

Knowledge is Power

DNA technology makes genetic defects more observable, more manageable.

Story & photo by *Kasey Brown*, associate editor

Genetic defects. Those two small words can strike fear into the heart of any Angus breeder. However, with the increased availability and use of DNA technology offered, the identification of more defects may be the reality sooner rather than later, Dorian Garrick told attendees of the Beef Improvement Federation (BIF) 45th Annual Research Symposium and Convention this summer.

His prediction rang true all too soon for American Angus Association members. A “new” genetic condition has been identified and documented in Angus cattle from research initiated in Australia with Jonathan Beever at the University of Illinois. This condition, inherited as a simple recessive, has been designated as developmental duplication (DD).

Before you sell your whole herd, know that more-frequent identification of genetic defects isn’t necessarily a bad thing. One can choose to look at a glass as being half full or half empty. Garrick, Iowa State University (ISU) animal scientist and Jay Lush Endowed Chair in Animal Breeding and Genetics, says he believes defects, which are in all actuality broken genes, in beef cattle can be a glass half full.

Genomic background

Genomics is a complicated field of study, though Megan Rolf, Oklahoma State University, simplifies it with an analogy.

Genomes are like a stack of phone books, says Rolf. The assistant professor of beef cattle management and state extension specialist likens the DNA that comprises the genome to a string of letters within a phonebook. The lists of people within the books are the coding regions (genes), and the ads interspersed within the book are the non-coding regions. The genome changes by generation similarly to how phone books change over time with people moving in and out of town.



► “An adult contains something like 50-100 trillion cells, and any error that occurred during the copying of the chromosomes or their division into daughter cells will be propagated in subsequent divisions of the cell,” says Iowa State University’s Dorian Garrick.

Single nucleotide polymorphisms (SNPs) are DNA markers. These SNPs, explains Rolf, are like a “typo” in the phone book. These typos are the most commonly used markers in DNA tests. There are millions of these typos in the bovine genome.

Other types of mutations are insertions (adding people to the phone book), deletions (forgetting to print a few of the names in the phone book), duplications (adding people more than once), inversions (flipping a section of names), translocations (moving the names to a new spot in the book) and substitutions (SNPs). These typos are where we can gain information, including information as to where genes are broken.

Explaining broken genes

Broken genes provide information, and with this information comes more options, Garrick says.

While most Angus breeders would say that the list of genetic defects is far too long, Garrick says the list is actually appallingly short. He cites some research by Matt Spangler at the University of Nebraska–Lincoln that shows there are only 11 defects being observed by U.S. beef breed associations (<http://ianrpubs.unl.edu/live/g2055/build/g2055.pdf>). Of these, seven are lethal and four are nonlethal.

Any malformed or dead calf should garner suspicion if the malformation reoccurs within families or at an increased frequency.

“Too often, seedstock producers use the ‘shoot, shovel and shut up’ method. Instead, samples from those calves should be sent in for testing. Many well-known defects have yet to be characterized because of the lack of availability of

DNA samples,” he says.

The fact that chromosomes occur in pairs means that an individual inherits two copies of every gene, one from each parent — except for some genes on the sex chromosomes. A mutation in one copy of the gene may not be very serious as long as the other copy is functional. When an animal is mated to its relatives, which may have inherited the same broken gene, mutations can be discovered in the progeny.

Genetic mutations are not a new occurrence. Every individual inherits a number of dysfunctional genes from both its sire and its dam, Garrick notes.

On average, half of these mutations will be passed on to the offspring, along with new mutations that are new to the sperm or the egg, or which occur between the time of conception and the time the animal becomes a parent. Due to the nature of the beef industry, many of these mutations never surface because those animals don’t become parents.

From a population perspective, there is balance between the creation of new mutations and the loss of existing mutations.

We are most likely to see genetic conditions arise from progeny of widely used sires, because they pass on their mutations to a large number of progeny. Because of this, certain rare mutations can occur more frequently in just one generation.

Detecting a genetic defect from these mutations may be more difficult when it is displayed as an embryonic lethal (the condition prevents the maintenance of pregnancy) or just slightly reduces performance.

Embryonic lethals require a high proportion of carriers before they become noticeable by reduced conception rate, increased rate of pregnancy failure or extended days to calving, he clarifies. These are unlikely to be detected in small herds, or herds that have a few progeny from multiple sires. Garrick says there is no chance of detection without total-herd reporting in these cases.

Mutations may be caused by deletions, duplications, inversions, translocations and substitutions of one or more of the bases, he describes. A mutation that changes an amino acid can sometimes affect the larger protein. A subtle change can stop the protein from working. He likens this to a baseball glove without the webbing. Other mutations may result in a premature “stop” instruction in the genetic code.

When the protein becomes dysfunctional, or “broken,” it is known as a loss-of-function mutation.

Managing defects

As long as carriers of these broken genes aren't bred to each other (avoiding inbreeding), these loss-of-function genes aren't a real issue, Garrick says. If relatives are bred and the defect is observed, the mutations can be found with a 50K high-density genomic test.

His tips to commercial producers to manage this genetic variation was to crossbreed (would require using breeds that don't share parent stock), because different breeds likely have different mutations; outbreed, by avoiding sons of herd sires; or put up with it and submit DNA samples on suspicious animals.

He advised seedstock producers to change the “shoot, shovel and shut up” mentality. Submit DNA samples on suspicious deaths. Using SNP genotyping on all prospective herd sires, and preferably all breeding stock, and DNA testing for known defects will also help. Garrick says culling all carrier parents, especially on outstanding animals, is *not* needed. Instead of culling, he suggested selecting clean offspring for subsequent use.

They're all carriers of something

Cattle typically have 30 pairs of chromosomes, comprising 29 pairs of autosomes and XX or XY sex chromosomes. Chromosomes are made from DNA, which consists of a sequence of bound paired chemical compounds, known as nucleotides, which are made up of a nitrogenous base, a sugar, and some phosphate groups. There are four kinds of nucleotides — adenine (A), guanine (G), thymine (T) and cytosine (C) — and the sequence of these four compounds dictates the genetic characteristics of an individual.

A typical cattle chromosome consists of 100 million base pairs and occurs in two versions, one inherited from the sire and the other inherited from the dam. Accordingly, the genome consists of 3 billion base pairs inherited from one parent, and a similar number inherited from the other. After fertilization, these 6 billion base pairs must be copied every time a cell divides, in a process known as mitosis. An adult contains something like 50-100 trillion cells, and any error that occurred during the copying of the chromosomes or their division into daughter cells will be propagated in subsequent divisions of the cell.

During development, cells specialize to form around 200 different cell types, including those different types found in muscle, fat, skin, blood and various organs. Most errors that occur in DNA replication are not passed on to offspring — only those cells that form parts of the testicular or ovarian tissue can contribute to the genomes of future generations.

Changes in genomic sequence such as those that arise from DNA copying errors are known as mutations. There are a number of different kinds of mutations that can arise. Sometimes one base pair (A, G, T or C) is mistakenly copied for an alternate base pair. This is known as a single nucleotide polymorphism (SNP). Other mutations might involve the accidental duplication of a piece of DNA; an accidental deletion of a piece of DNA; or an inversion, whereby the sequence is partially reversed.

Errors in copying DNA are very common, perhaps one in every 100 base pairs, but the cell has DNA repair mechanisms that identify and repair almost all of the errors. The typical error rate remaining after the repairs is something like one in every 30 million nucleotides each generation, or a little over three mutations per chromosome per generation.

— Dorian Garrick, excerpt from 2013 BIF proceedings, which can be found in its entirety beginning on page 250.

Genetic defects don't just affect breeders; they also affect artificial insemination (AI) companies. Garrick suggests using SNP genotype tests on all AI sires. For bulls that are to be very widely used, he says individually sequencing bulls is a good way to learn more. Liability is a tricky issue, so he says AI companies should have their bases covered with as much testing as they can manage.

For the beef industry and science community, he recommends sequencing widely used historical bulls, and annotating variants that might be damaging. These variants could then be populated in SNP-chip tests. He grants that these interesting variants must be validated and, thus, test results must be communicated. He urges the scientific community to further develop and implement decision-support tools to manage the selection and mating of carrier animals.

His advice to breed associations is quite applicable to the American Angus Association. He recommends collecting as much phenotypic data as possible, especially on reproductive traits from total herd records. He also encourages a wider use of genomic panels, which are particularly beneficial on entire (and those

unselected) cohorts; explore the opportunities to deliver decision-support tools; and to expect to record more single-gene information.

Garrick concluded that management is imperative. Selection and culling should be aimed at increasing the frequency of favorable alleles and reducing the frequency of unfavorable alleles.

Garrick spoke during the BIF symposium's general session focused on “Using Genetic Tools to Address Environmental Challenges and Cow Herd Efficiency Developments.” His proceedings paper is provided in its entirety in the BIF section of this issue and begins on page 250. To access the PowerPoint accompanying his presentation and/or to listen to the presentation firsthand, visit the newsroom at www.bifconference.com, the *Angus Journal's* event coverage site for the annual BIF symposium. Coverage of the event is made possible through collaboration with BIF and sponsorship of *LiveAuctions.tv*.

