Influence of genetics and inbreeding on disease

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Genetic influences on disease are far more common in epidemiology than those expressed through the phenomenon of inbreeding. However, it is useful to explore the associations between inbreeding and the occurrence of disease before considering the wider role of genetics, as the influence of inbreeding is most overtly seen in simple Mendelian diseases. In such cases, a single locus is responsible for disease manifestation, while in more complex diseases, genetic influences are commonly associated with a number of loci. While this article examines the role of genetics in cattle diseases, with a particular emphasis on inbreeding, all the principles discussed can be extended directly to other livestock, horses and companion animals.

The concept of inbreeding

Inbreeding occurs when related animals are mated together, and is a natural event that cannot be avoided over time. An individual will have four distinct grandparents, eight distinct great-grandparents, and so on, doubling each generation, which will soon exceed the historical census size of a population. Genetically, offspring from related parents have a probability of more than 0 of inheriting two copies of an allele carried by any one of their common ancestors, and when this happens the two alleles are said to be identical by descent (IBD). The measure commonly used to describe the degree of inbreeding in an individual – that is, its inbreeding coefficient (F) – is the probability that the two alleles carried at a locus by an individual are IBD. This definition is only tractable if the probabilities are calculated in relation to a 'base' generation, in which all the alleles carried by all the individuals are assumed to be different – that is, F is equal to 0 in each individual. This may seem artificial, but such a construction allows development of a theory that can make meaningful predictions. Such base generations are often defined in fully documented pedigree herd books.

From the gene pool formed by the base generation, inbreeding will accumulate and the average F of individuals in the population will increase over generations, not necessarily monotonically, but ultimately inescapably, unless there is introduction of new individuals from a different gene pool. As inbreeding occurs, populations will show the following:

- Random drift in allele frequency over generations, with alleles becoming lost or fixed in the population;
- Loss of heterozygosity (and therefore a gain in homozygosity), whereby loci are more likely to carry identical alleles. As heterozygosity is the biological source of hybrid vigour, this vigour is lost in what is called inbreeding depression; and
- A decrease in genetic variation for traits.

Other processes, such as mutation and migration, increase genetic variation and heterozygosity. Therefore, what is observed in an animal will depend on the balance between these processes.

A question often asked by breeders concerned about the impact of inbreeding is 'What is a safe level of inbreeding?'. However, there is no answer to this, because, as described above, over a long enough period of time, all closed populations will have inbreeding coefficients that exceed any predetermined level. The genetic variation in a population of cattle where F is 0·2 compared with a base 150 years ago, has been far better managed than one where F is 0·2 with a base 50 years ago. Therefore, the most appropriate way of considering the management of inbreeding in populations is to examine how quickly it is accumulating. When accumulation is faster, the reduction in variation and heterozygosity due to inbreeding will tend to dominate those processes with the opposing effect. The fact that the rate of accumulation of inbreeding is more critical than its absolute value explains why the arbitrariness

Fig 1: Ninety five per cent of dairy cow genes in the UK originate from the North American Holstein. Although black and white like the Holstein, the Friesian cow represents a distinct gene pool to the Holstein

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of the historical timing of the base generation is less important when looking forward, although the history is always important for understanding the current population.

This rate of accumulation is often described by geneticists as an 'effective population size' or N_e, but it should be noted that the lower the N_e, the higher the rate of increase in inbreeding. There is no theoretical threshold for what is a 'safe' rate of inbreeding, or what is a 'safe' N_e, but achieving an N_e of at least 50 is often taken empirically as a minimum target for livestock. N_e is not the same as the census size of the population. For example, in the Holstein breed of cattle (Fig 1), which contribute 95 per cent of the dairy genes in the UK, N_e is reported to be less than 50, meaning that less than 50 individuals randomly selected and mated each generation would be needed to give rise to the same rate of inbreeding as actually observed in the Holstein. Therefore, despite millions of cows globally, the value of N_e in the Holstein is similar to several much rarer cattle breeds, due to the way in which breeders manage its gene pool. While Holstein breeders have been somewhat reckless in their use of genetic variance in recent generations, it is a myth that the Holstein breed has no genetic variation. For example, sustained genetic progress continues to be made in the breed towards dairy objectives, and these would be expected to be among the first traits to show signs of reduced variation.

Good breeding management depends on all breeders, and an individual breeder can only do a limited amount to influence this unless they themselves control a large part of the gene pool. The rate of increase in inbreeding arising in a generation will depend on the squares of the proportions of the gene pool contributed by each of the parents in that generation. Therefore, individuals contributing large proportions will promote high rates of inbreeding. It is hence increased by small numbers of parents of either sex, which may happen in a rare breed, or by very unequal contributions among parents (even when many are contributing), which is the case in the Holstein. It is important to remember that N_e depends on the minimum of the number of male parents and the number of female parents in a generation, not on their average, so a small number of bulls used in a generation cannot be corrected for by a large number of cows. While the number of bulls used, and to what extent they are used, results from the actions of the community of breeders, one action that every individual farmer and breeder can take to reduce the risk of disease through inbreeding is to avoid the mating of related animals, such as full- or half-siblings or cousins, most easily through good record keeping.

Why do breeders inbreed their animals?

Historically, the justification for inbreeding may have been due to the lack of good comparisons across herds. Breeders trusted their own stock, which in turn led to an over-reliance on pedigree as a measure of genetic merit, a view reinforced by marketing. This over-reliance was expressed in the practice of 'line breeding', where close relatives were mated routinely, and is now much less common. It has been argued that the practice followed that of 18th and 19th century pioneers of modern livestock breeding. While this may be true, only their successes rather than failures will be evident. An experiment with sheep at the Animal Breeding Research Organisation (an antecedent to The Roslin Institute) showed that more than 50 per cent of such lines died out because they were unable to reproduce successfully (Wiener and others 1992). There were a number of reasons for this, including barrenness, reduced litter size, poor lamb survival and poor growth. While pedigree is often the most reliable source of information on breeding values, since it is 'proven', the fact that the majority of genetic variance within a breed is expressed within families is often neglected, and good offspring from more mediocre parents may be of more value to the future gene pool.

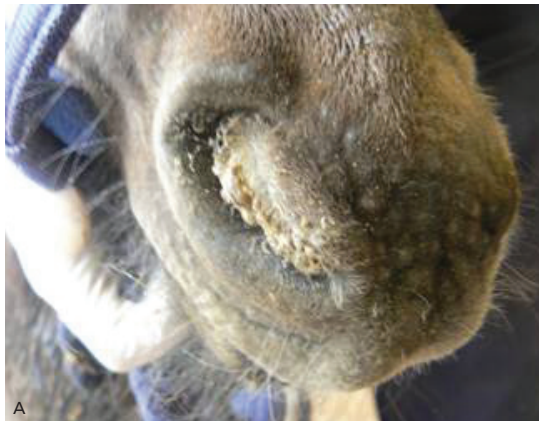
More recently, the publication of estimated breeding values, derived from data generated by recording schemes run by National Milk Records and Cattle Information Service for dairy farmers, and Signet and BreedPlan for beef farmers, give those interested in breeding the opportunity to compare across herds. These 'proofs' of genetic merit on bulls and cows appear as estimated breeding values (EBVs) or predicted transmitting abilities (PTAs) for many different traits in catalogues or on web pages. However, the use of artificial insemination, which has undoubted benefits for generating genetic progress through increased selection intensity among bulls, has, at the same time, the disadvantage of allowing very unequal contributions to the gene pool among bulls, which promotes faster inbreeding. There is therefore a need for risk management in such an approach. Selection aids have been developed to manage genetic gain and inbreeding simultaneously and efficiently, but, as indicated above, there is a need for a community approach (eg, breed societies finding imaginative ways to discourage the over-representation of popular sires in their pedigrees). New genomic approaches to estimating breeding values using high-throughput, dense-single nucleotide polymorphism (SNP) technology have the very real prospect of removing the over-emphasis on pedigree. Using this technology, which is already being implemented by Holstein breeders, it is feasible to confidently identify, at birth, better animals born to more mediocre families as well as those born to better families.

Inbreeding and disease

The most direct link between inbreeding and disease is seen in recessive Mendelian inheritance. A typical example is when a mutation causes a defect in either the regulation or functional properties of a protein. An individual possessing only one functional copy of a DNA sequence can often be healthy, as expression from this single copy is fully capable of providing normal metabolism. Both the wild-type homozygote, carrying two copies of the wild-type allele, and the heterozygote, carrying one copy of the defective allele, appear healthy and cannot be distinguished in their phenotype, whereas those with two copies of the defective allele show the disease. This is termed a recessive inheritance. Examples include bovine lymphocyte adhesion

Fig 2: Belgian Blue calf with crooked tail syndrome (Fasquelle and others 2009). (Picture, Arnaud Sartelet and Carole Charlier)

deficiency (BLAD) and complex vertebral malformation (CVM) in Holstein cattle, and crooked tail syndrome (Fig 2) and congenital muscular dystonia in Belgian Blue cattle. Such diseases in livestock populations give rise to the 'curse of the recessive' (Box 1), as the observed prevalence of the disease is only the tip of the iceberg in relation to the spread of the mutation through the population. Dealing with the problem is usually far more of a challenge than anticipated. A notable example of this challenge is the immunodeficiency syndrome affecting Fell and Dales ponies (Fig 3), in which failure to address the problem led to the mutation spreading to the extent that 40 per cent of the Fell pony population are now estimated to be carriers of the disease. In some conditions, expression of the disease may be partially masked by modifier loci that complicate recognition of the mode of inheritance.



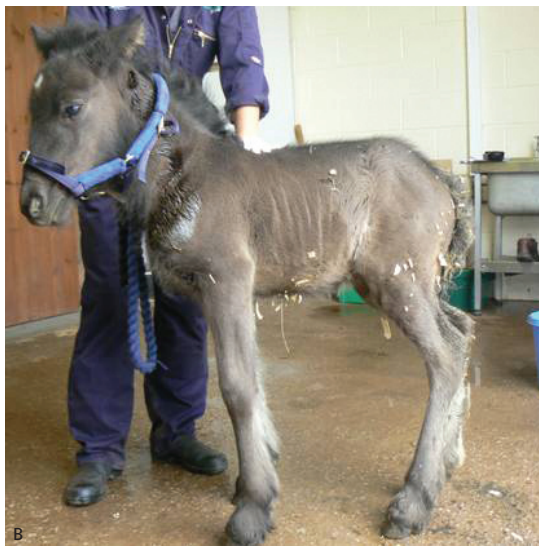
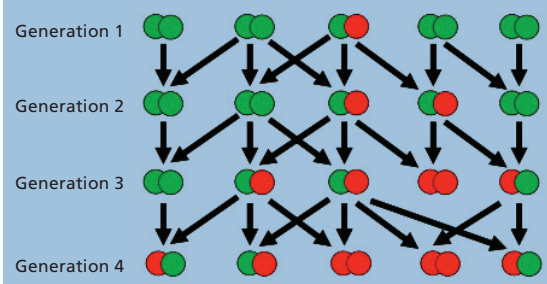


Fig 3a, b: Pony suffering from foal immunodeficiency syndrome. The failure to thrive results from an immunodeficiency and a progressive anaemia (AHT 2012). (Pictures, AHT)

Recessive diseases can become a problem due to inbreeding. When effective population sizes are small and rates of inbreeding are high, one of the consequences is that the random changes in allele frequency, which are a phenomenon of inbreeding (as described above), are much larger in magnitude. Therefore, a defective allele may be at low frequency in one generation, but at a much higher frequency in the next. For example, a popular bull makes de facto a large genetic contribution to the next generation, and if it carries what was previously a rare mutation, that mutation will no longer be rare, and if it is associated with disease, the prevalence of that disease will increase. The large genetic contributions of individuals determine that inbreeding rates will be large. This problem was well illustrated by an extremely popular Holstein bull, named Carlin-M Ivanhoe Bell, which carried two unrecognised deleterious mutations for BLAD and CVM. As a consequence of the bull's popularity, the frequency of these defective alleles rose to more than 10 per cent in elite populations of Holsteins, necessitating remedial action by

Box 1: 'Curse of the recessive'

Consider the initial generations of a mutation giving rise to a recessive disease, characterised in the figure below. In the first generation, there is a single heterozygote, the original carrier of the mutation. In the classical recessive disease, the carrier is fit and healthy and reproduces. In generation 2, each of the offspring of the original carrier has a half chance of inheriting the mutation, but all will appear fit and healthy as they will have inherited a normal allele from the other parent. Thus, the mutation may multiply without any expression of disease. Generation 3 is the first possible opportunity for the disease to appear, as it is possible that two carriers have been mated together; however, even two generations after the original mutation, this is unlikely, as livestock breeders generally avoid mating half-siblings and even then there is only a 25 per cent chance that the offspring will inherit two copies of the defective allele. Therefore, there is the possibility that the mutation will spread further. It is only in later generations that the disease will be observed. Note that if the mutation has frequency p in the population, the prevalence of the disease is much smaller, approximately p^2. Therefore, a disease prevalence of 1 per cent corresponds to a mutation frequency of 10 per cent – hence the idea that what is observed is only the tip of the iceberg.



Spread of a deleterious recessive mutation through a population. The green alleles are functional, while the red alleles are defective, with two copies causing disease

The spread of the mutation may be aided by a variety of other factors, such as selection in livestock. In pigs and poultry, many full siblings are born in a litter, so there is a good chance that the same disease will be observed in more than one individual. The expectation is that one in four will be affected, thereby helping to identify the genetic nature of the disease at an early stage. However this possibility is unrealistic in cattle, and the disease is likely to occur sporadically across the country, with only a small number of offspring of a carrier having the disease. If the frequency of the mutation is p, the frequency among the offspring of a carrier bull is only $\frac{1}{2}p$. It is also a natural temptation for a breeder to suppress the occurrence of disease, as it may compromise business. It may therefore be difficult for cattle breed societies to recognise and respond to the occurrence and spread of a recessive disease.

breeders and breeding companies – once the mutation had been identified. The prevalence of these diseases in commercial populations led to significant economic losses for producers. In some cases, the defective allele may also confer a selectively advantageous phenotype in the carrier, or be closely linked to an allele at another locus that confers such an advantage, which also helps the allele to spread through the population. An example of this is crooked tail syndrome in the Belgian Blue (Fig 2), in which carriers of the defective allele have also been shown to have better muscling (Fasquelle and others 2009).

Developments in genomics have now lifted the curse of the recessive. Dealing with a recessive disease can be achieved by identifying carriers, most effectively using DNA tests. Therefore, the sooner a DNA marker, or the mutation itself, is identified, the quicker the breeders can test potential parents to screen out carriers before breeding. The dense SNP chip technology (eg, BovineSNP50 Genotyping BeadChip; Illumina) mentioned above has made this task much simpler than it was before. Research has shown that it is possible to identify the mutation, or at least an identifiable short segment containing the mutation, with only a handful of well defined cases using a technique called homozygosity mapping. This technique relies on the observation that all cases of a recessive disease, however distantly related, will have two copies of the mutation and will also have two copies of a short segment of DNA either side of the mutation. This shared homozygous segment can be identified given the density of genotyping that is now routinely available. It is relatively cheap to obtain 700,000 SNP genotypes for an individual cow or bull, and sequencing individuals will be commonplace within the next five years. It is then a short step to develop a DNA test, which can be used to remove the mutation from the population. Given the relative ease and low cost with which recessive diseases can now be dealt with, it is important to be proactive. Therefore, once such a disease is observed, DNA should be taken from the cases and stored. By the time the disease has occurred in a small number of cases (eg, five) it is already possible that a test for carriers can be developed at an affordable cost for breed societies and individual breeders.

In some cases, such as immunodeficiency syndrome in the Fell pony, it is not advisable to immediately cull carriers of the defective mutation because the frequency has already risen too high. Removing the carriers restricts the gene pool and makes a breed with an already small effective population size even smaller, and in doing so increases the risk of promoting the appearance of another recessive disease. Management of inbreeding in a population is about managing the unknown risks. In relation to disease, it is about minimising the impact of diseases that are as yet unrecognised. In small breeds challenged with removing a recessive mutation causing disease, targets for reducing the frequency of the defective allele should be set, steadily reducing the number of carriers being allowed to breed over time. Testing should be compulsory with results made public, and carriers should always be mated with non-carriers. Ultimately, the mutation can either be removed completely, or the disease can be eradicated by not allowing carrier males to be registered and used.

Wider role of genetics beyond inbreeding

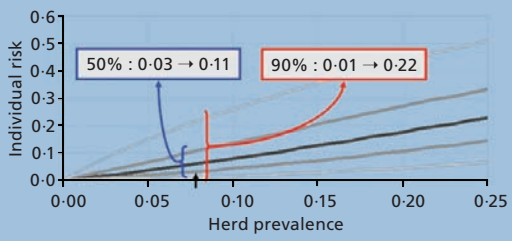
The role of genetics in cattle disease is not restricted to congenital defects. A growing body of evidence shows that genetics plays a significant role in most endemic diseases. There is a greater difficulty in discerning the influence of genetics in most diseases for several reasons. First, pathogenic diseases are generally multifactorial, with environmental factors influencing the degree of exposure to a pathogen, the condition of the animal at the time of exposure, and the likelihood of infection becoming established. Similarly, diseases of development and ageing are also likely to have multiple environmental risk factors. Secondly, the genetic risk of developing the disease (ie, determined by the genetic variation in susceptibility) is likely to be determined by multiple loci, not just a single locus considered above. Examples of the second point can be found in the medical literature (Tenesa and Dunlop 2009), where a very large dataset of 20,000 people was used to confidently identify 14 loci contributing to the risk of developing colon cancer, and yet the variants only accounted for less than 6 per cent of the genetic variance (which can be established from family data). The remaining undiscovered loci are each likely to have much smaller effects on the population as a whole than those discovered to date. In the veterinary field, studies tend to be smaller and less powerful, but a meta-analysis of studies of mastitis in dairy cattle and hip dysplasia in dogs, suggest multiple genomic segments harbouring putative risk variants.

Among cattle diseases, one that has received considerable attention from geneticists is mastitis in dairy cows. This is as a result of its impact on the welfare of the cows, the economic cost to the farmer, and the desire to reduce the use of antibiotics. Due to large environmental influences, the disease is not among the most heritable and the attention it has received has only resulted in limited success – genetic progress in milk yield has been made with little or no increase in mastitis incidence. This is not the reduction of mastitis incidence that would be desired, but the well established genetic associations between milk yield and mastitis incidence (genetic correlation of approximately 0·6) would have predicted an increase in incidence as yield increased. What success there has been to date has been due to the publication of bull proofs for mastitis incidence, which in the UK are primarily based on collection and genetic analysis of somatic cell count data, and the use of the proofs by breeders. However, progress could be made more dramatic by increasing selection pressure, as carried out in countries such as Norway, where increases in yield have been achieved with decreases in mastitis. Such outcomes underpin the current attractiveness of the Norwegian Red as a breed for crossing with the Holstein.

Of considerable interest in current genetic disease research are published findings showing that nearly 20 per cent of variation in risk of contracting bovine tuberculosis (TB) is genetic in origin (Brotherstone and others 2010). These reports have been obtained both in the UK and Ireland, and stem from genetic analyses of screening data obtained in the ongoing epidemic, and have been made possible in the UK by

Box 2: Impact of genetic variation on risk of culling for TB in a herd

Recent studies have shown that, within a herd, there is heritable variation in individual risk for susceptibility to TB. The heritability of the underlying risk has been estimated to be approximately 0·18 of the total variation. An illustration of the impact of this genetic variation is shown in the figure below. Within a herd, some individuals are more likely to contract the disease than others as a result of their genetic breeding value for susceptibility to TB. Therefore, if 7 per cent of cows are culled during a TB breakdown, then, within the herd, there are some cows that are much more likely to be culled due to their breeding value than others.



If 7 per cent of cows are culled, 5 per cent of the cows in the herd have a probability of less than 0·01 of being culled, while 5 per cent of the cows have a probability greater than 0·22. The 'middle' 50 per cent of the cows have probabilities ranging between 0·03 and 0·11. The five lines above show how these probabilities change as the degree of culling increases or decreases for the estimated heritability of 0·18 (see Brotherstone and others 2010).

Box 3: Data collection

Good data are the springboard for understanding and developing effective control strategies, and, in many diseases, the veterinary practitioner working in the field is on the front line for data collection. An important contribution that a clinician can make beyond treating the patient is to provide data to uncover the full panoply of epidemiological risks, including genetics, which can lead to a reduction in population prevalence. It is particularly important to ensure that an individual animal's identity is fully and accurately recorded alongside those of its parents.

improvements in the quality of data recorded by Defra and its agencies. At first glance, this seems modest, but the implications suggest not (see Box 2). As yet, the underlying mechanisms have not been identified (eg, it is possible that they are behavioural in avoiding exposure), although studies in other species suggest immune loci harbour genetic variation in susceptibility. Studies are now underway using dense SNP chip technology to advance this area, and publication of genetic evaluations is being explored.

One of the reasons why the work on bovine TB is important is that genetics has often been ignored as being irrelevant in the epidemiology of pathogenic diseases. Yet the work on TB is beginning to demonstrate the value of ensuring genetic information is made available at an early stage, so that its role in the epidemiology, and its possible role in control, can be identified. One of the criticisms made of genetic analyses of field data has been that field data suffers from variation in exposure among animals, and may contain errors arising from diagnostic tests having less than perfect sensitivity and specificity. However, the latest quantitative genetic research has clearly shown that the impact of such variables is inevitably to underestimate the extent of genetic variation, sometimes to a large degree (Bishop and Woolliams 2010). Therefore, it might be anticipated that the impact of genetics in TB has also been underestimated.

There are other reasons why the impact of genetics on pathogenic diseases may be underestimated. For example, typical field data (Box 3) may only contain information on animals that did or did not contract the disease, and not on the order of infection. While such information is valuable for providing information on genetic variation in susceptibility to disease, it gives no information on genetic variation in infectivity. There is a steady flow of reports in the scientific literature on the impact of super-shedders on the persistence and spread of various diseases (Chase-Topping and others 2008). It would be surprising if some of this variation in some diseases was not genetic in origin.

While there are good reasons to suppose that genetics can play a much greater role in controlling the impact of diseases in cattle, it is not being argued that it is a panacea for all ills. It is most likely that genetic variation in complex diseases is of the form that reduces the frequency and severity of outbreaks, rather than avoiding their occurrence altogether. For this reason, the most effective targets for utilising genetic variation should be endemic diseases.

A measure of how easily a pathogen spreads through a population is R_0. In endemic disease, the value of R_0 may not be much greater than 1. If R_0 is less than 1, then major epidemics will not occur. For these diseases, selection to reduce the susceptibility of the population would have the most impact on management of disease. For example, using genetics to reduce the very high R_0 for foot-and-mouth disease in cattle would not avoid the need for the current surveillance and response procedures, whereas reducing R_0 in TB (which has been estimated to be 1·1) may have an important impact, notwithstanding the environmental reservoir of infection.

Summary

Animal populations with small effective population sizes and high rates of inbreeding have an increased risk of developing diseases associated with recessive defective alleles. Historically, these have spread insidiously through populations due to the difficulty of identifying carriers, but new technology is promising to dramatically reduce this problem, providing that DNA from cases is obtained. The rapid development of genomic technology, including sequencing, is likely to raise the profile of genetic solutions to some endemic diseases. However, surveillance responses that recognise the critical role of DNA banks and biobanks are critical to realising this potential.

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Self-assessment test: Influence of genetics and inbreeding on disease

1. What is the curse in the 'curse of the recessive'?
   a. The associated disease is invariably fatal
   b. The deleterious allele is far more common than the prevalence of the disease
   c. Half the offspring of a sire carrying the defective allele develop the associated disease
   d. The occurrence of the associated disease shows the population is highly inbred

2. What effect does a diagnostic test with imperfect sensitivity and/or specificity have on identifying the genetic basis of a disease?
   a. It makes the genetic analysis untrustworthy as their impact is unpredictable
   b. It does not have much effect as diseases that suffer from these problems of field recording have no genetic variation anyway
   c. It causes the heritability to be overestimated and inflates the importance of genetics
   d. It causes the heritability to be underestimated and deflates the importance of genetics

3. When a breed has an average inbreeding coefficient greater than 0·3 then it should be crossed with another breed. True or false?

4. Which of the following is the most effective first step towards utilising genetics to control disease?
   a. Starting up a database on the disease within the practice
   b. Avoiding breeding from the dam of the case
   c. Avoiding breeding from the sire of the case
   d. Taking a sample from the case, from which DNA can be extracted and recording the details, and, with the owners permission, notifying the breed society and other vets

Answers

1. b. Diseases associated with defective recessive alleles do not have to be fatal although the term 'disease' implies a deleterious effect. The fraction of offspring of a carrier sire that develop the disease will depend on the frequency of the defective allele in the population. A disease caused by a recessive defective allele can occur in any population.
2. d. Theory shows that the heritability is systematically underestimated to a degree that is predictable given the test parameters and so, unless the estimates are appropriately corrected, the importance of genetics is underestimated. Diseases caused by all types of pathogen have been shown to have substantial genetic variation.
3. False. There is no threshold on the inbreeding coefficient that is meaningful in this way, as the inbreeding coefficient always depends on the genetic base used for the calculation and so, in isolation, gives no information on how well the breed has been managed genetically. A more meaningful criterion on whether a breed needs to open up its gene pool is whether there is evidence of lack of fitness concurrent with a high rate of inbreeding.
4. d, although none of the others do any harm. Minimising the suffering across the population relies on identifying the genetic basis of the disease and developing a test that predicts genetic risk as quickly as possible. Genomics using new DNA technology is increasingly effective in developing predictive tests even for complex multifactorial diseases. However, the existence of a reliable DNA bank is crucial.

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