



Common Genetic Defects in Domestic Animals

Michelle M. Balbin, DVM

Philippine Carabao Center
National Headquarters and Gene Pool
Science City of Munoz, Nueva Ecija

Livestock Production

- Improvement in the production of animals was based on the phenotype
- The demand for food also increased parallel to increased in population as well as urbanization

Commodity	Projected growth of consumption (%yr)	Total consumption (million metric tons)		Per capita consumption (kg)	
		1997	2020	1997	2020
Beef	2.9	27	47	6	7
Pork	2.9	47	81	10	13
Poultry	2.9	29	49	7	8
Meat	2.9	111	188	25	30
Milk	2.9	194	391	43	62

Production

Palay:	18.44 million metric tons
Corn:	7.38 million metric tons
Hog:	2.01 million metric tons
Chicken:	1.56 million metric tons
Number of Agricultural Farms: (2002)	4.82 million
Palay:	2.15 million
Corn:	1.46 million
Coconut:	2.60 million
Sugarcane:	0.17 million

In 2013, production of palay was 2.26 percent higher than the 2012 record. Corn production was down by 0.40 percent. Production of hog increased by 1.95 percent while that of chicken grew by 5.11 percent.

- Increasing the number of animals to meet the demand would also increase pollution
- There is a need to introduce new technologies even improve the animal production

Genetic Improvement Program

The prime objective is to increase the productivity and disease resistance ability of economically important farm animal breeds to meet the increasing demands of animal products.

- **Selection** of best animal in the herd to be used as a breeder animal
- **Cross-breeding** to a local breed or other breeds to increase the productivity of the offspring or next generation

The traditional method of livestock improvement was based on their phenotype

Marker-assisted selection vs Trait-assisted selection

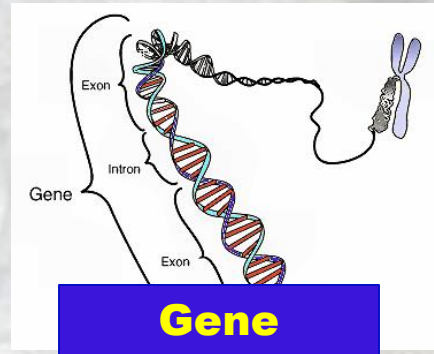
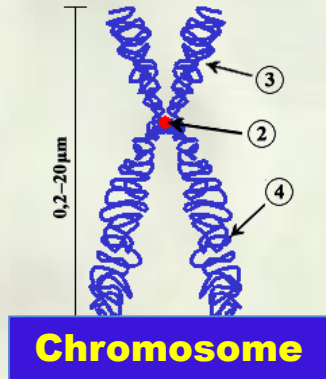
Trait-assisted

- Selection is based on phenotypes
- Requires pedigree and performance records
- Progeny test required
- Heritability based on predicted breeding value

Marker-assisted

- Selection is based on genes that have a favorable effect on the performance of the animal
- Identification of a useful trait at an early age

From Genotype to Phenotype



```
ATTCATTGTTGGATTGTGGCGCTTCACTCCTGCTGGCGGCCGGC  
AGGGGGCGGAGTTCGAGCCTGGATTCTCGGGGCCTCCCCGG  
GAGGCCGTCCCGCGTGGGGGAGGGGAGGACGGGGCGGGAG
```

DNA

The gene is the **blueprint** of a trait/response

```
ATTCATTGTTGGATTGTGGCGCTCACTCCTGCT  
GGCGGCCGGCAGGGGGCGGAGTTCGAGCCTG  
GATTCTCGGGGCCTCCCCGGAGGCCGTCCC  
GGCGTGGGGGAGGGAGGACGGGGCGGGAG  
GACGCG GTTC
```

RNA



```
IKRIVLELQG  
SETRFTCEYD  
DATVKAVEFL  
NKWITFCQSI
```

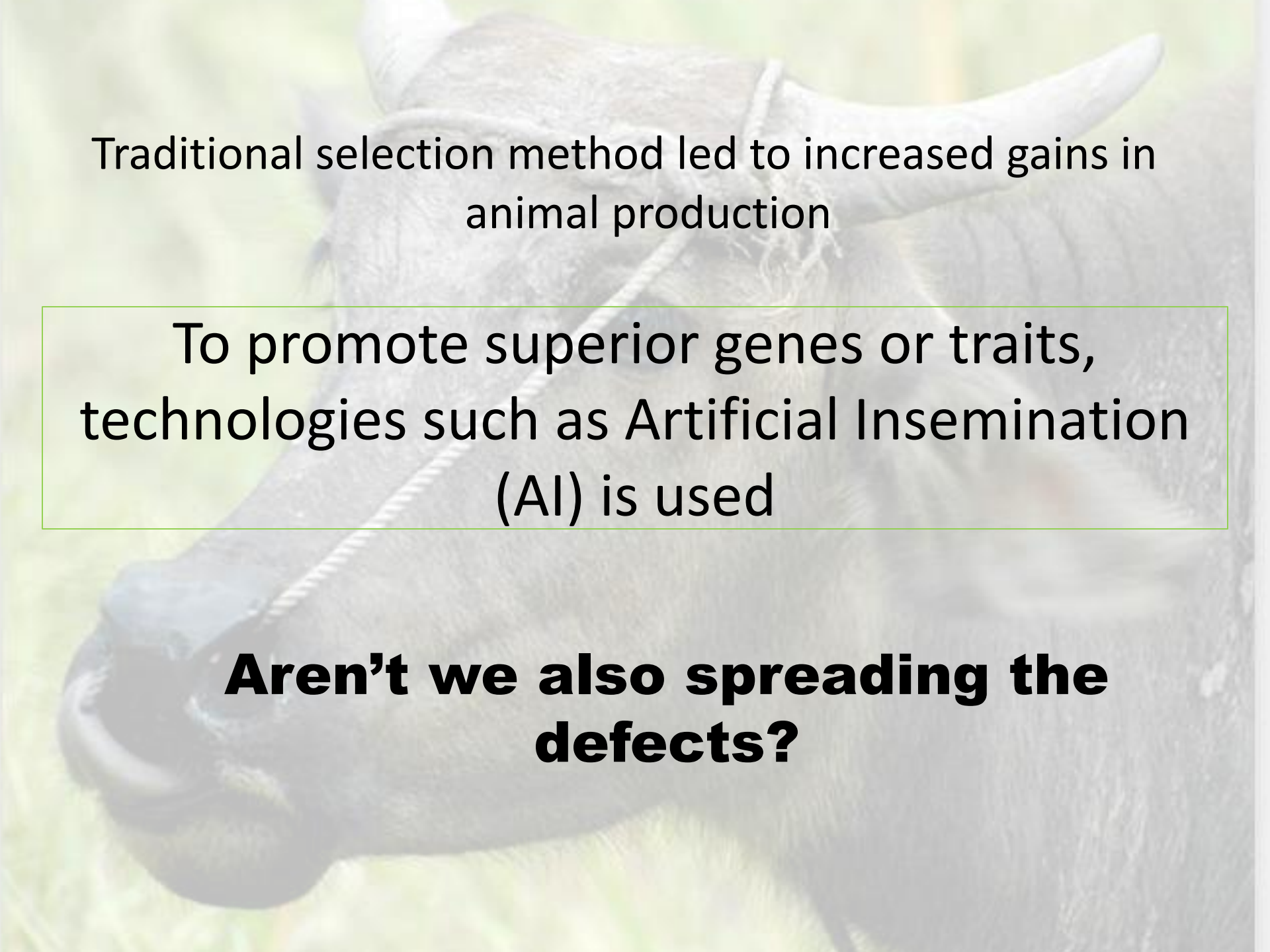
Protein



TRAIT

RESPONSE

DNA is transcribed to RNA which is translated to PROTEIN with specific **structure/ functions**



Traditional selection method led to increased gains in animal production

To promote superior genes or traits, technologies such as Artificial Insemination (AI) is used

Aren't we also spreading the defects?

A water buffalo with a decorative collar is the background of the slide. The buffalo is dark-colored and has a thick, shaggy coat. It is wearing a collar with intricate, light-colored patterns. The background is a soft, out-of-focus green, suggesting a natural outdoor setting.

Genetic Defect/Disease

- An illness caused by inborn abnormalities in genes or chromosomes
- Caused by vertical transmission of defective genes to the offspring
- Genetic defects are of minor concern in production, but increase in frequency and number of carrier animals of these alleles/defects may cause significant loss in the industry

Insertions, deletions, and substitutions may modify responses

CATTGTTGGATTG



CATTGTTGCATTG

Change
in
PROTEIN

Change in
structure or
function

Substitution in
gene sequence

Altered
protein

Change in
phenotype

Impact to the Industry

Animals with genetic defect:

- Poor animal performance (reduced production)
- Structural unsoundness (abnormal anatomy)
- Semi-lethal disease/Lethal disease

Most common inheritance pattern of genetic disease is a simple recessive trait



DAM (Mm)



SIRE (Mm)



NORMAL (MM)



CARRIER (Mm)



WITH DEFECT (mm)

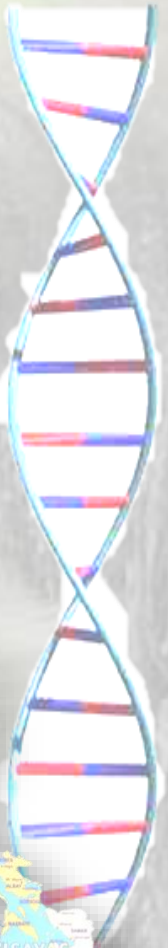


CARRIER (Mm)

Carrier animals does not manifest any signs of the underlying defect, therefore they can be the “silent transmitter” of the gene causing defects

Aren't we also spreading the defects?

Testing your herd will help avoid economic losses due to genetic defects





Genetic Defects Common in Domestic Animals

Arthrogryposis Multilpex (Curly Calf Syndrome)

- Generally found in Angus cattle
- Disease is due to deletion of a section of DNA (at least 38,000bp)
- this defect is an autosomal recessive trait
- no protein is produced due to the deletion
- Main clinical symptoms are:
bilateral tibia (twisted rear leg with ankylosed joints)
Abdominal hernia and cranial defect (cranioschisis with meningocele)



Syndactylism (Mule Foot)

- There is complete or partial fusion or non-division of the digits
- Caused by point mutation in the LRP4 gene that prevents normal splicing of the gene

Known to affect cattle (Holstein Angus) goat and sheep

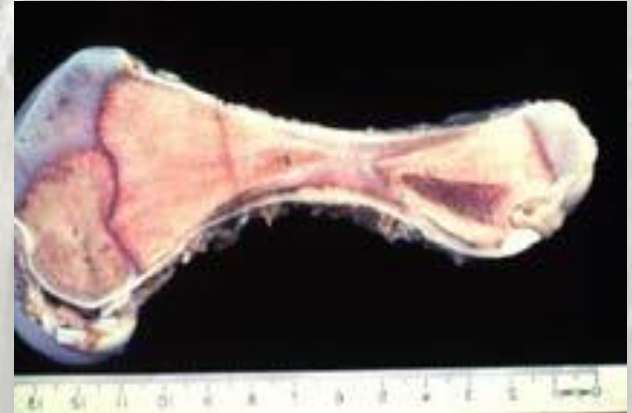
The affected animal is observed to have single hoof-like structure instead of normally paired claws

Animals walk slowly, have higher stepping gait, and are prone to hyperthermia



Osteopetrosis (Marble bone)

- A fatal autosomal genetic defect that affects Black and Red Angus, Hereford, Simmental and Holstein
- Calves are borne 10-30 days early
- They show head abnormalities such as brachygnathia inferior, impacted molars and protruding tongue
- The long bones of the affected animals are “shorter”
- Bones are very fragile and can be easily broken
- Caused by a deletion in SLC4A2 gene on chromosome 4



http://www.uwyo.edu/vetsci/undergraduates/courses/pat_b_4110/2009_lectures/31_genetic_disease/html/class_notes.htm



WYOMING STATE VETERINARY LABORATORY

Hypotrichosis (Hairless Calf)

- There is complete or partial loss of hair but it will grow like short curly coat hair
- Calf has black diluted charcoal or chocolate colored hair
- Affected animal is prone to environmental stress and skin infections
- Affected gene is PMEL 17 (BTA5) encoding the premelanosome protein.
- Defect is due to a mutation (3bp is deleted, CTT in exon 1)
- Described in Angus, Ayrshire, Brangus, Holstein Friesian, Hereford, Polled-Hereford, Guernsey, Gelbvieh, Jersey, Normandy Maine, Charolais, and Simmental crosses.
- Most have autosomal recessive and/or sex-linked mode of inheritance
- 13 types is described in cattle

Hypotrichosis in other Livestock

- Breed affected is the Polled-Dorset
 - Wool is of poor quality
 - HR gene is affected (1313C/T leads to 438Gln/Stop)
 - Hypotrichosis in goats is associated with goiter
 - In swine, 2 forms are known
Mexican Hairless and German
- associated with goiter and death of homozygote



KANSAS STATE UNIVERSITY

Atresia Ani/Atresia Coli

This is the most common congenital defect of the lower GIT

The affected animal is observed to have absence of anal opening

This results when the dorsal membrane separating the rectum and anus fail to rupture

In female lambs or kids, the terminal portion of the rectum may open into the vagina



Inguinal Hernia/Scrotal Hernia

The viscera pass through the inguinal canal and may lie in the cavity of the tunica vaginalis

In scrotal hernia, there may be testicular degeneration



Inguinal Hernia/Scrotal Hernia

- Common in male pigs,
- In female pigs, genital development is arrested (animal becomes sterile)
- In stallions, it is characterized by signs of constant and severe abdominal pain
- In cattle, this defect is not common
- Surgical correction is done to preserve the breeding potential of the animal but is not always successful

Albinism

- Result of recent studies shows that it is an autosomal recessive disease
 - A single base substitution (G1431A), leads to conversion of tryptophan into a stop codon
 - This produces inactive or abnormal protein
 - The animal is characterised with white coat, non-pigmented skin and eyes, and pink mucosa
 - Non-pigmentation in the iris and retina leads to
-
- True albinism is associated with pink or pale eyes and increased solar radiation-induced neoplasm of the skin
 - It is noted in Icelandic sheep, Guernsey, Australian White, Brown Swiss and Charolais cattle.





Epitheliogenesis Imperfecta (Aplasia Cutis)

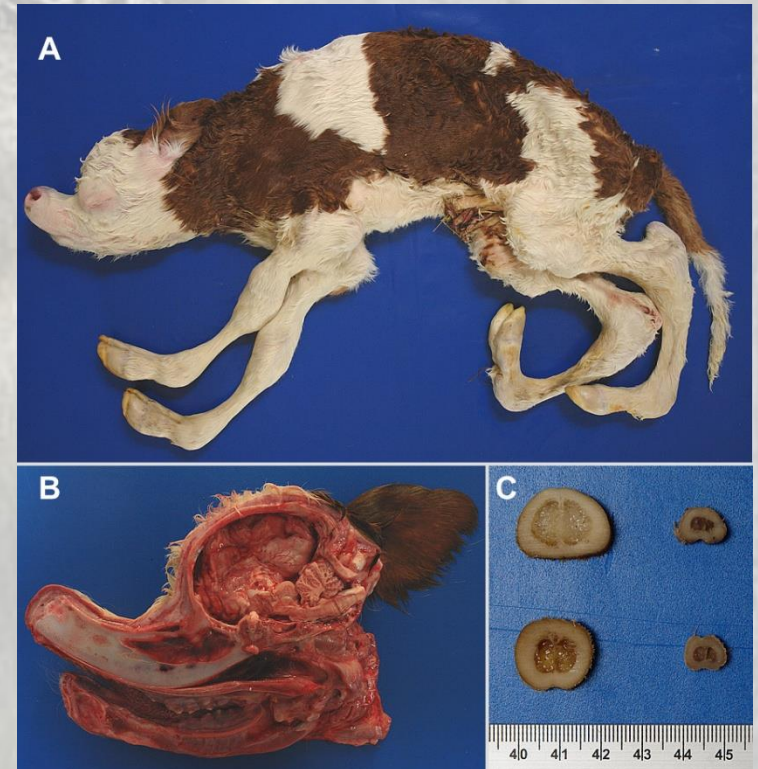
- **Lethal** and there is **lack of skin** on the distal parts of the limbs, deformed ear due to auricular epithelial defect, defects in the integument of the muzzle
- Related to **the defective metabolism of fibroblasts** impairing the nutrition of the epithelium
- Seen in cattle (autosomal recessive trait), horses, swine and sheep



Genetic Defects of Beef Cattle

Arachnomelia

- facial deformities characterised by short lower jaw and concave rounding of the dorsal profile of the maxilla is observed in affected animal
- deformities in the distal part of the hind leg (bilateral hyperextension of the fetlocks)
- Defect is due to SUOX gene (BTA5) encoding molybdehemoprotein sulphite oxidase
- Brown cattle – single base insertion (c.363-364insG) in exon 4 leading to premature stop
- Simmental cattle – single base deletion (c.1224-1225delC)

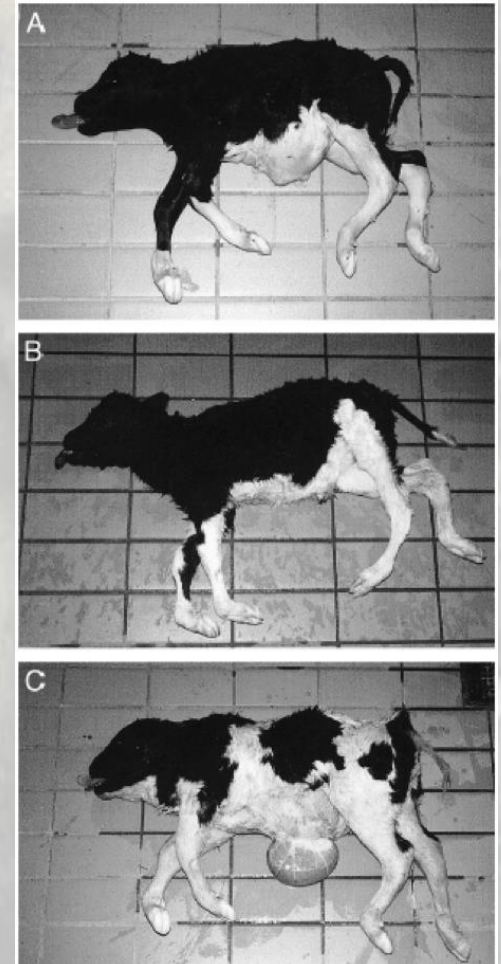




Genetic Defect in Dairy Cattle

Complex Vertebral Malformation (CVM)

- A lethal genetic defect in a single recessive gene
- Causes fetal resorption, abortion or stillbirth, have reduced fertility manifested as poor conception rate
- Skeletal malformations such as shortened neck and thorax, deformed carpal and metacarpal joints, distortion, twisting and hypoplasia of the tail
- The affected calf posses this mutation in both alleles, indicating autosomal recessive disorder
- It is observed in Holstein breed of cattle



Complex Vertebral Malformation (CVM)

- This is due to single base substitution in SLC35A3 gene
- There is missense (valine to phenylalanine) in genes SLC35A3 (Solute Carrier 35 Member 3) coding for uridinediphosphate-N-acetylglucosamine transporter.
- There is abnormal nucleotide-sugar transport into the Golgi apparatus, thus disrupting the normal protein glycosylation
- Prevalence:
 - Turkey: 3.4%
 - Japan: 32.5%
 - Denmark: 31%
 - Sweden: 23%
 - Poland: 24.8%
 - Germany: 13.2%

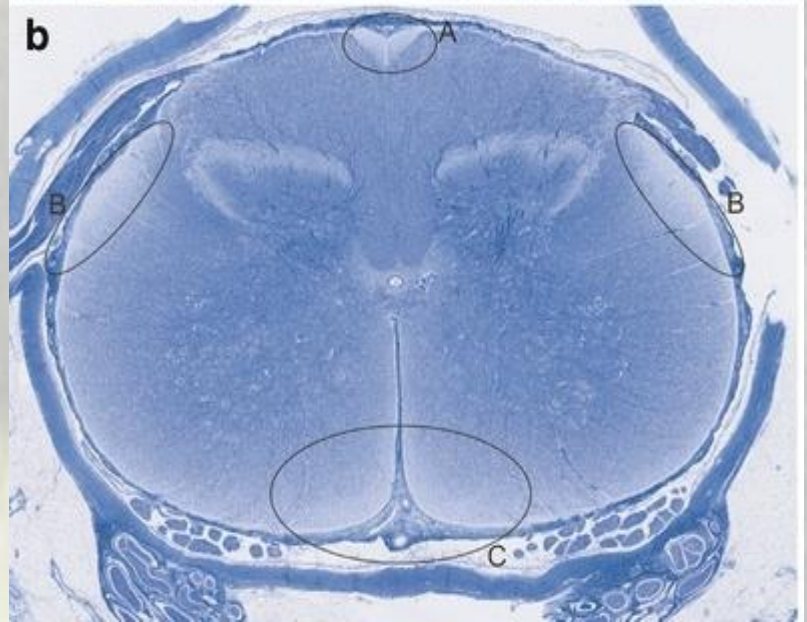
Weaver Syndrome (Bovine Progressive Degenerative Myelopathy)

- There is functional disturbance or pathological change in the spinal cord
- Most commonly observed in brown Swiss cattle
- Mutations in EZH2 (Histone-lysine N-Methyltransferase)
- The animal have an odd weaving gait and this is due to weakness and lack of coordination in all limbs.
- Clinical symptoms starts to appear at 6 months and becomes progressively worse until the animal dies



Spinal Dysmyelination

- Affects American Brown Swiss cattle
- The SPAST gene (BTA11), encoding the spastin protein has a missense mutation c.560G>A (p.Arg560Glu)
- A congenital neurodegenerative disease in cattle
- Recumbency and spastic extension of the limbs
- There is variable degrees of denervation atrophy in the skeletal musculature



Bovine Leukocyte Adhesion Deficiency (BLAD)

- An immunological disorder caused by substitution of A to G at nucleotide 383 in the CD18 gene (ITGB2)
 - This leads to replacement of aspartic acid with glycine at position 1228 in the glycogen protein (D128G)
 - The affected animal is observed to have frequent bacterial infection, delayed wound healing and stunted growth
 - Severe and recurrent mucosal infection such as pneumonia
 - The reproductive performance and milk production is poor
 - Most common among Holstein cattle
- | | | |
|------------|--------------|------------|
| Turkey: 4% | Brazil: 2.8% | Japan: 4% |
| USA: 4% | Poland: 3% | Iran: 3.3% |

Bovine Leukocyte Adhesion Deficiency (BLAD)

Normal	GTCCTGCATCATATCCACCAGCCTCAGAGAATGGGGGAGTCCTGAGGGT
Mutant	GTCCTGCATCATATCCACCAGCCTCAGAGAATGGGGGAGTCCTGAGGGT
	TCTGAGGCCTGCAAGAGGCATCAGTGCCCCTGAACCCCCCACCACCAG
	TCTGAGGCCTGCAAGAGGCATCAGTGCCCCTGAACCCCCCACCACCAG
	ACCAGGTGGTACACCCTGACTCTCTCCCAAATCCTGGCAGGTCAGGCAG
	ACCAGGTGGTACACCCTGACTCTCTCCCAAATCCTGGCAGGTCAGGCAG
	TTGCGTTCAACGTGACCTTCCGGAGGGCCAAGGGCTACCCCATCGACCT
	TTGCGTTCAACGTGACCTTCCGGAGGGCCAAGGGCTACCCCATCGGCCT
	GTACTACCTGATGGACCTCTCCTACTCCATGGTGGATGACCTCGTCAACG
	GTACTACCTGATGGACCTCTCCTACTCCATGGTGGATGACCTCGTCAACG
	TCAAGAAGCTGGGGGGGTGACCTGCTCCGGGGCCCTCAATGGCATCACCGA
	TCAAGAAGCTGGGGGGGTGACCTGCTCCGGGGCCCTCAATGGCATCACCGA
	GTCGGGGCCGCATTGGTGAGGCAGCTACTCCATCTTCCCCTGAAAC
	GTCGGGGCCGCATTGGTGAGGCAGCTACTCCATCTTCCCCTGAAAC

Congenital Erythropoietic Porphyria

- It is a hereditary enzyme deficiency in the haeme (essential part of hemoglobin) biosynthesis
- The affected gene is the UROD gene (uroporphynogen decarboxylase) which encodes the enzyme uroporphyrinogen III synthase
- There is photosensitization which causes subepidermal blistering and dermal necrosis
- Affected animal have varying degrees of reddish-brown discoloration of bones, teeth and urine

Hereditary Zinc Deficiency (HZD)

- This defect is due to single substitution in gene SLC39A4, wherein there is impaired intestinal zinc absorption
- It is characterised by parakeratosis and dermatitis and it occurs in areas/regions that are subjected to abrasion
- Lesions could be found around the mouth, eyes, base of the ear, joints, and lower parts of the thorax, abdomen and limbs.



Citrullinemia

- Fatal hereditary metabolic defect of Holstein-Friesian calves (mainly in Australian and New Zealand)
- This defect involves substitution of C-T in exon 5 of argininosuccinate synthetase (ASS), which converts CGA codon (Arginine) to TGA (translational termination codon)
- Clinical signs include ammonemia (increased circulatory ammonia) and related neurological signs
- Calves may also present ataxia, aimless wondering, blindness, head pressing, convulsion and death
- Frequency in US Holstein (0.3%) and Chinese Holstein (0.16%)
- Case in Australia: due to importation of semen from US

Factor XI Deficiency (FXID)

- Mutation in the F11 (Blood Coagulation Factor 11) caused the defect
- There is 76bp insertion in the exon 12 in bovine chromosome 27
- FXID results to prolonged bleeding (after birth, dehorning, castration, etc.)
- Affected cows frequently have pink-colored colostrum
- It also reduced reproduction performance and animals affected are more susceptible to diseases (pneumonia, mastitis and metritis)
- Affected animals have higher morbidity and mortality
- This defect have significant economic impact in the dairy industry

Turkey: 1.8%

X-linked Anhydrotic Ectodermal Dysplasia

- An X-linked recessive disease
- It is caused by 19 bp deletion in EDA, which encodes Ectodysplasia A, a protein involved in the formation of hair follicles and tooth bud
- Clinical findings include hairlessness, tooth abnormalities, and reduced sweat glands
- Only males present full form, whereas heterozygous females (carriers) are asymptomatic or show light symptoms (hypotrichosis and reduced number of teeth)



Parakeratosis (Edema Disease, Lethal trait A46)

- An inherited defect caused by
 - (a) Simple Autosomal lethal factor
 - (b) Chromosomal anomaly
- Associated with poor intestinal uptake of zinc therefore develops conjunctivitis, diarrhea and increase susceptibility to infection
- Calf is normal at birth but develops parakeratosis at 5 weeks old and eventually dies
- Head and neck: thickened, with scales, cracks and fissures
- Eye area: abraded

A close-up photograph of a water buffalo's head, facing left. The buffalo has dark, wet-looking fur and prominent, curved horns. A thick, light-colored rope is tied around its head, passing over the top of its head and under its chin. The background is a soft, out-of-focus green field. A semi-transparent white rectangular box is overlaid on the center of the image, containing the text "Genetic defects in Water Buffalo".

Genetic defects in Water Buffalo

Acantholytic Mechanobullous Dermatosis



- This is group of heritable disorder characterised by trauma-induced sloughing of haired skin, hooves and horns
- An autosomal recessive mode of inheritance in affected animal
- Caused by mutation (G to A) in gene KRT5 (Keratin 5)
- High doses of glucocorticoids are used to control the lesions
- The animal affected has very poor long term prognosis

Hereditary Myotonia (Muscle Hyperexcitability)

- It is phenomenon wherein there is a delayed muscle relaxation after contraction
- The defect is due to a mutation in the CLCN1 gene, which encodes the main skeletal muscle chloride channel (CLC1)
 - *G to C, leads to 885Ala to Pro (GCC to CCC)
- Mutation in CLCN1 results in decreased activity of CLC1, thereby causes myotonia (Hyperexcitability)
- The animal's muscles become stiff thereby affects movement/gait
- Rigidity is present but more severe in hindlimb
- There is muscle hypertrophy and males with severe disorder is not able to mate naturally

Hereditary Myotonia (Muscle Hyperexcitability)

A.S. Borges et al. / Neuromuscular Disorders 23 (2013) 206–213

209



Fig. 1. Startle response in an affected myotonic buffalo. Muscle stiffness was severe, and this animal exhibited recumbency after startle that lasted approximately 20–30 s.

A close-up, slightly faded photograph of a water buffalo's head in profile, facing left. The buffalo has dark, coarse fur and a prominent, curved horn on its right side. A thick, light-colored rope is tied around its head, passing over the top of its head and under its chin. The background is a soft, out-of-focus green field. A semi-transparent white rectangular box is overlaid on the center of the image, containing the text.

Genetic Defects in Swine

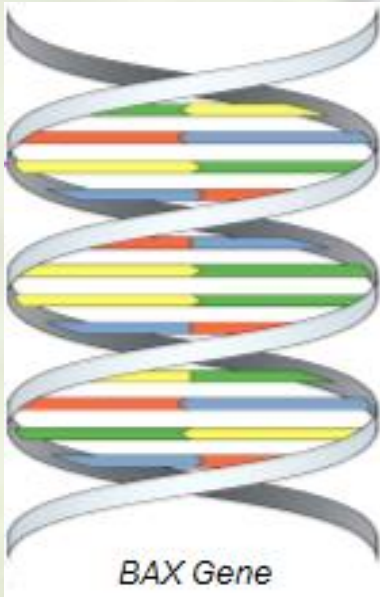
Porcine Stress Syndrome

- Mutation (C to T) in the Halothane gene (RYR1) causes this syndrome
- This mutation is responsible for the increase of occurrence of PSS and PSE (Pale, soft and exudative pork)
- Animals with PSS are easily stressed by environmental conditions (heat or increased in temperature, transportation, breeding, etc.,)
- PSE is described as pale, watery pork meat and is associated with rapid drop of pH and strong muscle post mortem rigor contraction
- The affected animal could die when subjected to stressful condition



Scrotal Hernia

One of the most common diseases in swine that is characterized by the protrusion of internal organs to the scrotum.

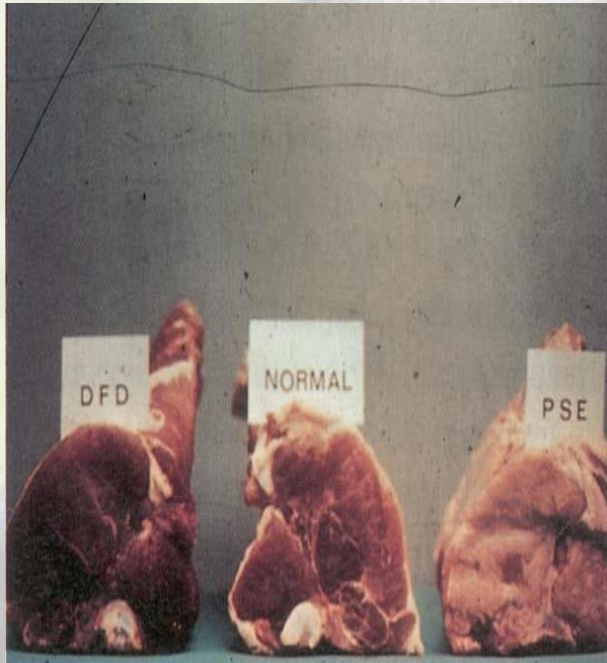


SNPC119T



Affects their efficacy in feeding, thus altering their capacity to grow. Moreover, these individuals would require higher feed quality plus additional health care considerations increasing the losses for the breeder.

Acid Meat Condition



The Acid Meat condition is a dominant genetic defect in the Rendement Napole (RN) gene that causes:

- reduced water holding capacity
- low pH
- pale color
- reduced processing and cooking yield due to increased drip
- and strong metallic taste that often leads to poor meat quality.



Rendement Napole Gene

- This mutation is related with higher level of glycogen, pale meat color and high drip loss
- A single mutation on the Monophosphate-activated protein kinase (PRKAG3) inhibits the activity of the enzyme to break down storage glycogen
- Frequent in Hampshire and commercial white breed population

Genotyping in the Philippines

Genetic Defect	Genotype	No. of samples	Total
PSS	Normal (NN)	1122	1195
	Carrier (Nn)	51	
	Mutant (nn)	22	
Scrotal	Normal	310	376
	Carrier	63	
	Mutant	3	
Acid meat	Normal	135	200
	Carrier	43	
	Mutant	22	

A close-up photograph of a water buffalo's head, facing left. The buffalo has dark, coarse fur and prominent, curved horns. A thick, light-colored rope is tied around its head, passing over the top of its head and under its chin. The background is a soft, out-of-focus green field. A semi-transparent white box with a thin green border is overlaid on the center of the image, containing the text.

Genetic defect in sheep and goat

Chondrodysplasia (Spider Lamb)

- An autosomal recessive defect of the black-faced breeds of sheep (Suffolk and Hampshire)
- The limbs of the affected animal is disproportionately long and spider-like
- Animal is also observed to have medial deviation of the carpus, the tarsus, severe scoliosis or lordosis, concave sternum and severe roman nose
- In US, progeny testing is utilized to decrease/eliminate the occurrence of this syndrome
- A national task force was formed to deal with this defect



Beta mannosidosis

- An autosomal recessive defect
- The deletion (1398G) in MANBA (Mannosidase beta A), leads to premature stop codon
- It causes recumbency and cerebellar signs in newborn Nubian goats a



A close-up photograph of a water buffalo's head, facing left. The buffalo has dark brown fur and large, curved, light-colored horns. A thick, light-colored rope is tied around its head, passing over the bridge of its nose and under its chin. The background is a soft, out-of-focus green field. A semi-transparent white rectangular box is overlaid on the center of the image, containing the text "Genetic Defects in Horse".

Genetic Defects in Horse

Parrot Mouth/Sow mouth

- Parrot mouth: shorter lower jaw
- Sow mouth: mandible is longer than maxilla
- In foals that are severely affected, suckling/grazing may be impossible




The current situation

Recessive autosomal diseases are very low in frequency but, have significant economic impact

(Massive) dissemination of hereditary defects through extensive use of elite sires that could be “silent carriers” of the defective gene and intensive use of artificial insemination and other techniques

We do not test for these defects (herd, imported animals, semen etc.,)

Genetic control of animal diseases can reduce the costs associated with diseases, improve animal welfare and provide animal products to consumers

A close-up, profile view of a water buffalo's head. The buffalo has dark, wet-looking fur and a prominent, curved horn on the right side. A thick, light-colored rope is tied around its head, passing over the top and under the chin, with a knot visible on the forehead. The background is a soft, out-of-focus green field.

Thank you and have a good day!