

2014 - 9



Genetic Defects

Alison Van Eenennaam

University of California, Davis
alvaneennaam@ucdavis.edu

Dr. Darrh Bullock
Dr. Jared Decker
Dr. Megan Rolf
Dr. Matthew Spangler
Dr. Alison Van Eenennaam
Dr. Robert Weaver



What is a genetic defect?

Chromosomes inherited from parents determine an animal's genetic make-up. Chromosomes come in pairs; one chromosome from each pair is inherited from an individual's sire and the other chromosome is inherited from its dam. There are thousands of genes on each chromosome. **Genes** are the basic units of inheritance and they comprise distinct sequences of DNA (A's, T's, C's and G's) that contain all of the instructions for making proteins. It is common for the DNA sequence that makes up a gene or "locus" to differ between individuals. These alternative DNA sequences or forms of a gene are called **alleles**, and they can result in differences in the amount or sequence of protein being produced by that gene among different individual animals. A single nucleotide polymorphism, or **SNP** (pronounced "snip"), occurs when alleles differ from each other by the sequence of only a single nucleotide base pair (e.g. one individual has a G and another has a T at a particular position in the gene as shown in **Figure 1**).

However, when the SNP does produce an allele that can cause a phenotypic difference between individuals this variation provides the basis for selection programs and genetic improvement. Mutations are not always associated with decreased fitness, and in fact mutations can have positive effects and are the driving force of adaptive evolution. Mutations are a relatively common occurrence, and it has been estimated that the average human carries approximately 1,000 detrimental SNP mutations.

It is important to understand that these differences between individuals occur because of mutations in the DNA sequence and that this variation provides the basis for selection programs and genetic improvement. Mutations are not always associated with decreased fitness; in fact mutations provide the starting variation for adaptive evolution. Mutations are relatively common, occurring every generation. It has been estimated that the average human carries approximately 250-300 loss-of-function mutations in known genes, and 50-100 mutations previously implicated in inherited disorders.

A **genetic defect** is a mutation that results in an allele with an undesirable **phenotype** (i.e. disease or trait). Some mutations result in gross hereditary defects such as abnormalities in skeleton, body form, and body functions.

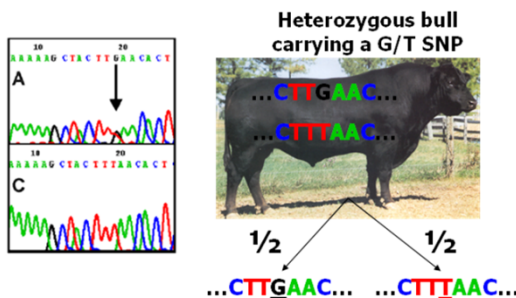


Figure 1. A heterozygous bull with a G/T SNP produces 50% sperm carrying the "G" SNP and 50% sperm carrying the "T" SNP.

This factsheet was developed as part of USDA NIFA grants # 2013-68004-20364 #2011-68004-30367 #2011-68004-30214



United States Department of Agriculture
National Institute of Food and Agriculture

Others are associated with a phenotype that may be advantageous in some situations and disadvantageous in others (e.g. presence or absence of horns). **Homozygous** is a term used to refer to an animal that carries two identical alleles of a gene (e.g. AA), and the term **heterozygous** is used to describe an animal that inherited differing alleles of a gene from each of its parents (e.g. Aa). Alleles can be **recessive**, meaning that an animal must inherit the same allele from both parents (i.e. be homozygous) before there is an effect, **additive** meaning that the effect is proportional to the number of alleles inherited by the animal (i.e. carrying two copies of a particular allele produces double the effect of carrying one copy), or **dominant** meaning that the inheritance of a single dominant allele can completely mask the expression of the allele inherited from the other parent.

Coat color is an example of a trait with complete dominance where the black

coat color allele (B) is completely dominant to the red coat color allele (b). Crossing a homozygous dominant “BB” black bull to a homozygous recessive “bb” red cow will result in all heterozygous black “Bb” offspring.

Many genetic defects are recessive, and the reason for this is that mutant alleles often render the resulting protein nonfunctional. In many cases if an individual inherits a functional allele from one parent, there is no phenotype associated with inheriting the nonfunctional mutant allele from the other parent. As such a heterozygous “Aa” (A symbolizes the dominant allele, a the recessive allele) animal, or carrier, appears normal. Because carriers appear normal, recessive alleles can increase in frequency in a population more easily than dominant or additive alleles. It is only when two carriers mate that there is the possibility of producing offspring that have by chance inherited both of the non-functional alleles from

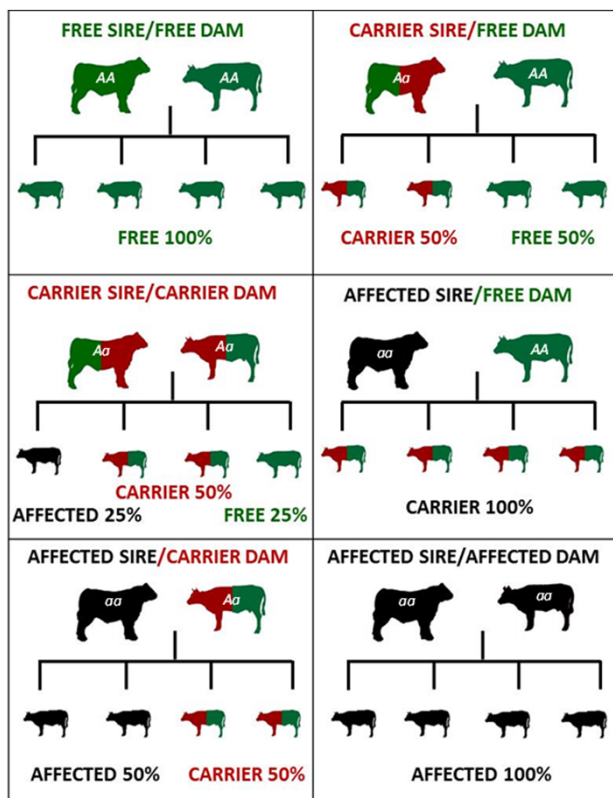


Figure 2. Mating combinations that are possible for an autosomal (non sex-associated) recessive genetic condition. Free means that the animal is carrying two functional copies of the allele. Affected means two loss-of-function copies.



This factsheet was developed as part of USDA NIFA grants # 2013-68004-20364 #2011-68004-30367 #2011-68004-30214



their parents. The example gene combinations that can occur with a recessive genetic condition are shown in **Figure 2**. Note that if this is a lethal genetic condition then all of the animals that are represented as solid black would not be alive and so the only possible matings would be between unaffected (green) and carrier (green and red) individuals.

All animals are carriers of mutations somewhere in their DNA for one or many recessive traits. Because an animal must inherit two copies of a given recessive mutation to be affected, and with only a few animals typically sharing the same mutation in the whole population, there is rarely a mating that has the potential to create affected offspring. It is when relatives are mated that there is an increased possibility that offspring will inherit the mutant allele on both sides of the family tree.

Although the cumulative costs of testing for genetic defects have been substantial, they are dwarfed by what it would have cost to eliminate all of the descendants of widely used carrier

bulls. The speed with which these genetic tests were developed is testament to the power of having access to the bovine genome sequence information, and is perhaps the greatest success story of genomics never told. The proactive response of the breed association in making genotypes available also helped to rapidly and transparently address the problem. The sooner a defect is recognized and the genetic cause identified, the sooner it can be managed.

The term **genotyping** refers to the process of using laboratory methods to determine which alleles an individual animal carries, usually at one particular gene or “locus” in the genome. The **genotype** identifies which alleles an animal carries. Producers must send in samples containing DNA from animals to be tested to the testing lab. Because all cells contain DNA, it is possible to genotype many different tissue types; however, laboratories may differ in their preferred sample type. Typical samples include blood vials or cards, semen, and tail hair samples. It is important that tail hair samples include the roots - ideally 30-50 hairs with intact roots.



Table I. Recessive genetic conditions currently being monitored by U.S. breed associations.

<i>Genetic Abnormality</i>	<i>Primary Breed(s) of Incidence</i>	<i>Lethal or Nonlethal</i>	<i>DNA Test Available</i>
Alpha (α)-Mannosidosis (MA)	Red Angus	Lethal	Yes
Arthrogryposis Multiplex (AM)	Angus	Lethal	Yes
Beta (β)-Mannosidosis	Salers	Lethal	Yes
Bovine Blood Coagulation Factor XIII Deficiency (F13)	Wagyu	Nonlethal	Yes
Chediak-Higashi Syndrome (CHS)	Wagyu	Nonlethal	Yes
Claudin 16 Deficiency (CL16)	Wagyu	Nonlethal	Yes
Contractural Arachnodactyly (CA)	Angus	Nonlethal	Yes
Developmental Duplication (DD)	Angus	Nonlethal	Yes
Dwarfism (D2)	Angus	Nonlethal	Yes
Bulldog Dwarfism (BD)/ (Chondrodysplasia)	Dexter	Lethal	Yes
Erythrocyte Membrane Protein Band III Deficiency (Spherocytosis) (Band 3)	Wagyu	Often lethal	Yes
Hypotrichosis (hairless calf)	Hereford	Nonlethal	No
Factor XI Deficiency (F11)	Wagyu	Nonlethal	Yes
Freemartin (FM)	All	Sterile female	Yes
Idiopathic Epilepsy (IE)	Hereford	Nonlethal	Yes
Neuropathic Hydrocephalus (NH)	Angus	Lethal	Yes
Osteopetrosis (OS)	Angus and Red Angus	Lethal	Yes (Red Angus)
Protoporphyrria	Limousin	Nonlethal	Yes
Pulmonary Hypoplasia and Anasarca (PHA)	Maine-Anjou and Shorthorn; Dexter	Lethal	Yes
Tibial Hemimelia (TH)	Shorthorn and Maine-Anjou	Lethal	Yes

This factsheet was developed as part of USDA NIFA grants # 2013-68004-20364 #2011-68004-30367 #2011-68004-30214



There are videos on sampling DNA from cattle tail hair at

<http://tinyurl.com/eBEEF-TailHair> and using an FTA blood card at <http://tinyurl.com/eBEEF-FTA>.

If you are sampling DNA from a deceased animal, call the testing laboratory to determine the best protocol. It is important to get a good quality sample to ensure the DNA test will be able to generate results. The cost of testing varies depending upon the company and how many tests are performed but ranges from \$10-40/test; with an average of ~\$25/test. Irrespective of carrier animals in its pedigree, an animal that has been tested and found to be a non-carrier did not inherit the mutant allele and will not transmit the genetic defect to its progeny.

Test Abbreviations

AM - Arthrogyposis Multiplex
BLAD - Bovine leukocyte adhesion deficiency
BD - Bulldog Dwarfism - Chondrodysplasia
CA - Contractural Arachnodactyly /Fawn Calf
CC - Black/Red Coat Color
CVM - Complex Vertebral Malformation
D2 - Angus Dwarfism
DD - Developmental Duplication
DL - Dilution
IE - Idiopathic Epilepsy
FM - Freemartin
HY - Hypotrichosis
MA - Alpha-Mannosidosis
NH - Neuropathic Hydrocephalus
PHA - Pulmonary Hypoplasia with Anasarca
OS - Osteopetrosis
TH - Tibial Hemimelia
NH - Neuropathic Hydrocephalus

GENETIC TESTING COMPANIES

Agrigenomics <http://www.agrigenomics-inc.com/index.html>

P: 217-762-9808

Tests available: AM, BD, CA, CC, D2, DD, DL, IE, FM, HY, MA, NH, PHA, OS, TH

Gene Seek/Neogen

<http://www.neogen.com/agrigenomics/Beef.html#Seedstock> P: 1-877-443-6489

Stand Alone tests: AM, BD, BLAD, CA, CC, CVM D2, DD, DL, IE, FM, HY, MA, NH, PHA, OS, TH, Slick coat, Dunn color, Slick Coat, Brachyspina, and Hypotrichosis

(bald calves). The following genetic tests are included in the GGP_HD (~80K) panel:

Angus Dwarfism (D2), Brahman Dwarfism (BD), Arachnomelia, Crooked tail syndrome Belgian Blue, Epidermolysis bullosa, GSDV myophosphorylase, Mannosidosis, Beta (β)-Mannosidosis, MFN2, Degenerative Axonopathy MSUD (maple syrup urine disease), Mulefoot, OS, Protoporphyrin, SDM (spinal dysmyelination), SMA (spinal muscular atrophy), Tyrosinase OA (oculocutaneous albinism), BLAD, CHS, Citrullinemia, Congenital muscular dystony (CMD1) Belgian Blue, Dilated Cardiomyopathy, DL, Dun Color, Ichthyosis Fetalis (IF), Brachyspina, Fish Milk, Hypotrichosis KRT71, HY, PMel1, IE, NH, PHA, TH, TH-outcast (tibial hemimelia)

Genetic Visions

<http://www.geneticvisions.net/index.aspx>

P: 608-662-9170

Tests available: BLAD, BLG (Beta-lactoglobulin), Calpain 316/530, CC/RF, Citrullinemia, CVM, DUMPS (Deficiency of Uridine Monophosphate Synthase), FM, KCN (Kappa-Casein)

Genex

<http://genex.crinet.com/page3767/BEEFDNATES>

TING P: 1-888-333-1783

Tests available: AM, CA, NH, OS

SEK Genetics

<http://www.sekgenetics.com/testing.html#am-nh-test>

P: 1-800-443-6389

Tests available: AM, CA, NH, PHA, TH, PHA

Stockman's Resource Center, LLC

www.stockmansresource.com

P: 1-641-969-4111

Tests available: AM, CA, and NH

Quantum Genetics (Canada)

<http://genetix.quantumgenetix.com/services>

Ph: 306-956-2071

Tests available: AM, CA, Leptin, MA, NH, OS,

University of California, Veterinary Genetics Laboratory

<http://www.vgl.ucdavis.edu>

Ph: 1-530-752-2211

Tests available: BD, DL, FM, Dexter Dun, Extension (Red/Black), PHA

Zoetis

<https://www.zoetis.com/products/animal-genetics/testingresultsforanimalgenetics.aspx>

Ph: 1-877-233-3362

Tests available: AM, CA, DD, IE, MA, NH, OS, PHA, TH



This factsheet was developed as part of USDA NIFA grants # 2013-68004-20364 #2011-68004-30367 #2011-68004-30214



United States Department of Agriculture
National Institute of Food and Agriculture