? We would predict that by chance the overwhelming majority of genetic disease present in Europeans would be absent in Tristan da Cuhna, because it was absent in the 15 founders. This is precisely what we see. Equally, and again entirely by chance, some of the 15 founders would have been carriers of rare specific human genetic diseases that should be prevalent at a high level in their descendants. Asthma and glaucoma levels in Tristan da Cuhna are among the highest in the world.

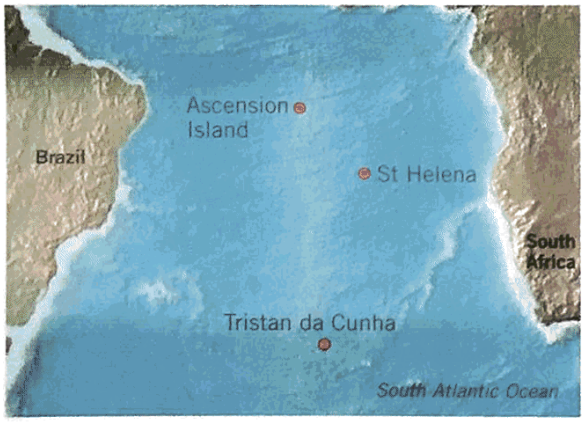

Figure 1 Tristan da Cunha is in the South Atlantic Ocean.

Pedigree dogs

Perhaps the most extreme example of founder effect can be seen in pedigree dogs. Many of the breeds we see today are derived from small founder populations from the 1890s that have been maintained by mating dogs with their close relatives. The problems associated with inbreeding on such a grand scale were investigated in the BBC television programme *Pedigree Dogs Exposed*, first broadcast in 2008. Scientists from Imperial College in London studied the scale of genetic variation in the UK population of pugs, and calculated that the UK's population of 10000 pugs is so inbred that they have the genetic variation you might expect from just 50 individuals. Geneticist Professor Steve Jones is quoted as saying:

> People are carrying out breeding which would be first of all entirely illegal in humans, and secondly is absolutely insane from the point of view of the health of the animals. In some breeds they are paying a terrible price in genetic disease.


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Inbreeding limits the genetic variation found in pedigree dogs such as pugs. They can suffer severe health problems as a result of inherited medical conditions.

Inherited medical conditions in pedigree dogs can arise as a simple but inevitable accident of inbreeding. For example, around 30% of Dalmatians suffer hearing impairment, simply because that inherited condition existed by chance in their founder population. However, active selection of specific characteristics of a breed can lead to severe medical complications. For example, the flat face of pugs compacts their breathing passageways, leaving them unable to breathe properly and unable to regulate their body temperature efficiently via evaporation from the tongue (i.e. panting).

Why study the founder effect or genetic bottlenecks?

As well as being of interest to evolutionary biologists, founder effect and genetic bottlenecks have a critical role to play in the search for mutant genes that cause inherited medical conditions.

Most common medical conditions are complex, so the probability of any one individual suffering from asthma, diabetes or heart disease depends on a number of factors. Some of these, especially environmental factors such as diet, exercise and personal hygiene, you have some control over. However, you have no control over the genetic variation you are born with. Geneticists would like to find the genes that contribute to your medical risk, but this is extremely difficult, because in large populations there are a lot of genetic variants and a lot of environmental factors. Geneticists are interested in finding small, inbred populations where a specific medical condition is common. As these founder populations are often derived from relatively few individuals, so the genetic variation in the population is very low, and it should be easier to find the mutant gene that is associated with a

specific inherited medical condition. But does this theory work in practice?

Huntington's disease

Huntington's disease is a rare and progressive neurological condition. Sufferers are born healthy, but later in life their nervous system deteriorates. As Huntington's is a dominant single gene condition, it is passed directly from parent to child and can be followed within families from generation to generation. Worldwide there are about ten cases per 100000 births, but around Lake Maracaibo in Venezuela the frequency is as high as 700 per 100000. This founder effect is due to one woman, Maria Concepcion Soto, who settled in the region around 200 years ago. Despite suffering from Huntington's disease she had ten children, and is estimated to have 14000 descendants alive today. Studies of this affected population by US researcher Nancy Wexler was key to finding the gene that causes Huntington's disease.

Huntington's disease is caused by a mutation in a single gene, so with a large set of related sufferers the defective gene should be relatively easy to find. So what about more complex conditions where variation at many gene loci is likely to contribute to an individual's risk of developing a condition? Can well-documented founder populations help us identify risk genes?

Asthma

As mentioned earlier, the current population of Tristan da Cuhna is around 250 — descended from 15 settlers who arrived on the island about 200 years ago. However, that is not the whole story. Tristan da Cuhna is the top of an enormous underwater volcano. In 1961, the volcano erupted and the entire population was evacuated to Calshot near Southampton. It was here that Noe Zamel, a young doctor from the University of Toronto, first noticed the high prevalence of asthma among the evacuees. Some people are more susceptible to asthma than others, and it is clear that variants of many genes contribute to this. But finding contributing genes in large, genetically complex populations is extraordinarily difficult. What Noe Zamel has shown is that susceptibility to asthma in the Tristan da Cuhna population must be associated with very few genes, and perhaps only a single mutation. In fact, it is likely that genetic susceptibility to asthma was present in just three of the original founder population. This gives us the very realistic chance of at last identifying one of the genes associated with asthma susceptibility.

Asthma is an inherited medical condition.

Further reading

O'Brien, S. J., Wildt, D. E. and Bush, M. E. (1986) 'The cheetah in genetic peril', *Scientific American*, Vol. 254, pp. 68–76.

Websites

The BBC documentary *Pedigree Dogs Exposed* can be found at various unofficial sites. There are also a number of forums that discuss the relative merits of issues arising from the programme.

The BBC Newsnight film on Huntington's disease and Lake Maracaibo, can be found at:
http://tinyurl.com/ctmzcuu

Noe Zamel's homepage can be found at:
http://tinyurl.com/d7pcsdn

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Key points

- Chance plays an important evolutionary role, especially in small populations.
- Inbreeding usually decreases the amount of genetic variation in a population.
- Inbreeding usually decreases the fitness of individuals.
- In small populations, otherwise rare genetic conditions may be found at a relatively high frequency, which helps researchers find the gene(s) responsible for that genetic condition.