IE Q&A

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Following the announcement that a DNA-based test had been identified for idiopathic epilepsy (IE) (*Hereford World* March issue, Page 12, and April issue, Page 10), many questions have been asked about the test and how to use the information it provides in a breeding program. The following is a list of commonly asked questions and answers to help breeders better understand the test and the defect itself.

How accurate is the DNA test for IE?

There are two distinct components that contribute to the accuracy of any DNA test. The first component involves the scientific data that underlie the test. The second component is the design and execution of the diagnostic assay performed as part of the testing procedure.

From a scientific standpoint, the IE test is based on the presence of a specific change or mutation in the DNA sequence of an animal. This change occurs within a gene (i.e., a sequence in the DNA that encodes a protein) that is expressed in the nervous system of the animal. The mutation results in the production of a protein that is unable to carry out its normal function.

An example of how this happens can be demonstrated by comparing this protein to a simple sentence composed of three letter words, THE CAT SAW THE DOG. If a single letter (M) is inserted within these words, as in the case of the IE mutation, then the new sentence (i.e., containing the insertion) would be THE CMA TSA WTH EDO G. Clearly, the sentence, like the protein, does not have the same meaning after the change has occurred.

After the specific mutation was identified, several experiments were conducted to validate the relationship between the mutation and IE. Two types of validation experiments were performed, which included the blind testing of animals with previously known IE status and analyzing the frequency of the mutation among unaffected cattle within the Hereford and other beef breeds.

In all validations, the test performed as expected. All blind samples were correctly classified by the test in accordance with their known IE status. Additionally, no unaffected animal tested as homozygous for the mutation and the mutation was only found in lines of cattle that had produced affected IE calves. The mutation was also not found in any of the other breeds of cattle examined. Therefore, we believe that the scientific basis of the test is accurate; in other words, testing for this specific mutation will lead to correct classification of any animal.

In regard to the diagnostic assay that is used for determining an animal's IE status, the test has undergone several optimizations that also lead us to believe that the test is highly reproducible and accurate.

However, as with any task requiring human intervention, errors can occur. Of course, we do our best to limit any errors by automating portions of the test and appropriately incorporating testing controls. Although we cannot guarantee perfection, we estimate the assay may have an error rate of around 1 in 10,000. Related to the accuracy of the test, breeders should be reminded that part of the testing process depends on accurate collection and documentation of the samples being submitted for testing.

How do I interpret the results of the IE test?

In genetics terminology, different variants (DNA sequences) of the same gene are referred to as alleles. Each individual has two alleles for every gene, one inherited from its father and one inherited from its mother. These two alleles can be the same, termed homozygous, or they can be different, termed heterozygous. The DNA test detects both the normal and mutant alleles of the IE gene. Thus, according to the basic principles of genetics, there are three possible outcomes of the test. An individual can be homozygous for the normal DNA sequence (i.e., both chromosomes have the normal allele), heterozygous for one normal allele and one mutant allele or homozygous with the mutant allele.

Animals that are homozygous for the normal allele can never produce a calf affected with IE or pass on the IE mutant allele to any of their offspring. As such we refer to these animals as IE-Free (IEF). Animals that are heterozygous are referred to as IE-Carrier (IEC) because, although they are normal in appearance, they have one IE mutant allele and can pass it on to their offspring. An animal that has IE symptoms is homozygous for the mutant allele and is referred to as IE-Affected (IEA).

Where did IE come from?

The mutation causing IE is most likely the result of a spontaneous error during the normal cellular process of DNA replication (i.e., the synthesis of new DNA prior to cell division). If this error occurs in an animal's reproductive cells, such as sperm and eggs, the DNA mutation becomes heritable (meaning that it can be passed on to the next generation of offspring).

This is a normal occurrence that happens with a predictable frequency. In fact, this is one of the mechanisms that contribute to genetic diversity within populations. The vast majority of these mutational events have no consequence. However, on rare occasions, these mutations occur in important regions of the DNA sequence. In these instances, some of the changes can result in desirable changes in the "fitness" of an individual (e.g., enhanced performance or production). Alternatively, some mutations can have deleterious effects, as in the case of IE. These mutations often go undetected and naturally disappear from the breeding population. If the mutation has a positive effect or occurs in an individual that is used heavily for breeding, the mutation will eventually increase in frequency. As the frequency increases, there is an increased chance of producing individuals that are homozygous for the mutation; and at which point, deleterious mutations are recognized as genetic defects.

It should be noted that although linebreeding results in a more rapid increase in homozygosity, linebreeding or inbreeding is not the cause of genetic mutation.

Is there a specific line of cattle that is associated with IE?

Because the spontaneous mutation rate is very rare, specific mutations occur only within a single individual, called a founder. As such, within the population, all individuals that have the mutation can be traced to the founder. Thus, specific mutations are unique to

certain "lines" within populations. In the case of IE, all individuals with the mutation can be traced to a single individual born in 1982.

Within the Hereford breed, there are many lines of cattle that are frequently named based on the origin of the genetic resource. The IE founder individual is classified as a Line 1 animal, named for the linebreeding experiment that was initiated at the Fort Keogh Livestock and Range Research Laboratory in Miles City, Mont.

However, it is very important to recognize that cattle tracing back to the IE founder individual only represent a very small fraction of the population of Hereford cattle classified as Line 1. Furthermore, this founder individual was born outside the Miles City Research Station, and no animals within the Miles City herd have tested as IEC.

Thus, referring to IE as a "Line 1" problem is blatantly incorrect and should be vigorously denounced. Additionally, it is equally incorrect to suggest that the IE mutation was "caused" by the presence of non-Line 1 germplasm within the founder individual. In fact, molecular evidence (i.e., DNA sequence information) generated while the IE research was being conducted clearly indicates that the mutation occurred on a chromosome originating within Line 1 genetic material.

In summary, IE is restricted to a line of cattle defined by their relationship to a specific founder individual; however, breeders should be cautioned against referring to IE relative to the broader classification of Line 1 cattle within the Hereford breed.

What is the frequency of IE within the Hereford breed?

As indicated above, the IE mutation is restricted to a relatively small subpopulation within the breed. Thus, it is difficult to accurately estimate the frequency of the mutation for the entire Hereford population. Since the development of the DNA test for IE, almost 10,000 animals have been tested for the mutation. The vast majority of these samples were submitted based on the presence of IE-suspect relatives within their pedigrees.

Approximately 15% of the tested individuals were tested as IEC. Although this appears to be a relatively high frequency, it is important to remember that this estimate is biased due to selected testing of suspect cattle only. On the other hand, it is also important to recognize that with this moderate frequency of the mutation, IE should not be considered as a "negligible" issue within the breed.

Is there a publicly available list of animals that have been tested for IE?

Currently, there is not a publicly available list indicating the IE status of specific individuals that have been tested. However, since the development of the IE test, the American Hereford Association staff and Board have been actively working to establish policies regarding the listing of both IEF and IEC individuals.

Do other breeds have IE?

Although there are documented "epilepsy-like" disorders in other cattle breeds, it is highly unlikely that the underlying genetic basis is the same as that found in Hereford cattle. Furthermore, while a disorder may be generally described as epilepsy, each condition may have subtle differences in the pathology or presentation. This would indicate differences in underlying causes including both genetic and environmental conditions. Also, as mentioned above, spontaneous mutation is a relatively rare event. Thus, it would be virtually impossible for the same mutation to occur in another individual or highly unlikely for an independent mutation to occur within the same gene affected in IE. Additionally, because the mutation causing IE can be traced to a relatively recent founder individual within the Hereford breed, it would also be unlikely that seizure disorders described in other breeds prior to 1982 would be the same as IE.

Is it acceptable to use an IEC animal in a registered breeding program?

The general purpose of every breeding program is to accumulate genetic value from one generation to the next. To accomplish this goal, individual breeders use a number of criteria (e.g., phenotype, performance, EPDs, etc.) for making selective matings between parent individuals. For some breeders, an animal that is IEC has no value, and thus, they will choose not to use it. Over the long-term, this choice should be the goal of all seedstock producers.

However, at the same time, breeders should also recognize that there may be IEC animals with superior genetic merit for other traits that cannot be found among IEF animals. Availability of a DNA test for IE allows breeders to use IEC animals in order to extract the positive genetic merit for other traits while directly selecting against IE by testing the offspring and selecting those with the highest merit that are IEF.

This being said, breeders might consider the following guidelines for using IEC individuals. In regard to bulls, young or unproven individuals should be removed from the breeding population as soon as possible. Proven herd sires should be used on a limited basis until a potential IEF replacement can be produced. Females that are below average for performance should be culled or moved into a commercial production environment. Above average females can be bred to IEF bulls until a suitable IEF replacement is produced or potentially used as recipients for an ET program. Very few elite IEC females will merit use as ET donors. It should be noted that in all these situations, increased management of these animals will be required to ensure control over the inadvertent spread of IE.

How about using IEC animals in a commercial program?

Although it would be best to limit the use of IEC animals in any breeding program, IEC individuals may have some utility within the commercial production environment where calves are destined for terminal use. Because IE is a recessive genetic defect, calves affected with IE cannot be produced if at least one of the parents is IEF.

Thus, in a commercial production environment, producers would not need to worry about losses due to mortality of affected calves. Because this IE mutation is only found within Hereford cattle, the use of IEC animals in an intercross crossbreeding system would not produce any affected calves in the initial two-breed cross. The danger in using IEC animals in these situations is the potential for retention of replacement animals that may be IEC. If these IEC replacements were to be mated back to another IEC individual, affected calves may be produced. Therefore, with appropriate breeding management practices, IEC individuals can be used without economic consequence. **HW**