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REVIEW

A critical analysis of disease-associated DNA polymorphisms in the genes of cattle, goat, sheep, and pig

Eveline M. Ibeagha-Awemu · Patrick Kgwatalala · Aloysius E. Ibeagha · Xin Zhao

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Abstract Genetic variations through their effects on gene expression and protein function underlie disease susceptibility in farm animal species. The variations are in the form of single nucleotide polymorphisms, deletions/insertions of nucleotides or whole genes, gene or whole chromosomal rearrangements, gene duplications, and copy number polymorphisms or variants. They exert varying degrees of effects on gene action, such as substitution of an amino acid for another, shift in reading frame and premature termination of translation, and complete deletion of entire exon(s) or gene(s) in diseased individuals. These factors influence gene function by affecting mRNA splicing pattern or by altering/eliminating protein function. Elucidating the genetic bases of diseases under the control of many genes is very challenging, and it is compounded by several factors, including host × pathogen × environment interactions. In this review, the genetic variations that underlie several diseases of livestock (under monogenic and polygenic control) are analyzed. Also, factors hampering research efforts toward identification of genetic influences on animal disease identification and control are highlighted. A better understanding of the factors analyzed could be better harnessed to effectively identify and control, genetically, livestock diseases. Finally, genetic control of animal diseases can reduce the costs associated with diseases, improve animal welfare, and provide healthy animal products to consumers, and should be given more attention.

E. M. Ibeagha-Awemu · P. Kgwatalala · A. E. Ibeagha · X. Zhao (✉)
Department of Animal Science, McGill University, 21,111 Lakeshore Road, Ste Anne De Bellevue, Montreal, QC, Canada H9X 3V9
e-mail: xin.zhao@mcgill.ca

E. M. Ibeagha-Awemu
e-mail: Eveline.ibeagha-awemu@mcgill.ca

E. M. Ibeagha-Awemu
e-mail: Eveline.ibeagha-awemu@mcgill.ca

Introduction

Since the unraveling of the genetic material and the rapid development of molecular genetic tools, the last 50 years has witnessed a tremendous growth in the knowledge base and exploitation of genetic information in tackling human and animal diseases. The genetic material in farm animal species harbors a rich collection of genetic variations with either useful or harmful consequences on health and productivity. These variations are usually in the form of single nucleotide polymorphisms (SNPs), deletions/insertions of nucleotides or whole genes, gene or whole chromosomal rearrangements, gene duplications, copy number polymorphisms (e.g., variable number of tandem repeats and microsatellites), copy number variations (represents a copy number change involving a DNA fragment that is 1 kb or larger [Feuk et al. 2006]), and presence/absence of transposable elements (e.g., *Alu* elements). Although these variations constitute just a small percentage of the genome (<1% in humans; Check 2005), they form the basis of biodiversity or individual variability in response to environmental stimuli. They could be found in both the coding and the regulatory regions of genes with the ability to modify gene function or expression and therefore may result in undesirable conditions, like diseases.

Compared to the human genome and with the exception of the *Bos taurus* genome which is now about 95% complete, sequencing of the genome of some farm animal species like the goat, pig, and sheep is still in the initial or

planning stages. With the available genome information, however, there is an explosion of information in studies relating to genome variation and various aspects of disease, production, and adaptation. However, genome research in relation to diseases in farm animals is less intense and also differs in several respects from that in humans. The main focus of research into the genetic basis of animal diseases is the prospect of increasing productivity for human benefit or using such as models for human disease research. The attention now is also being directed toward breeding for disease resistance. Effective exploitation of disease-resistant livestock or complete elimination of diseased livestock must be backed by knowledge of the genes, the causal mutations, and interactions with other factors that confer resistance. Although diseases controlled by monogenic loci tend to be eliminated through years of breeding from the stock, they still occur from time to time with associated losses. The specific mutations responsible for some of these diseases with a simple Mendelian mode of inheritance still eludes investigation and therefore still pose a great challenge to geneticist. On the other hand, some of the most economically important diseases of livestock are controlled by variations on many genes, further compounded by host × pathogen × environment interactions. Elucidating the genetic basis of such diseases has been most challenging and research efforts are intensifying in this regard. In this review, we shall attempt to summarize and analyze the types of reported mutations responsible for some animal (cattle, goat, pig and sheep) diseases in today's agriculture.

Functional consequences of DNA polymorphisms in single-locus-disease genes

About 200 diseases of cattle, goat, pig, and sheep are thought to be caused by sequence variations in single genes, of which the causal mutations in less than half of them have been elucidated. The causal mutations are found in the coding and noncoding regions with profound consequences on mRNA processing and stability of the protein product. Further information on animal diseases with a simple mode of inheritance can be seen at http://www.omia.angis.org.au/. Table 1 presents a summary of the genes and type of mutations implicated in several diseases of livestock.

Coding region disease variants and the consequences for causal mutations

The coding region is the portion of a gene that is transcribed and translated into proteins and does not include such regions as a recognition site, initiator sequence, or termination sequence. All the different types of polymorphisms have been reported in monogenic disease genes of livestock. The majority of cases are caused by SNPs with varying degrees of effects on gene action, such as substituting one amino acid for another, duplications and deletions that lead to frame shift and premature termination of translation, and complete deletion of entire exon(s) or gene(s) in diseased individuals. These changes in coding regions have been recognized to influence gene function by affecting mRNA splicing patterns (Cartegni et al. 2002) or by altering protein function.

In a simple amino acid exchange caused by a SNP, one may not expect much change in protein function or abundance because only one amino acid out of hundreds of others has been altered. However, the amino acid in question or the part of the protein where the change takes place determines the effect of the mutation. In most reports, pathologic mutations are found to occur in functionally conserved regions of the protein, with effects ranging from reduced expression of the mutant protein, to altered function, to complete abolition of expression. In a disease condition like complex vertebral malformation in cattle, Thomsen et al. (2006) found the causal mutation to be a substitution of thymine for guanine (nucleotide 559) of the *SLC35A3* gene, which led to a change in amino acid 180, from valine to phenylalanine. This mutation results in abnormal nucleotide-sugar transport into the Golgi apparatus, thus disrupting normal protein glycosylation. In bovine Ehlers-Danlos syndrome, Tajima et al. (1999) reported a SNP (G254A) that occurred in the serine-glycine dipeptide repeat region of the binding portion of *DSPG3* gene. The G254A substitution might be considered a simple nucleotide change, but it caused an amino acid change (serine to asparagine) that is responsible for functional abnormality in cutaneous tissues of carrier individuals. Another mutation, A383G or Asp128Gly, detected in a highly conserved region of the extracellular portion of the *CD18* gene (codes for a glycoprotein), is responsible for leukocyte adhesion deficiency (LAD) in Holstein cattle (Shuster et al. 1992). Shuster et al. (1992) estimated the carrier frequency of the Asp128Gly allele at about 15% in bulls of U.S. Holstein populations and at about 6% in cows. This mutation is also present in Holstein cattle throughout the world, making LAD one of the most common genetic diseases of Holstein cattle. Also, substitution of an evolutionarily conserved glutamic acid by lysine (p.Glu1200Lys), caused by a c.3598G>A transition in the *FBN1* gene, results in bovine Marfan syndrome (Singleton et al. 2005). The glutamic acid residue is part of a calcium-binding epidermal growth factor-like molecule, which is also frequently altered in human Marfan syndrome (Rantamaki et al. 1999).

In some instances, different SNPs on the same gene are known to be responsible for the same genetic disorder in different breeds. A good example is bovine lysosomal α-mannosidosis whereby a T961C (or Phe321Leu) is

Table 1 DNA mutations responsible for disease conditions in farm animals

Disease/trait	Species	Gene name	Gene symbol	Variant or mutation[a]	Reference	Genetic test
Anhydrotic ectodermal dysplasia	Cattle	Ectolysplasin 1	ED1	IVS8 +2T>G leads to deletion of 51 or 45 bp in the c-terminal region	Drögemüller et al. 2002	No
Beta mannosidosis	Cattle	Mannosidase beta A, lysosomal	MANBA	G2574A leads to premature stop codon (Trp858Stop)	Leipprandt et al. 1999	Yes, Leipprandt et al. 1999
	Goat	mannosidase beta A, lysosomal	MANBA	1398delG, leads to frame shift and premature termination	Leipprandt et al. 1996	Yes, Leipprandt et al. 1996
Bovine leukocyte adhesion deficiency	Cattle	Integrin beta 2	ITGB2 or CD18	A383G leading to D128G	Shuster et al. 1992	Yes, Shuster et al. 1992
Bovine lysosomal alpha-mannosidosis	Cattle	Alpha mannosidase class 2B member 1	MAN2B1	T961C leads to Phe321Leu in Angus, G662A leads to Arg221His in Galloway	Tollersrud et al. 1997	Yes, Healy and Malmo 1998
Bovine myoclonus	Cattle	Glycine receptor α1	Glra1	156C→A changes a tyrosine codon in exon 2 to a termination codon (Y24X)	Pierce et al. 2001	Yes, Healy et al, 2002
Chondrodysplasia or spider lamb syndrome	Sheep	Fibroblast growth factor receptor 3	FGFR3	T>A in exon 17 leads to V700E	Beever et al. 2006	Yes, Beever et al. 2006
Citrullinemia	Cattle, Buffalo	Argininosuccinate synthetase	Ass	C→T in exon 5, Arginine 86 (CGA) to nonsense codon (TCA)	Dennis et al. 1989	Yes, Dennis et al. 1989
Coat color albinism	Cattle	Tyrosinase	TYR	926_927insC, frameshift and premature stop codon at residue 316	Schmutz et al. 2004	Yes. Schmutz et al. 2004
Complex vertebral malformation	Cattle	UDP-N-acetylglucosamine (UDP-GlcNAc) transporter member A3	SLC35A3	559 G→T, homozygosity for V180F	Thomsen et al. 2006	Yes, Kanae et al. 2005; Danish Institute of Agricultural Research
Congenital myasthemic syndrome	Cattle	Cholinergic receptor, nicotinic, epsilon polypeptide	CHRNE	470del20 in exon 5 leads to frame shift followed by premature stop codon	Kraner et al. 2002	Yes, Thompson et al. 2007
Deficiency of uridine monophosphate synthase	Cattle	Uridine monophosphate synthetase	UMPS	C→T, Arginine 405 (CGA) to stop codon (TGA), heterozygotes are carriers, homozygote embryos die	Schwenger et al. 1993	Yes, Schwenger et al. 1993
Ehlers-Danlos syndrome	Cattle	Dermatan sulfate proteoglycan 3	DSPG3	G254A, serine to asparagine.	Tajima et al. 1999	Yes, Tajima et al. 1999
Ehlers-Danlos syndrome, Type VII	Cattle	A disintegrin-like and metalloprotease with thrombospondin type 1 motif 2	ADAMTS2	17-bp deletion that changes reading frame of message	Coligne et al. 1999	Yes, Coligne et al. 1999
Epidermolysis bullosa	Cattle	Keratin 5	KRT5	4051G>A, leads to E478K	Ford et al. 2005	No
Factor XI deficiency	Cattle	Blood coagulation factor XI	F11	76-bp insertion in exon 12	Marron et al. 2004	Yes, Marron et al. 2004; Kunieda et al. 2005; Mukhopadhyaya et al. 2006
				15-bp insertion in exon 9	Kunieda et al. 2005	
Fish-odor syndrome (Trimethylaminuria)	Cattle	Flavin containing monooxygenase 3	FMO3	62C→T in exon 6 leads to premature stop codon (R238X)	Lundén et al. 2002	No
Hypotrichosis	Sheep	Hairless	HR	1312C/T leads to 438Gln/Stop	Finocchiaro et al. 2003	Yes, Finocchiaro et al. 2003

Table 1 continued

Disease/trait	Species	Gene name	Gene symbol	Variant or mutation[a]	Reference	Genetic test
Glycogen storage disease II	Cattle	Acidic alpha-glucosidase	AAG	(1) Dinucleotide deletion in exon 18 in Shorthorns (2454ΔCA) leads to frameshift and premature termination (2)Dinucleotide deletion in exon 7 in Brahman 1057ΔTA) leads to frameshift and premature termination (3) 1783C→T in exon 13 in Shorthorns lead to Arg595X	Dennis et al. 2000	Yes, Dennis et al. 2000
Glycogen storage disease V	Cattle	Myophosphorylase	PYGM	C→T, 489 Arg (CGG) to Trp (TGG)	Tsuijino et al. 1996	Yes, Tsuijino et al. 1996; Bilstrom et al. 1998
	Sheep	Muscle glycogen phosphorylase	PYGM	G→A substitution at the 3′ splice site of intron 19 leads to a 8-bp deletion at the 5′ end of exon 20, creating a frameshift and resulting in a premature stop codon	Tan et al. 1997	Yes, Tan et al. 1997
Goiter familial	Cattle	Thyroglobulin	TG	C→T transition in exon 9 creates a stop codon at position 697	Ricketts et al. 1987	Yes, Ricketts et al. 1987
	Goat (Dutch)	Thyroglobulin	TG	C→G in exon 8 leads to premature stop codon (TAC or Tyr → TAG or stop codon Also C→T in exon 5 leads to Ser →Leu	Veenboer and de Vijlder 1993	Yes, Veenboer and de Vijlder 1993
	Goat	Thyroglobulin	TG	537C→T in exon 5 leads to 160Ser →Leu, 360-bp insertion in intron 5, G→A/ C→T in opposite strand in 3′ UTR	van Ommen et al. 1989	
Hypercholesterolemia	Pig	Low-density lipoprotein receptor	LDLR	250C→T leads to 84cgc to tgc (R84C)	Hasler-Rapacz et al. 1998; Grunwald et al. 1999	Test, Hasler-Rapacz et al. 1998; Grunwald et al. 1999
Immotile short-tail sperm defect	Pig	KPL2 protein	KPL2	Insertion of a 9000-bp retrotransposon in intron 30 leads to aberrant splicing	Sironen et al., 2006	Yes, Sironen et al. 2006
Lethal trait A46	Cattle	Solute-linked carrier 39A4	SLC39A4	G→A in first nt. of intron 10 leads to deletion of exon 10	Yuzbasiyan-Gurkan and Bartlett 2006	No
Malignant hyperthermia or porcine stress syndrom	Pig	Ryanodine receptor 1 (skeletal muscle)	RYR1	1843C→T leads to R615C	Fujii et al. 1991	Lee et al. 2002
Maple syrup urine disease	Cattle	Branched-chain keto acid dehydrogenase E1-α	BCKDHA	C1380T leads to Pro372Leu in Poll Shorthorns C248T leads to Glu6X in Poll Hereford	Zhang et al. 1990 ; Dennis and Healy, 1999	Yes, Dennis and Healy 1999
Marfan syndome	Cattle	Fibrillin 1	FBN1	c.3598G>A leads to p.E1200K (GAA→AAA)	Singleton et al. 2005	Yes, Singleton et al. 2005
Mucopolysaccharidosis IIID	Goat	Glucosamine (N-acetyl)-6-sulfatase	GNS	C→T leads to CGA→UGA, premature stop codon at position 102	Cavanagh et al. 1995	Yes, Hoard et al. 1998
Mule foot disease (syndactyly)	Cattle (Holstein)		LRP4	CpG/ApT nonconservative substitution in exon 33 (C4863A, G4864T)	Duchesne et al. 2006	No
	Cattle (Angus)		LRP4	G→T in first nt of intron 37 prevents normal splicing	Johnson et al. 2006	No

Table 1 continued

Disease/trait	Species	Gene name	Gene symbol	Variant or mutation[a]	Reference	Genetic test
Myopathy of the diaphragmatic muscles	Cattle	Heat shock 70-kDa protein 2	HSPA1B	Deletion of HSPA1B	Sugimoto et al. 2003	No
Myotonia	Goat	Chloride channel 1	CLCN1	G→C, leads to 885Ala→Pro (GCC→CCC)	Beck et al. 1996	No
Neuronal ceroid lipofuscinosis	Cattle	Ceroid-lipofuscinosis, neuronal 5	CLN5	c.662dupG leads to frame shift and premature termination (p.Arg221GlyfsX6)	Houweling et al. 2006	Yes, Houweling et al. 2006
	Sheep	Cathepsin D	CTSD	G→A leads to conversion of an active site Asp to Asn that results in an enzymatically inactive but stable protein	Tyynelä et al. 2000	No
Nonshivering thermiogenesis	Pig	Uncoupling protein 1	UCP1	Deletion of exons 3, 4, and 5.	Berg et al. 2006	No
Polled intersex syndrome	Goat		PISRT1/ FOXL2/ SRY	Deletion of 11.7-kb regulatory region including the *PISRT1* and *FOXL2* genes. *SRY* gene inhibits *PISRT1* and *FOXL2* genes in XY (normal) males	Pailhoux et al. 2001, 2005	No
Porcine dense deposit disease or membranoproliferative glomerulonephritis type II	Pig	Factor H		T3610G leads to I1166R which causes a block in protein release, resulting in intracellular accumulation of mutated protein. Also, C1590G leads to L493V	Hegasy et al. 2002	No
Porphyria cutanea tarda	Sheep	Uroporphyrinogen decarboxylase	UROD	C→T leads to Leu131Pro, located within the active cleft site of UROD protein	Nezamzadeh et al. 2005	No
Protoporphyria	Cattle	Ferrochelatase	FECH	1250G→T changed stop codon to leucine (X417Leu)	Jenkins et al. 1998	Yes, Jenkins et al. 1998
Renal tubular dysplasia	Cattle	Claudin 16	CLDN–16	Deletion of 37-kb region including exons 1 to 4 (type 1 mutation).	Ohba et al. 2000	Yes. Hirano et al. 2002
				56-kb deletion containing exons 1 to 4 and 21 bp of exon 5 (type 2 mutation).	Hirano et al. 2002	
Sex reversal: XY female	Cattle	Sex determining region Y	SRY	Possible deletion of *SRY* gene	Kawakura et al., 1996	Yes, Kawakura et al. 1996
Spherocytosis	Cattle	Solute carrier family 4, anion exchanger, member 1	SLC4A1	C→T leads to CGA→TGA (Arg→Stop i.e. R664X)	Inaba et al. 1996	Yes, Inaba et al. 1996; Kageyama et al. 2006
Vitamin D-deficiency rickets, type I.	Pig	Cytochrome P450C1 or CYP27B1	P450C1	173 or 329 bp deletions involving exons 5, 6, and 7 leads to expression of nonsense products	Chavez et al. 2003	No

[a] Variant or mutation notations are as used in their original publications

responsible for the condition in Angus cattle, while G662A (or Arg221His) is the causal polymorphism in Galloway cattle (Tollersrud et al. 1997). The amino acids substituted in both cases are conserved among the α-mannosidase class-2 family, indicating important roles in protein function. Their independent substitution therefore disrupted the function of the protein, to the same extent, leading to a deficiency of lysosomal α-mannosidase. Molecular heterogeneity also exists in bovine maple syrup urine disease (MSUD) (Dennis and Healy 1999; Zhang et al. 1990) and glycogen storage disease II (Dennis et al. 2000). Zhang et al. (1990) investigated Polled Shorthorn with MSUD and found the causal mutation to be 248C→T in exon 2 of the *BCKDHA* gene that is responsible for converting 6 glutamine to a premature stop codon. In Polled Herefords conversely, the same condition is caused by a 1380C→T (Pro372Leu) mutation in the same gene (Dennis and Healy 1999). In both cases an important functional part of the gene is either absent (premature stop codon) or altered (Pro372Leu). Further investigations with crosses of Polled Herefords and Polled Shorthorns with the disease showed heterozygosity for both mutations (Healy and Dennis 1994).

SNPs that change an amino acid to a stop codon bring about premature termination and, in some of the monogenic-disease loci in livestock, lead to a complete disruption in protein synthesis or the production of shorter transcripts with decreased activity. Such conditions are usually responsible for nonsense-mediated mRNA decay (Culbertson 1999). Goiter in both cattle and goats develops from SNPs that cause premature termination of mRNA translation of the *TG* gene (Ricketts et al. 1987; Veenboer and de Vijlder 1993). A nonsense mutation (R238X) in the *FMO3* gene that underlies fishy off-flavor in cow's milk was shown to eliminate about 50% abundance of the gene in heterozygous carriers (Lundén et al. 2002). Complete lack of *FMO3* activity, necessary for complete oxidation of trimethylamine to an odorless compound, may therefore be the case in homozygous carriers of the condition. Pierce et al. (2001) observed that the molecular basis of bovine myoclonus is the substitution of tyrosine by a termination codon (Tyr24X) in exon 2 of the *Glra1* gene. The stop codon results in a prematurely truncated protein that lacks ligand-binding and membrane-spanning domains. In bovine beta mannosidosis, the lack of 22 C-terminal amino acids in mutant proteins, the result of a nonsense mutation in the *MANBA* gene, indicates their importance in the stability and proper functioning of the enzyme (Leipprandt et al. 1999). In the same condition in goats, an earlier termination of mRNA synthesis is brought about by a single base deletion (1398delG) that results in a shift in the reading frame and production of a shorter peptide, 481 amino acids compared with 879 amino acids of the normal protein (Leipprandt et al. 1996). Deficiency of uridine monophosphate synthase in cattle also results from a mutant protein lacking 76 C-terminal amino acids (Schwenger et al. 1993). A rare situation occurs in bovine protoporphyria where a SNP changes a stop codon to a coding amino acid (TGA to TTA or X417Leu) thereby adding 27 more amino acids to mutant proteins (Jenkins et al. 1998). This addition affects catalytic activity of the enzyme since it occurs in the carboxyl terminal, known to play important roles in catalytic function.

Single-base-pair (bp) deletions or insertions to exons and whole genes are also important players in altering protein function and causing disease conditions in farm animals. In addition to the single-bp deletion that caused caprine mannosidase beta described above, a 17-bp deletion in *ADAMTS2* is responsible for Ehlers-Danlos syndrome type VII in cattle (Colige et al. 1999), while a 20-bp deletion in *CHRNE* causes bovine congenital myasthemic syndrome (Kraner et al. 2002). Larger deletions involving whole exons are reported for genes causing bovine renal tubular dysplasia (Hirano et al. 2002; Ohba et al. 2000) and porcine nonshivering thermiogenesis (Berg et al. 2006). On a more dramatic note, whole genes are deleted or suspected of being deleted in conditions like bovine myopathy of the diaphragmatic muscles (Sugimoto et al. 2003), sex reversal (XY female) in cattle (Kawakura et al. 1996), and polled intersex syndrome in goats (Pailhoux et al. 2005). Reports of pathologic insertions range from single bp to several hundred bp in conditions like bovine factor XI deficiency and bovine neuronal ceroid lipofuscinosis (Houweling et al. 2006; Kunieda et al. 2005; Marron et al. 2004). The effects of these deletion/insertion mutations include shift in reading frame and premature termination and, in extreme cases like whole gene deletions, total absence of protein activity.

Consequences of causal SNPs in noncoding regions

The noncoding regions of genes constitute the promoter, 5′ and 3′ untranslated regions (UTRs), introns, and intergenic or large regions between genes. In these regions are found regulatory sequences that affect gene splicing, transcription, and translation. Polymorphisms in these regions can alter gene expression as has been demonstrated as the genetic basis of some animal diseases with a simple mode of inheritance.

Deletion of a 11.7-kb intergenic region on the Y chromosome triggers intersexuality and polledness in goats (Pailhoux et al. 2001). This region contains mainly repetitive sequences and its deletion affects the transcription of two genes, namely, *PISRT1* that encodes a 1.5-kb mRNA devoid of open reading frame, and *FOXL2*, known to be responsible for blepharophimosis epicanthus inversus

syndrome in humans (Crisponi et al. 2001). The deletion, even though located 20 (*PISRT1*) and 200 (*FOXL2*) kb away from the genes, contains regulatory sequences whose absence has direct consequences on the transcription of both genes. In goats with XX sex-reversed gonads, the expression of *PISRT1* decreases between 36 days post-coitus (dpc) and 40 dpc accompanied with an increase in *SOX9* expression (Pailhoux et al. 2001). *SOX9* gene is an important regulator of testis development that functions by triggering *AMH* transcription (Arango et al. 1999; Koopman 1999). On the other hand, *FOXL2* is involved in early ovarian differentiation and development, possibly by having a function in folliculogenesis (Crisponi et al. 2001; Pailhoux et al. 2001). In normal circumstances, therefore, *PISRT1* functions by inhibiting *SOX9* as an antitestis gene while *FOXL2* promotes ovarian development. In normal males, another gene, *SRY*, has the inhibitory function of inactivating the transcription of both genes.

Intronic splice-site mutations are responsible for ovine glycogen storage disease, mule foot, lethal trait A46, and anhydrotic ectodermal dysplasia diseases of cattle (Drögenmüller et al. 2002; Johnson et al. 2006; Tan et al. 1997; Yuzbasiyan-Gurkan and Bartlett 2006). In ovine glycogen storage disease, a G→A transition at the 3′ splice site of intron 19 of the *PYGM* gene causes a frame shift in translation, resulting in a premature codon and the removal of the last 31 amino acid residues from the C-terminal of the protein in affected individuals (Tan et al. 1997). Consequently, there is a deficiency of the muscle glycogen phosphorylase enzyme which is responsible for catalyzing breakdown of muscle glycogen stores to glucose-1-phosphate in affected individuals (Schmid and Mahler 1959). Another G→A transition at the first nucleotide of intron 37 of the *LRP4* gene completely disables this donor splice site, thereby abrogating the normal splicing of the gene (Johnson et al. 2006). The effect of the mutation of this highly conserved guanine base is the disruption of the normal functioning of the protein in affected individuals through the production of a dysfunctional membrane-anchored receptor lacking the normal cytoplasmic domain (Johnson et al. 2006). There is reduced mobility accompanied by painful fusion of hooves in affected subjects. A further splice-site variant, also a G→A transition of the first nucleotide of intron 10 (*SCL39A4* gene) leads to the out-splicing of the entire exon 10 in affected animals (Yuzbasiyan-Gurkan and Bartlett 2006). The resultant protein is predicted to lack two critical motifs implicated in the formation of a pore responsible for impaired zinc absorption in diseased individuals (Yuzbasiyan-Gurkan and Bartlett 2006). Another splice-site donor variant involves a G→T transversion located at the second position of intron 8 of the *ED1* gene resulting in anhydrotic ectodermal dysplasia phenotype in cattle (Drögenmüller et al. 2002). The effect of this mutation is a translated protein with a large deletion in the functionally important C-terminal tumor necrosis factor-like domain. Recent findings suggest that the *ED1* gene plays a role in the development of mucous glands, the absence of which resembles a feature of X-linked anhydrotic ectodermal dysplasia in human patients (Seeliger et al. 2005).

A rare situation in causal SNPs in noncoding regions is the insertion of a 9000-bp retrotransposon within intron 30 of the *KPL2* gene which causes immotile short-tail sperm defect in pig (Sironen et al. 2006). Interestingly, the inserted retrotransposon affects splicing of the *KPL2* transcript in two ways: it causes either skipping of an upstream exon or inclusion of an intronic sequence as well as part of the insertion in the transcript. Both scenarios alter the reading frame leading to premature termination of translation. Sironen et al. (2006) further demonstrated that the aberrantly spliced exon is expressed predominantly in testicular tissue, thus explaining the tissue specificity of the immotile sperm defect and the importance of the *KPL2* gene in correct axoneme development.

Functional consequences of DNA variations in multigenic-disease loci

Several economically important diseases of farm animals, including mastitis, transmissible spongiform encephalopathies (TSEs), brucellosis, dermatophilosis, trypanosomiasis, and tick resistance, pose a problem for satisfactory control or complete eradication because of the complex interplay of factors that support their development, namely, the pathogen, the environment, and animal-related factors. Initial methods of control like changes in management, treatment, vaccination, pathogen control, movement control, slaughter, isolation, and quarantine of diseased animals are no longer attractive due to increased pathogen resistance to chemotherapeutic and prophylactic drugs and antibiotic residues in the environment and animal products, just to mention a few. The option of exploiting host genetic resistance to control these diseases does not suffer these drawbacks in the broad sense and is the key to cheap and effective control. Unfortunately, these diseases are under the interplay of many gene loci that must be identified and characterized before satisfactory control can be achieved. The search for disease-resistance markers involves screening for association between disease resistance and a variety of polymorphisms in candidate genes and anonymous markers and mapping for quantitative trait loci (QTLs). In particular, genetic traits of innate and acquired immunity related to resistance have received considerable attention and there is now evidence linking variations within some of these genes with resistance to diseases.

In particular, genes of the major histocompatibility complex (MHC) or BoLA system (http://www.ebi.ac.uk/ipd/mhc/) are thought to play a role in host resistance against the development of these diseases. In cattle, the BoLA system is located on chromosome 23 and includes three classes of loci: class I (locus A); class II, divided into IIa (includes loci DRA, DRB1-3, DQA, DQB, etc.) and IIb (includes DOB, DYA, DYB, DIB, etc.); and class III (includes TNF, 21-OH, C4, BF, HSP70-1 and -2, EAM, PRL, etc.) (Rothschild et al. 2000; http://www.ebi.ac.uk/ipd/mhc/). The first two groups of loci code for surface molecules relevant in the induction and regulation of immune responses. Some of these genes are highly polymorphic, with about 100 different alleles described for DRB3 exon 2 and about 39 for DQB (Maillard et al. 2001; da Mota et al. 2004; http://www.projects.roslin.ac.uk/bola/). Numerous lines of evidence indicate that the extensive polymorphisms reported for these molecules are responsible for the differences among individuals in immune responses to infectious agents. Some of the advances achieved so far for a few of these diseases and their associated resistant/susceptible polymorphisms will now be examined individually.

Mastitis

Mastitis is one of the most frequent, complex, and costly diseases of dairy cattle, goat, and sheep and its development is influenced by many genes, the environment, and pathogen factors. Host genes that are receiving attention are immunity traits and mainly include antibody response and functionality of neutrophils whose presence and functionality are essential in the innate defense against udder infections. The genetic variability of the immune mechanisms underlying mastitis resistance, including such genes as *CD14*, *CD18*, lactofferin, lysozyme, and class I and class II genes of MHC, have been reviewed by Detilleux (2002), Paape et al. (2003), and Rupp and Boichard (2003) and could therefore aid in selection for mastitis resistance.

In dairy cattle, most studies have focused on exon 2 of the class II BoLA DRB3 because of its high polymorphism. In an early study, Dietz et al. (1997) associated DRB3.2*16 with an increased risk for acute intramammary infection (mastitis). In the same year, Kelm et al. (1997) associated the same allele with higher estimated breeding value (EBV) for somatic cell score, and also *DRB3.2*8*, $IgG2^b$, and $CD18^{A1}$ with increased EBV for clinical mastitis. On the contrary, Sharif et al. (1998) significantly associated DRB3.2*16 with lower somatic score or lower risk of mastitis in Holsteins but reported significant association of DRB2.3*23 with occurrence of severe mastitis. The presence of glutamic acid at position β74, a motif present in DRB3.2*22, *23, and *24 alleles, was recently associated with occurrence of mastitis caused by *Staphylococcus* spp. (Sharif et al. 2000). Similarly, the same authors indicated that the presence of arginine or lysine at position 13 of a motif present on DRB3.2*23 and *8 alleles showed a tendency toward association with a higher risk of clinical mastitis; likewise, with presence of arginine at position β71 (present in alleles *23 and *22). More recently, Rupp et al. (2007) associated DRB3.2*3 and *11 with lower somatic cell counts (SCC), alleles *22 and *23 with higher SCC, allele *3 with less clinical mastitis, and *8 with a higher mastitis risk. For MHC Class I molecules, several studies have reported a relationship between different alleles with mastitis resistance or susceptibility (Mallard et al. 1995; Mejdell et al. 1994). Conflicting as some of these results may seem, most still point to the fact that variations within the BoLA system genes predispose to mastitis.

On immune genes, *CXCR2*, a chemokine receptor required for neutrophil migration to infection sites, contains a SNP (+777G→C) (Grosse et al. 1999; GenBank No. U19947) that is located in a region involved in mediating calcium signaling and mobilization as well as G-protein binding. Youngerman et al. (2004) showed that the +777GG genotype was associated with decreased percentages of subclinical mastitis, while genotype CC had increased percentages of subclinical mastitis in Holstein cows. No difference in clinical mastitis incidence was observed between genotypes. In the same light, cows with +777CC or CG genotype showed significantly lower neutrophil migration to recombinant human (rh) IL-8 than those of GG genotype (Rambeaud and Pighetti 2005). Furthermore, they also demonstrated that neutrophil migration of +777CC genotype to zymosan-activated serum was slower compared to the other genotypes, and upregulation of CD18 expression after stimulation with rhIL-8 was also decreased. Further to the search, Rambeaud et al. (2006) reported a significant increase in survival of neutrophils from cows with genotype +777CC in response to IL-8 compared with genotype +777GG. On the other hand, they observed a significant reduction in neutrophil reactive oxygen species (ROS) generation in response to phorbol-13-myristate-12 acetate by neutrophils of +777CC than of +777GG, although no differences in bactericidal activity or glutathione levels were observed among genotypes. These results indicate that neutrophils from cows with different *CXCR2* genotypes vary in their ability to suppress apoptosis and produce ROS and therefore may partly explain the inter- and intraindividual variations observed in the development of mastitis. In *CCR2*, another chemokine receptor gene, Leyva-Baca et al. (2007) associated c.414C>T with estimated breeding value for somatic cell score and udder depth in Canadian Holsteins, which indicates possible relationships with mastitis-related traits and estimated breeding values.

Other attempts at finding markers responsible for mastitis incidence/resistance include anonymous markers in genome scan approaches (Van Tassel et al. 2000) and mapping of QTLs with effects on SCC and clinical mastitis on the 29 autosomes of cattle (Khatar et al. 2004; Sugimoto et al. 2006). The mapping of a QTL to a particular location of the genome points to the location where the actual gene(s)/mutations responsible for the effect in question may be located. As a result, genes in the vicinity of a QTL are targets for possible associations with the condition in question. For example, Sugimoto et al. (2006) sequenced three genes in the vicinity of a QTL for SCC and reported a three-base insertion in the glycine-coding stretch of *FEZL* gene (a transcription factor with a role in neuronal development) that resulted in the extension of 12 glycine (12G) residues to 13 (13G). Further analysis indicated that 12G *FEZL* influences resistance to mastitis. Their results also indicated that *FEZL* induced lower expression of *SEMA5A* (axon-attracting molecule semaphorin 5A) in susceptible animals (13G). Meanwhile, in resistant animals (12G), enhanced *SEMA5A* induced expression of at least nine genes related to immune responses, including *TNF-α* and *IL-8*. The implication of their findings is that susceptibility to mastitis results from an impaired immune response due to the lower transcription activity of *FEZL*.

Transmissible spongiform encephalopathies or prion diseases

Transmissible spongiform encephalopathies (TSEs), also known as prion diseases, are caused by the conversion of the host-encoded prion protein (PrP) or normal cellular prion protein (PrP^{c}) into a misfolded abnormal form of the protein. The misfolded prion protein (PrP^{sc}) results from point mutations at the *PRNP* locus. There is, however, recent evidence implicating other genes or agents involved in the etiology of TSE (Diaz et al. 2005; Lloyd et al. 2001; Marcos-Carcavilla et al. 2007) thus making it a polygenic trait whose resistance/susceptibility is controlled by one major gene (*PRNP*) and modulated by several other genes. For this reason, we have decided to discuss TSE in this section.

TSEs may occur as genetic, infectious, or sporadic disorders in humans, cattle, sheep, goat, deer, and other domestic animals (reviews by Priola and Vorberg 2004; Doherr 2006). The most common forms of TSEs are scrapie in sheep and goats and bovine spongiform encephalopathy (BSE) in cattle. One human form of TSE, variant Creutzfeldt-Jacob disease, is thought to be caused by BSE through the consumption of beef (Scott et al. 1999), making TSE elimination from the food chain a priority by most governments.

In sheep, about 23 SNPs in the *PRNP* gene have been reported, of which three SNPs causing amino acid changes within the protein-coding sequence have been associated with scrapie development (incubation period, pathology, and clinical signs) (reviewed by Baylis and Goldmann 2004). The most important SNPs in terms of scrapie susceptibility/resistance are SNPs that lead to amino acid changes at codons 136 (A→V), 154 (R→H), and 171 (Q→H or Q→R) (Belt et al. 1995; Goldmann et al. 1990). 136V has been associated with scrapie susceptibility in both natural and experimental conditions, while 171R is associated with low incidence (Belt et al. 1995; Hunter et al. 1993; Maciulis et al. 1992). These common variants, however, define five *PRNP* haplotypes, namely, ARQ ($A_{136}R_{154}Q_{171}$), ARR, ARH, AHQ, and VRQ, that result in 15 genotype combinations, each with an associated degree of risk (Table 2). For instance, animals homozygous for VRQ rapidly develop clinical signs of scrapie when infected and are considered highly susceptible, while animals homozygous for ARR are resistant (Belt et al. 1995; Hunter et al. 1996). Susceptibility of the haplotypes ARQ, AHQ, ARH, and ARK is more complex and varies with breed. For example, ARQ/ARQ is the common genotype for scrapie cases in Suffolk sheep (Hunter et al. 1997a, b), while scrapie is rare in Texel sheep of this genotype (Dawson et al. 1998). Furthermore, 171R is dominant for increased scrapie resistance, implying that flocks derived from 171RR founder animals are expected to remain scrapie-free, even under exposure. In a recent study, Green et al. (2006) reported 36 previously unreported polymorphisms in the *PRNP* gene and further defined regions of strong linkage disequilibrium with the common resistant/susceptible haplotypes. In their study, the amino acid residues A136, R154, and Q171 were found within nine larger haplotypes spanning the entire *PRNP* gene (promoter, 5′UTR, coding region, and 3′UTR). Also, VRQ was observed on two of these larger haplotypes and ARR, ARH, and AHQ on one each. The significance of these observations to scrapie susceptibility, which may explain the variation observed with some genotypes, remains to be elucidated.

QTLs involved in resistance/susceptibility to scrapie and other TSEs in a region close to *IL1B* and *IL1RN* genes on sheep chromosome 3 and mouse chromosome 2 (Lloyd et al. 2001; Manolakou et al. 2001; Moreno et al. 2003a, b) and in cattle (Zhang et al. 2004) have been reported. Marcos-Carcavilla et al. (2007) recently characterized the *IL1B* and *IL1RN* genes in sheep and also reported, respectively, 29 SNPs and 1 insertion and 2 SNPs and a 14-bp deletion within the genes. Expression analysis of the two genes by real-time RT-PCR found a significant increase in mRNA concentration of the genes in the cerebellum of scrapie-infected sheep but not in healthy sheep. Their findings are in agreement with previous studies (Campbell et al. 1994; Cunningham et al. 2005) that revealed an altered proinflamatory cytokines profile

Table 2 A summary of prion protein gene (*PRNP*) genotypes associated with different scrapie phenotypes in sheep and goat

Species/ breed	*PRNP* genotype	Scrapie phenotype	Reference
Sheep	ARR[a]	Resistant genotype	Belt et al. 1995
	VRQ	Susceptible genotype	Belt et al. 1995
	ARH	May be neutral	Dawson et al. 1998
	AHQ	Associated with resistance in some breeds but not in others	Dawson et al. 1998
	VRQ/VRQ	Carriers develop rapid clinical signs of scrapie when infected	Belt et al. 1995; Hunter et al. 1996; Baylis et al. 2002
	ARQ/ARQ	Scrapie susceptible in some breeds and not in others	Hunter et al. 1997a, b; Dawson et al. 1998
	ARR/ARR	Carriers are highly resistant	Belt et al. 1995; Hunter et al. 1996; Baylis et al. 2002
Goat	VV_{21}, LL_{23}, GG_{49}, SS_{49}, HH_{143}, HR_{143}, RR_{154}, PP_{168}, PP_{240}, SP_{240} and SS_{240}	Variants found in scrapie affected goats	Billinis et al. 2002
	R_{143} and H_{154}	Moderately protective against scrapie	Billinis et al. 2002
	K222	Associated to healthy animals or scrapie resistance	Acutis et al. 2006; Vaccari et al. 2006
	Q168	Associated with scrapie susceptibility	Acutis et al. 2006
	M142	Associated with prolonged incubation period of scrapie and BSE in goats	Goldmann et al. 1996

[a] ARQ are amino acids at codons 136, 154, and 171, respectively

associated with nervous tissues during scrapie infection. They concluded that the increase in the mRNA levels of the genes in the cerebellum of infected sheep may explain the neurodegeneration associated with the disease and the differences in susceptibility observed between individuals of the same scrapie *PRNP*-associated genotypes. These observations thus make the genes good positional and functional candidates involved in the modulation of the scrapie incubation period in sheep. More insights into the significance of the identified polymorphisms are needed for meaningful conclusions to be drawn. The possible role of other genes within this QTL region may not be ruled out. Other agents causing unexplained types of scrapie or atypical scrapie first reported in Norway in 1998 are now widespread (Benestad et al. 2003; Moum et al. 2005; Orge et al. 2004), and, recently, Lühken et al. (2007) have associated microsatellites *MCMA53* and *MCMA16* on sheep chromosome 15 with susceptibility to atypical scrapie. Other polymorphic microsatelittes also occur within the ovine and bovine *PRNP* gene (Geldermann et al. 2003)

In goats, polymorphisms involving amino acid changes at codons 21 (V→A), 23 (L→P), 37 (G→V), 49 (G→S), 102 (W→G), 110 (T→N or T→P), 127 (G→S), 133 (L→Q), 137 (M→I), 142 (I→ M), 143 (H→ R), 146 (N→S),154 (R→H), 168 (P→Q), 211 (R→Q), 218 (I→L), 220 (Q→H), 222 (Q→K), and 240 (S→P) of the caprine PrP have been reported (Acutis et al. 2006; Agrimi et al. 2003; Billinis et al. 2002; Goldmann et al. 1996). Results following experimental challenge and natural infection indicate that variations at some of these codons may be relevant for scrapie susceptibility (Billinis et al. 2002; Goldmann et al. 1996, 1998). Variants associated with scrapie-affected goats include VV_{21}, LL_{23}, GG_{49}, SS_{49}, IM_{142}, HH_{143}, HR_{143}, RR_{154}, PP_{168}, PP_{240}, SP_{240}, and SS_{240} (Billinis et al. 2002; Goldmann et al. 1996). In addition, all scrapie-affected animals in Billinis et al. (2002) carried $HH_{143}RR_{154}$. Furthermore, they associated seven PrP haplotypes with scrapie-affected goats and five with healthy goats, while two genotypes were common to both groups. In another study, Agrimi et al. (2003) found associations between scrapie susceptibility and the distribution of genotypes at codons 37, 143, and 240 in the Italian Ionica breed of goats.

SNPs resulting in amino acid substitutions in the bovine *PRNP* gene have not been found. However, silent mutations and a variable number of octapeptide repeats in the coding region as well as three mutations in the untranslated exon 1 and its 5′ flanking region have been reported (Goldmann et al. 1991; Humeny et al. 2002). Furthermore, no or few associations between *PRNP* polymorphisms and BSE incidence have been found (Neibergs et al. 1994; Sander et al. 2004). A polymorphism (T174M) in another

gene close to *PRNP* in humans, the flanking prion doppel gene (*PRND*), is involved in susceptibility to sporadic Creutzfeldt-Jacob disease (Croes et al. 2004; Jeong et al. 2005). This gene was identified in a search for genes paralogous to *PRNP* in mouse and a linked expression between the two genes has been demonstrated (Moore et al. 1999). In contrast to the *PRNP* gene, SNPs in the bovine *PRND* gene have been observed to result in amino acid substitutions (R50H, N110H, R132Q) (Comincini et al. 2001; Luhrs et al. 2003). In addition, two synonymous SNPs, C4819T and T5063A, have been reported in German cattle breeds (Balbus et al. 2005). Haplotype and genotype analyses of BSE and control animals revealed significantly different distribution of C4815T and R13Q polymorphisms in German Simmental, while no BSE susceptibility was associated with R50H and A5063T (Balbus et al. 2005). Two synonymous SNPs are also known to occur in the ovine *PRND* gene.

Brucellosis

Natural resistance to brucellosis has been reported in several species, including cattle and humans (Montaraz and Winter 1986; Templeton et al. 1990). Through breeding studies with cattle, Templeton et al. (1990) reported that natural resistance to *Brucella* could be dramatically increased by selective breeding. With initial evidence linking the *Nramp1* gene to resistance/susceptibility in mice (Vidal et al. 1993), a later survey of the genes of several bovid species and the mode of inheritance of brucellosis in cattle suggest that other genes are involved in the development of this disease (Adams and Templeton 1998). In addition to several host factors that are associated with innate immunity against *Brucella abortus* (reviews by Baldwin and Parent 2002; Wyckoff 2002), polymorphisms within the *Nramp1* gene in cattle are associated with natural resistance to brucellosis (Adams and Templeton 1998; Barthel et al. 2001). Basically, these polymorphisms involve a $(GT)_n$ repeat microsatellite in the 3′UTR of *Nramp1*. Adams and Templeton (1998) associated the GT_{13} allele with resistance toward *B. abortus* and the other alleles, $GT_{14–16}$, with susceptibility. In another study, Paixão et al. (2006) detected GT_{13} in cattle genotypically resistant to brucellosis and detected GT_{14}, GT_{13}/GT_{14}, or GT_{13}/GT_{15} in genotypically susceptible cattle. However, a number of studies have found a lack of association of GT_{13} with resistance to bovine brucellosis (Kumar et al. 2005; Paixão et al. 2007). In humans, Bravo et al. (2006) found no association of susceptibility to brucellosis with several polymorphisms of the *Nramp1* gene, while significant associations have been reported in Koreans (Ryu et al. 2000). A *Nramp1* SNP that actually led to a change in an amino acid in mice (G169D, Vidal et al. 1993) has not been detected in any other mammalian species, including cattle. However, monocytes from naturally resistant cattle can more efficiently resist the intracellular growth of *B. abortus* than those from susceptible cattle (Qureshi et al. 1996; Templeton et al. 1990). From these accounts, it is clear that host ability to control the development of brucellosis is under the control of more than one gene, many not yet identified and characterized.

Trypanosomiasis

In many parts of Africa, Asia, and South America, trypanosomiasis is one of the main debilitating and limiting factors to animal productivity, infecting about 50 million cattle and costing producers and consumers about US$1–1.2 billion in losses (Kristjanson et al. 1999). Present control measures include limitation of the tsetse vector through the widespread use of insecticides and the use of trypanocidal drugs to treat sick animals. The use of insecticide comes with extra cost and associated environmental problems, while trypanocidal drugs are limited and resistance to them is growing steadily. However, some local breeds of cattle (N'Dama, Muturu, Namchi), sheep (West African Dwarf), and goats (West African Dwarf) in the central/west African region show natural resistance to the disease (Agyemang 2005). The ability to naturally resist trypanosome infections, also known as trypanotolerance, results from several biological mechanisms under multigenic control (review by Naessens 2006). Understanding of the genes that control the trypanotolerant trait may offer new, cheaper, and safer approaches to improving productivity of animals in endemic zones.

To date, numerous studies have been conducted but the key genes responsible for susceptibility/resistance have not been identified and characterized. The results of several studies have shown that trypanotolerant livestock have a remarkable capacity to control parasitemia and, thus, the development of severe anemia during infection (Dolan 1987; Gibson 2001; Trail et al. 1991, 1992). In an analysis of Boran/N'Dama chimeric twins, Naessens et al. (2003) confirmed that trypanotolerance is mediated by two independent mechanisms, (1) a better capacity to control parasitemia, which was suggested not to be due to differences in immune responses, and (2) a better capacity to control associated anemia, mediated by cells from the hemopoietic system. Therefore, two pools of genes are involved but none of the numerous studies, including zootechnical surveys (d'Ieteren et al. 1998; Murray et al. 1991), quantitative genetic studies (Trail et al. 1994), electrophoretic analysis of targeted proteins (Queval and Bambara 1984; Queval and Petit 1982), and genotyping of genes of the MHC (Maillard et al. 1989), have been able to identify trypanotolerance genes. Using the QTL approach,

Hanotte et al. (2003) analyzed 16 bovine phenotypes, including anemia, body weight, and parasitemia, and identified 18 QTLs linked to trypanotolerance. Their study further indicated that trypanotolerance is a highly polygenic trait with each gene or locus explaining only about 10–12% of the phenotypic variance of the trait. Most of the identified QTLs were linked to the control of anemia, suggesting that anemia control is complex and of major significance, and only a few were linked to parasitemia. Some authors have recently used the serial analysis of gene expression (SAGE) approach and have identified 187 genes that changed their expression in N'Dama leukocytes after infection by *T. congolense* (Berthier et al. 2003; Maillard et al. 2004, 2005). In another study using SAGE, Berthier et al. (2006) have constructed four different mRNA transcript libraries from the white blood cells of a N'Dama trypanotolerant animal obtained at different stages of development of experimentally induced trypanosomiasis (by *T. congolense*). The libraries contain about 75,000 sequences, including several known genes, described or expressed sequence tags, and completely new genes that may be functional in trypanotolerance. The availability of these libraries may now facilitate the identification of genes and the functional mutations responsible for trypanotolerance in cattle and therefore better options for control. In humans, on the other hand, Courtin et al. (2006) have associated two SNPs ($IL10_{-592\ C/A}$ and $TNF_{-308\ G/A}$) with the development of African trypanosomiasis whereby the $IL10_{-592\ A}$ allele was found to present a lower risk of disease while $TNF_{-308\ A}$ presented a higher risk of developing the disease early after exposure.

Dermatophilosis and other tick infections

Dermatophilosis, a severe skin disease of ruminants, is caused by the filamentous actinomycete bacterium *Dermatophilus congolensis* and is aggravated by the presence of the tick *Amblyomma variegatum* (Ambrose et al. 1999; Morrow and Compton 1991). It results in the death of up to 15% of infected stock. Present control measures are hampered by the development of chemoresistance to acaricides and antibiotics and there is little success in the development of a vaccine against the disease. However, field studies indicate differential breed response to the development of severe dermatophilosis, particularly a higher resistance by the west African N'Dama (taurine) breed, intermediate resistance by zebu breeds like the Sanga of Ghana and Gudali of Cameroon, and high susceptibility by imported (into tropical regions) breeds like Friesian (Koney et al. 1994; Leroy and Marchot 1987; Mattioli et al. 1995). Several studies on host immunity to dermatophilosis suggest two possible mechanisms of immunity: antibody-mediated prevention of the establishment of infection and antibody- or cell-mediated clearance of infection (How and Lloyd 1988; Martinez et al. 1993). Consequently, immune genes of the MHC in cattle have been studied for their role in the development of dermatophilosis. In a study on Brahman zebu cattle in Guadeloupe, classified according to absence or presence of clinical signs into, respectively, dermatophilosis resistant or susceptible, Maillard et al. (1996) reported an amino acid sequence in exon 2 of BoLA *DRB3* gene associated with a BoLA class I specificity as a possible genetic marker of resistance to dermatophilosis. The sequence EIAY, located at amino acid positions 66, 67, 74, and 78 within the antigen recognition sites (ARS), was found in 12 animals classified as resistant, and 10 of them also displayed class I BoLA-A8 specificity. Furthermore, only 3 of 18 susceptible animals showed simultaneously the *DRB3* EIAY sequence and BoLA-A8 specificity. Also, they found a serine residue at position 30 of the ARS of eight susceptible animals which was completely absent in all resistant animals. Their results thus associate MHC haplotypes, BoLA-A8 specificity and the BoLA-DRB3 EIAY, and lack of serine at position 30 with resistance to dermatophilosis. Other BoLA-DRB3 and BoLA-DQB alleles in relation to dermatophilosis have been characterized in cattle (Maillard et al. 1999, 2001; http://www.ri.bbsrc.ac.uk/bola/). One of the most significant markers strongly associated with dermatophilosis susceptibility (96%) involves two linked alleles of exon 2 DRB*09 (amino acid sequence C-E-S-F-L-QK-N in APS positions 11-28-30-37-67-70/71-74, respectively) and DQB*1804 genes (Maillard et al. 2002). Elimination of animals possessing this haplotype by marker-assisted selection reduced the incidence of dermatophilosis from 76% to 2% over a period of 5 years (Maillard et al. 2002). A recent study also found a MHC allele associated with hypersensitivity to dermatophilosis in previous studies of the Renitelo cattle of Madagascar (Razafindraibe et al. 2006). The DRB*09 marker sequence may be exposed to proteases possibly hindering recognition by a T cell receptor (Maillard et al. 2003). In the Maillard et al. (2002) study, only about 30% of susceptible animals possessed the DRB*09/DQB*1804 marker, indicating the possibility of the involvement of other markers or minor players.

Like dermatophilosis, host ability to develop tick resistance has been recorded in ruminants and has also been a subject for study for many years. Tick infestations of several species, e.g., *Boophilus microplus, B. decolorants, Amblyomma americanum, A. bebraeum, A. variegatum*, have received differential host responses by different cattle breeds located in different regions. For example, the N'Dama (taurine) cattle of west Africa and many tropical zebu breeds are known to have greater tolerance to tick infestations than taurine breeds of temperate regions or origin (Latif et al. 1991; Mattioli et al. 1993; Rechav et al.

1990). Thus, it is believed that tick resistance tends to be acquired with exposure (Latif et al. 1991). However, the report by Kerr et al. (1994) about evidence of a major gene for tick resistance in cattle and evidence from previous reports (Stear et al. 1984, 1990) began the earnest search for the gene or genes that control genetic resistance to tick infestations. Several reports today have associated alleles of genes of the BoLA system with various aspects of resistance/susceptibility to tick infections in cattle. Initial reports of associations came from Stear et al. (1984, 1990) who related BoLA class I alleles w6.1 and w7 to tick protection. In a preliminary study, Martinez et al. (2004) found putative associations between tick counts and alleles BoLA-DRB3.2*10 and *42 and between warble counts and alleles *31 and *42 in cattle. In a more recent study, associations of BoLA alleles with lower tick number were found for alleles DRB3.2*18, *20, and *27 and a weaker association with allele *26 (Martinez et al. 2006). From another perspective, dermal mast cells (DMC) are also thought to play a role in the host's resistance to tick infestations. Some reports have indicated that zebu breeds known to be highly resistant to ticks have twice the number of DMC than taurine cattle (of temperate origin) in *B. microplus*-parasitized skin biopsies (Moraes et al. 1992). F_2 crossbred Gir × Holstein cattle were recently demonstrated to acquire resistance against *B. microplus*, probably the result of an increase in DMC (Engracia Filho et al. 2006). The massive migration of mast cells to the dermis during tick infestations is certainly under the control of yet unidentified genes. Given the above reports, it is clear that host immune genes play a major role in developing resistance to tick infestations. The major challenge now is to identify such genes and incorporate them into breeding programs for the generation of resistant livestock.

Exploitation of genetic information and engineering in controlling livestock diseases

The knowledge of the molecular genetic basis of livestock diseases has offered or is offering geneticists and breeders new avenues of tackling these diseases safely and cheaply. It should be noted that conventional methods of control such as change in management practices, culling, vaccinations, antibiotics, and other types of medications have succeeded to control many livestock diseases but with extra cost and associated problems, including antibiotic resistance and residues in the environment, and thus are a major cause of environmental and human health problems. A genetic means of control is one route of action that may prove beneficial to the animals, producers, and consumers. Genetic control of diseases that are under the control of single genes, if known, is easily achievable. For example, genetic tests (Table 1) exist for genotyping breeding animals for disease-causing mutations and the elimination of carriers from the breeding herd, thus limiting the spread of disease. Using this method, several of these diseases have been successfully controlled or eliminated from the herd. However, the causal mutations of many more diseases of cattle, goat, pig, and sheep that are under the control of single genes are yet to be determined and effectively controlled.

Diseases under multigenic control, which is complex, are not as easily determined and controlled as are those under unigenic control. Also, the interaction of many host genes is further compounded by pathogenic and environmental factors. This does not, however, make genetic control unattainable but calls for deeper knowledge of the interacting factors. With classical methods of breeding, disease traits with high heritability have been used successfully to reduce the incidence of some infectious diseases of farm animals. However, the heritability of most disease traits is very low and genetic control is not easily achievable through breeding. With the continued advancement in molecular genetic techniques and knowledge of the genome of farm animals, there is hope that molecular information can actually play a major role in effectively controlling livestock diseases. Available genome sequences and high-resolution molecular maps of some livestock species have opened new insights into the genetic bases of infectious diseases (McKay et al. 2007). Location of significant QTLs for some disease traits has actually led to the identification of responsible genes and causal SNPs and thus the possibility of disease control.

Apart from QTLs, genetic engineering through targeted disruption or addition of genes may be one avenue of control. Recently, Wall et al. (2005) produced transgenic cows secreting lysostaphin in their milk and further demonstrated that the transgenic cows have enhanced resistance to *Staphylococcus aureus* mastitis. In this case only enhanced resistance and not complete control because of the effects of other genes and the presence of other factors prompted Donovan et al. (2005) to think about introducing other genes or using other techniques like RNA interference to deal with more mastitis pathogens and also handle potential resistance issues. For prion diseases, Denning et al. (2001) and Perrier et al. (2002) indicated the possibility of a genetic engineering approach to control diseases through their observations in sheep and mice, respectively. Recently, Richt et al. (2006), by the method of sequential gene-targeting, produced cows deficient in normal cellular prion protein (PrP^c); they were clinically, physiologically, histopathologically, immunologically, and reproductively normal thus opening an avenue for the production of cattle and products free of prion proteins. The application of genetic engineering in controlling livestock

diseases is still at its infancy stage due to ethical issues and yet unidentified risk factors related to the technique.

Implications of current findings and future perspectives on farm animal disease control

Molecular markers have been used extensively to control diseases and to map QTLs that control resistance to certain diseases in farm animals, as exemplified in this review. However, much work is still required for many other diseases. To adequately control livestock diseases by exploiting genetic information, deeper knowledge of genome variations is required. As exemplified in humans, the near complete sequencing of human chromosomes has facilitated accurate characterization and assessment of all classes of genomic variation, and with the application of genome-wide scanning technologies (e.g., microarray-based comparative genomic hybridization, genome-wide SNP platforms), a new, previously unrecognized degrees of larger-sized genomic variations have been detected. These larger-sized variations include copy number variants (>1 kb), large-sized inversions, insertions, deletions, and other complex rearrangements, most times not detectable by standard DNA sequencing procedures and cytogenetics (Feuk et al. 2006). It has been well established in studies of monogenic, oligogenetic, and complex diseases of humans that the study of such large-sized chromosomal rearrangements can be the fastest approach to identifying candidate disease loci (variants) and genes (Lugtenberg et al. 2006; Rosenberg et al. 2006; Vissers et al. 2005). Studies on such large-sized chromosomal rearrangements on livestock genomes could therefore facilitate detection of the genetic bases for some of those diseases (monogenic and complex) of livestock that still elude investigation. This implies that the genome sequences for these livestock species must first be available before such studies can be undertaken. For the genome sequences, including candidate genes and loci that are currently available, more detailed studies involving all sections of candidate genes and more genes in the vicinity of a QTL have to be carried out in order to identify candidate SNPs and copy number variants for more effective livestock disease control.

Furthermore, resistance or susceptibility to complex diseases of livestock (e.g., mastitis) pose great challenges to research efforts in terms of developing new methodologies for detection and integration of various genetic variants. Much research on disease-resistance phenotypes, conserved sequence homologies, and conserved functions has been done in human and mouse genes, and farm animals should be used as excellent models for investigation. Development and application of microassay-based techniques for genomics (DNA and mRNA), proteomics (protein), protein-protein interaction, and protein-DNA interaction and the role of small functional RNAs will no doubt facilitate our search for disease-resistance genes in farm animals. Furthermore, recent interest in and study of epigenetics in human medicine should greatly influence our research on disease resistance in farm animals. Epigenetic disorders give rise to several significant human diseases (Eggar et al. 2004). Epigenetic inheritance is the transmission of information from a one-cell or multicell organism to its descendants without that information being encoded in the nucleotide sequence of the gene. Epigenetic mechanisms such as DNA methylation, post-translational modifications of histone proteins, remodeling of nucleosomes, and expression of small regulatory RNAs also contribute to the regulation of gene expression, determination of cell and tissue specificity, and assurance of inheritance of gene expression levels. All these could affect disease resistance. At this time, the epigenetic mechanisms underlining disease resistance in farm animals are unclear.

It is apparent that we are just at the beginning of understanding the contributions of genetics and epigenetics to diseases in farm animals. Despite many difficulties ahead of us, identification of the genes and mutations responsible for variation in disease resistance could greatly enhance the efficiency of breeding animals that possess innate disease resistance. Furthermore, it will provide new tools to facilitate research into the mechanisms of infection, possibly leading to additional pharmacologic and management approaches for the control of disease transmission. Finally, genetic control of animal diseases can reduce the costs associated with diseases, improve animal welfare, and provide healthy animal products to consumers, and it should be given more attention.

Generally, the less attention paid to research and control of animal diseases compared to diseases in humans is not a healthy trend of events. This is because an outbreak of a livestock disease can affect us directly or indirectly. The more recent outbreaks of BSE in livestock has lead to widespread loss of income, at both the farm and the government levels, and the Avian flu virus has led to the loss of hundreds of human lives. In the last century, losses of human lives due to livestock disease outbreaks were even more dramatic. Therefore, controlling livestock diseases should not be considered any less important.

Conclusion

Different types of changes that describe genetic variations of the genetic material have been implicated in one disease of livestock or another. These variations affect mRNA splicing patterns and result in alteration or complete

elimination of protein function thereby leading to pathologic conditions in farm animals. However, information on genome variations involving large sections of the genetic material, including complex chromosomal rearrangements shown to explain some disease conditions in humans, is not available for livestock species. Knowledge of the genetic bases of some livestock diseases has led to control through breeding and is also opening new avenues of control through genetic engineering. For diseases under multigenic control, more research efforts have to be expended to fully understand the roles of controlling genes and develop effective control measures. Also, more effort has to be made in sequencing the genomes of the sheep, goat, and pig; this will provide the much needed baseline information for genetic studies into diseases. With increasing knowledge and advances in molecular biology, efforts at searching for and characterizing genes that control livestock diseases should intensify. The tool of genetic engineering should be fine tuned and safer alternatives to antibiotics and other therapeutic measures should be developed. Finally, a better understanding of all these factors could be better harnessed to effectively identify and control livestock diseases.

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