Rev. Sci. Tech. Off. Int. Epiz., 2015, **34** (1), 185-197

Genetic resistance: tolerance to vector-borne diseases and the prospects and challenges of genomics

H. Bahbahani [1, 2] & O. Hanotte [1]

(1) School of Life Sciences, University of Nottingham, NG8 2NG, Nottingham, United Kingdom
E-mail: plxhb1@nottingham.ac.uk
(2) Department of Biological Sciences, Faculty of Science, Kuwait University, Safat 13060, Kuwait
E-mail: plzoh@nottingham.ac.uk

Summary

Vector-borne diseases in cattle and small ruminants (e.g. trypanosomosis, Rift Valley fever and East Coast fever) are associated with major economic losses in tropical countries, and particularly on the African continent. A variety of control strategies (e.g. management, vaccination and/or acaricide treatments) are used to minimise their negative impacts. These strategies are often associated with environmental, technical and/or economic drawbacks. However, several indigenous livestock populations have been reported to show a level of genetic tolerance or resistance to such disease challenges (e.g. trypanotolerant N'Dama cattle and Djallonké sheep). Use of these populations represents a sustainable alternative approach to minimising the negative impact of such infection/infestation on livestock production. This review summarises the current understanding of the genetic control of these adaptations, identifies knowledge gaps and critically examines the possible impacts of genomics approaches to the genetic improvement of tolerance and/or resistance to vector-borne diseases.

Keywords

Candidate gene – Genetic marker – Genomic selection – Marker-assisted selection – Phenotype – Quantitative trait locus – Trypanotolerance – Vector-borne disease.

Introduction

The aetiology and pathology of vector-borne diseases remain important research topics. These diseases are caused by several pathogens (bacteria, viruses and protozoa) transmitted by different vectors (including mosquitoes, ticks, biting midges and flies). In livestock, vector-borne diseases are often linked to high direct or indirect mortality rates, which have substantial impacts on farmers' livelihoods and the agricultural economy of the affected country (1, 2, 3). Climatic changes are expected to affect such disease prevalence, with negative impacts on livestock health, and hence the farming industry, in both the developed and the developing world (4, 5, 6). Strategies such as treatment with drugs and animal immunisation may be used to some extent for disease control, but they have several drawbacks (see Eisler *et al.* and Di Guilio *et al.* for reviews [7, 8]). A 'natural' alternative is to promote the use of livestock breeds that are genetically tolerant/resistant to these diseases. However, while their survival traits are unquestionable, these breeds compare poorly with their exotic counterparts for productivity traits. Understanding the genetic mechanisms behind such 'indigenous tolerance' has remained beyond reach until now.

In this review, the authors discuss the progress made to date in identifying genetic factors associated with tolerance/resistance to vector-borne diseases in livestock (Table I). The focus is on three livestock species, cattle, sheep and goats, and vector-borne disease challenges traditionally associated with sub-Saharan Africa. The authors end by emphasising and critically analysing the promise of genomics to produce vector-borne disease-tolerant/resistant livestock breeds for the tropics.

Table I
Major vector-borne diseases affecting cattle, sheep and goats, their causative parasites and transmitting vectors and evidence for genetic control

Diseases	Parasites	Vectors	Evidence for genetic control (ref. no.)
Trypanosomosis	*Trypanosoma* spp. (e.g. *T. brucei*)	Flies (*Glossina* spp.)	9, 10, 11, 12
Rift Valley fever	Single-stranded RNA virus of the *Bunyaviridae* family and *Phlebovirus* genus	Mosquitoes (*Culex* and *Aedine* spp.)	None
East Coast fever (cattle only)	*Theileria parva*	Ticks (*Rhipicephalus appendiculatus*)	None
Tropical theileriosis	*Theileria annulata*	Ticks (*Hyalomma* spp., e.g. *H. anatolicum*)	13, 14, 15
Babesiosis	*Babesia* spp. (e.g. *B. bovis*)	Ticks (*Ixodes scapularis*)	None
Anaplasmosis	*Anaplasma* spp. (e.g. *A. marginale*)	Ticks (*Ixodes ricinus*)	None
Heartwater (cowdriosis)	*Ehrlichia ruminantium*	Ticks (*Amblyomma* spp., e.g. *A. variegatum*)	None

Genetic control of vector-borne diseases in livestock

An important prerequisite for breeding strategies to improve disease tolerance/resistance is to understand the underlying genetic control mechanisms. Filling this gap in knowledge is not an easy task. Genome-wide association studies have been performed for a few vector-borne diseases using pedigree resources and microsatellite association studies. As indicated in Table I, a number of studies have identified associations between such genetic markers and vector-borne disease tolerance/susceptibility.

Cattle

Trypanosomosis

The genetic control of trypanotolerance (defined as a reduction of the deleterious effects of pathogen burden on the host [16]) and of trypanoresistance (a mechanism mediated by the immune system aimed at reducing pathogen burden following infection [16]) in livestock has been extensively studied (9, 10). This followed increasing awareness of the genetic tolerance of West African indigenous taurine cattle (e.g. N'Dama, Baoulé) (17, 18, 19, 20, 21, 22). Trypanosome challenge is not limited to West Africa, and cattle populations from other African regions have been reported to have the same adaptation, e.g. Sheko (Ethiopia), Orma Boran (Kenya), Mursi cattle (Ethiopia) and Nuba Mountain cattle (Sudan) (23). However, when compared with the West African taurine, the genetics of trypanotolerance have been much less studied in these populations.

Trypanotolerant cattle show a lower mortality rate, level of parasite infestation and degree of anaemia, as well as better weight gain and reproductive performance, than susceptible animals (20, 21, 22). In 2003, an important step was made towards understanding the genetic control of trypanotolerance in African cattle. A total of 199 F2 (second hybrid generation) cattle of *Bos taurus taurus* (N'Dama) × *B. t. indicus* (Kenyan Boran) ancestry, and their parents and grandparents, were genotyped with 477 autosomal microsatellite loci (10). Eighteen quantitative trait loci (QTL) were identified to be associated with different traits related to trypanotolerance, e.g. anaemia, parasitaemia and body weight (Table II; see Table III for the definitions of the traits). Not surprisingly, given the correlation observed between phenotypes, most of these QTL were associated with more than one trait. Different genetic effects were observed, i.e. dominant, recessive, additive, overdominant and negative overdominant relationships, with a recessive mode of inheritance/expression the commonest. The 18 QTL identified explained 6–20% of the total phenotypic variance of the traits (10).

This study illustrated the difficulty of defining disease tolerance or resistance phenotypes in a simple and precise way, while demonstrating the genetic inheritance of trypanotolerance and its polygenic nature. Interestingly, the 'tolerant/resistant' alleles at two of the QTL originated from the Kenyan Boran ancestors, the 'susceptible breed'. Also, the study found that distinct QTL probably explain the genetic control mechanisms for parasitaemia and anaemia. Subsequently, it was shown that introgression (gene flow brought about by backcrossing of hybrids) of these QTL from African N'Dama cattle into the Kenyan Boran increased the trypanotolerance of the latter. Moreover, the level of tolerance observed was positively correlated with the level of N'Dama introgression into the zebu genome (24).

Table II

Characteristics of the mapped trypanotolerance quantitative trait loci (QTL)

For each chromosome–trait combination, the significance, genetic model and breed origin of the QTL are indicated as well as the percentage of the F2 phenotypic variance explained by the QTL. The origin of the allele conferring higher trypanotolerance or increase in body weight is indicated by black (for N'Dama) or grey shading (for Kenyan Boran) (10)

Trait [a]	***Bos taurus* chromosome**																	
	1	**2**	**4**	**7**	**8**	**13**	**14**	**16**	**17**	**20**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
PCVI	D*** 14.3	(R) 9.3																
BWI		(A) 7.4															R** 7.7	
BWM		(A) 9.9		(A) 6.3	R* 9.6										D* 7.8		R* 6.8	
PCVM		A* 7.4									R* 15.6		A* 7.2					
PCVF									R** 8.2									
PCVIF		R*** 11.9							R** 7.9									
PCVIM		R*** 15.3						D** 9		R* 7.7				D* 8.1		R* 8.1		
PCVFM				(D) 10				(D) 5.2	R* 7.4									
PCVV									R*** 11.7	R* 8.2				(D) 6.9		R* 8.1		
PCVD150		A* 9				D** 12.9			R*** 12	(R) 5.6			A* 6.6		A* 7.2	R** 8.7		
PCVD100		(A) 6.7			(R) 7.1	D* 11.3	R* 6.8		R*** 10.5						D** 9.9	R*** 10.7		
BWF_BWI															A* 6.7			
BWD 150				(A) 7				D** 6.2		(R) 6.6					R* 7.6			D* 20.4
PARMLn			R*** 16.4															
PARLnM				D** 11.2	(D) 6.1					(R) 7.6								D* 13.4
DR60–150				(R) 8.2		D* 6.7						D* 8.8						

a) See Table III for the definitions

A: additive

R: recessive

D: dominant

D: overdominant

R: negative overdominance

Level of significance:

( ) $P < 0.1$

* $P < 0.0185$ (false discovery rate [FDR] 20%)

** $P < 0.0043$ (FDR 10%)

*** $P < 0.0008$ (FDR 5%)

Trypanotolerance has also been studied at the gene expression level. Several genes have been found to be differentially expressed following *Trypanosoma congolense* infection in N'Dama (11) and Kenyan Boran (12) cattle. These genes are involved in different biological pathways and include genes related to innate and acquired immunity, genes encoding protein kinase C subunits, and bovine ribosomal genes. More particularly, two candidate genes (ARHGAP15 and TICAM1), which belong to bovine immune response pathways and are mapped within previously identified trypanotolerance QTL (10), have been shown to be differentially expressed in spleen and lymph nodes following *T. congolense* infection (9). The genomic regions containing these two genes show a signature of positive selection in West African cattle (9).

Tropical theileriosis

The pathology of *Theileria annulata* infection starts with a tick bite, followed by infection of macrophages in the lymph nodes by the causative parasite. These macrophages start to proliferate and invade other tissues. In addition to the infected macrophages, T-lymphocytes are also transformed and become hyper-proliferative (13). Host tolerance to theileriosis has been documented in Sahiwal zebu, when compared with European taurine cattle (25). Protein analyses conducted on Sahiwal cattle artificially challenged with *T. annulata* showed lower levels of the plasma α^1 acid glycoprotein in the blood serum of Sahiwal compared with the more susceptible Holstein-Friesian cattle (25). A subsequent study analysing Holstein-Friesian

Table III
Phenotypic traits for mapping analysis of trypanotolerance quantitative trait loci (10)

Trait	Definition
Pre-challenge (non-trypanotolerance traits)	
PCVI (initial packed cell volume)	Mean PCV before challenge (days 21–0)
BWI (initial body weight)	Mean body weight before challenge (days 21–0)
Ambiguous (trypanotolerance or non-trypanotolerance traits)	
BWM	Mean body weight after challenge (days 0–150)
Post-challenge (trypanotolerance traits)	
PCVF	Final PCV (day 150 or day before treatment)
PCVM	Minimum PCV recorded during the post-challenge period (days 0–150)
PCVI minus PCVF (PCVIF)	PCVI (day 0) minus PCVF
PCVI minus PCVM (PCVIM)	PCVI (day 0) minus PCVM
PCVFM	PCVF minus PCVM
PCV variance (PCVV)	Variance of the PCV values post challenge (days 0–150)
PCVD150	Percentage decrease in PCV up to day 150 after challenge
PCVD100	Percentage decrease in PCV up to day 100 after challenge
BWF/BWI	Final body weight scaled by BWI
BWD 150	Percentage decrease in body weight up to day 150 after challenge
PARMLn	Mean of natural logarithm ($ni + 1$), ni = number of parasites at day i after challenge (days 11–150)
PARLnM	Natural logarithm of the mean number of parasites after challenge (days 11–150)
Detection rate (DR60 – 150)	Number of times an individual is detected to be infected (days 60–150)

and Sahiwal monocytes infected with *T. annulata* indicated that the Sahiwal theileriosis tolerance network probably involves immune-related (e.g. toll-like receptor [TLR]-10 and fibrinogen-like protein [FGL]-10) and cell adhesion (e.g. intercellular adhesion molecule [ICAM]1) genes (14). This supports a tolerance mechanism involving interaction between infected and immune cells, leading to the control of T-lymphocyte activation. The tolerance of Sahiwal cattle to tropical theileriosis has also been associated with a lower capacity for invasiveness of the infected transformed leucocytes, i.e. macrophages, a possible consequence of a lower level of expression of the transforming growth factor TGF-b2 gene (15).

Tick resistance

Tick infestation may cause anaemia, weight loss and death if it involves large numbers of the parasites. The heritability of tick resistance has been estimated to be as high as 34% in Asian zebu cattle (e.g. Brahman zebu) (26, 27). Upon artificial infestation with the cattle tick *Rhipicephalus microplus*, Brahman cattle showed a lower number of ticks carried than Holstein-Friesian cattle (28). Gene expression analysis indicates that pro-inflammatory genes, such as TLR-5, chemokine ligand-2 and chemokine receptor-1, are involved in resistance mechanisms. These genes are expressed at a lower level at attachment sites in Brahman cattle than in Holstein-Friesian cattle (29). Moreover, subsequent studies have identified candidate QTL explaining about 3.3–5.9% of the phenotypic variance in tick burden. It is possible that different QTL may be expressed, depending on the environment. For example, QTL on BTA 2 (*Bos taurus* chromosome 2) and 10 were associated with tick resistance during the dry season, while QTL on BTA 5 and 11 were associated with the same trait during the wet season (27, 30).

Sheep and goats

There are fewer research studies on tolerance or susceptibility to vector-borne diseases in small ruminants than in cattle (31, 32, 33, 34), perhaps because the latter have higher economic and market value in most livestock production systems in the tropics. Nevertheless, several studies have reported examples of vector-borne disease tolerance/susceptibility in sheep and goats, for diseases such as anaplasmosis (35, 36, 37), babesiosis (38, 39), theileriosis (40, 41, 42) and trypanosomosis (43). The genetic control behind such adaptation remains largely unknown, with the last disease the most studied.

Several African small ruminant breeds have been reported to be trypanotolerant, e.g. Djallonké sheep and West African

dwarf (WAD) goats in West and Central Africa, and Galla goats and Red Maasai sheep in East Africa (31, 32, 44). Both Djallonké sheep and WAD goats show a degree of resilience against trypanosome infection, being able to live with such infection by limiting its pathogenic effect (45). In Djallonké sheep distinct mechanisms for the control of parasitaemia and anaemia may be involved (46). Here, resistance to trypanosomosis is characterised by a longer prepatent period and superior control of parasitaemia, when compared with Djallonké × Sahelian crossbred sheep, upon artificial infection with *T. congolense* (46). It has been suggested that Djallonké sheep may be more trypanotolerant than WAD goats (45, 47). However, introgression of Sahelian goats into WAD goats (48), and of Sahelian sheep into Djallonké (46), has now been documented. This may influence the level of trypanotolerance, and make comparison among populations or species difficult.

The genetic control of disease tolerance/resistance in sheep and goats has not been extensively investigated for vector-borne diseases, but this is not the case for non-vector-borne diseases. As the mechanism of tolerance/susceptibility to these infections is expected to involve immune response pathways, a summary of major findings is worth providing. Such non-vector-borne diseases include mycotoxicoses, mastitis, footrot, scrapie and nematode parasite infections/infestations (reviewed in 49). The most advanced findings concern the association between genetic markers and disease resistance traits for infestations with gastrointestinal nematode parasites. Many sheep and goat breeds living in tropical areas (e.g. East and West Africa, Thailand, Indonesia, and the Caribbean islands), as well as in Australia and New Zealand, have been shown to display a degree of resistance to a variety of nematode species, e.g. *Haemonchus contortus*, *Trichostrongylus columbriformis* and *Teladorsagia circumcincta* (50, 51, 52, 53). Associated QTL have been identified mainly in sheep, on chromosomes 1, 2, 3, 6, 14 and 19 (reviewed in 49), as have several candidate genes related to immunity, e.g. those encoding toll-like receptors (TLR-2 and TLR-4) and interleukin receptors (IL-2R) (54, 55, 56).

The challenges of unravelling the genetic control of resistance or tolerance to vector-borne diseases

As summarised above, several QTL and candidate genes have been reported to be associated with host tolerance/resistance to different vector-borne diseases. However, relative to the number and extended geographical distribution of vector-borne diseases affecting livestock, evidence linking genetic factors to parasitic disease tolerance/resistance remains scanty. Most is related to the identification of large QTL that often explain a small proportion of the phenotypic variation of the trait, and to differentially expressed candidate genes. Fine mapping of the candidate genomic regions and/or the identification and validation of specific causative variants has so far remained beyond reach.

We are faced with three major difficulties:

– definition and correlation of the phenotypes, including making the distinction between the phenotypic expression of primary mechanisms (resistance to parasitic infection) and that of secondary mechanisms (control of the effects of infection, e.g. anaemia) of tolerance/resistance

– the polygenic nature of the genetic mechanism of resistance/tolerance to vector-borne diseases (e.g. 9, 10, 14)

– the complexity of episodes of infection on farms where animals are exposed to multiple vector-borne disease challenges.

The complexity of the phenotypes

We need not only to define phenotypes accurately, but also to record them in a large number of animals as well as in several independent populations. In one study, the recording of three major phenotypes (parasitaemia, body weight and anaemia) and subsequently of 16 phenotypic traits led to the identification of 18 QTL on 18 chromosomes (10). Recording these measurements took approximately five years of observation, largely because of the breeding time constraints linked to the establishment of the F2 resource families. Moreover, this experiment was conducted on an experimental farm and animals were infected only once with a single *T. congolense* strain. Nevertheless, several of these QTL were subsequently shown to be of relevance *in situ* in West African cattle populations (57, 58), as well as in East African zebus (Kenyan Boran introgressed with N'Dama) (24).

The polygenic nature of the genetic mechanism of resistance/tolerance to vector-borne diseases has been further illustrated by a recent and so far unique study in livestock (59). A multidisciplinary team monitored, *in situ* on smallholder farms, more than 540 East African shorthorn zebu calves from their first week of birth until one year of age (60). Health checks and diagnostic tests were conducted for more than 100 pathogens (including more than 25 vector-borne diseases), providing a unique infection/infestation history profile for each calf. Each animal was also genotyped using the illumina BovineSNP50 Genotyping BeadChip (59, 61).

Here, Murray *et al*. (59) found a positive association between the death rate and illness (caused by several infectious diseases) in the cattle and genome-wide reduction of heterozygosity in the population (inbreeding depression). The results indicate that survival of multiple infectious disease challenges on-farm (*in situ*) is under polygenic control. In the field, cattle are exposed to different species of pathogens, and interactions among these infections/infestations add another level of complexity (60).

In addition to accurate phenotypic recording, equally important is the number of records. Murray *et al*. (59) also found a positive association between introgression of an 'exotic' (European taurine) genetic background into the indigenous cattle and episodes of clinical illness (outbreeding depression). However, this type of association was not observed for the mortality rate. One possible reason for this finding is the low number of introgressed animals included in the study that died (n = 13), in comparison with the number of introgressed animals that became sick (n = 30).

All the above findings emphasise the importance of designing detailed phenotypic recording protocols and building large-scale phenotypic databases when conducting any genome-wide association analysis (49).

The genomics tools

The integration of recent advances in genomics technologies (e.g. genome-wide single-nucleotide polymorphism [SNP] genotyping and full genome next-generation sequencing) into livestock genome-wide association studies allows the mapping and increased understanding of the genetic control of disease tolerance/resistance. In cattle, the availability of the BovineSNP50 Genotyping BeadChip, versions 1 and 2 (62), which were followed by the high-density BovineHD Genotyping BeadChip (63), now allows the integration of the whole cattle genome with informative genetic markers. Although ascertainment bias on the available SNP chips may be an issue (62), overall these tools have shown their general applicability to cattle worldwide (64). These 'SNP chips' have been widely used in cattle for the identification of signatures of selection (65, 66, 67) and for analyses of genome-wide diversity and introgression (59, 61), as well as in genome-wide association studies (68). In sheep, the Ovine SNP50 BeadChip has been used for similar purposes (69, 70), and a genome-wide SNP chip is now also available for goats (71).

The livestock industry is benefiting from the availability of reference genomes. Annotated reference genomes for taurine cattle (*B. t. taurus*) and sheep (*Ovis aries*), but not yet for zebu cattle (*B. t. indicus*) and goats (*Capra aegagrus*), are now publicly available in genome browsers such as Ensembl and the National Center for Biotechnology Information. Although these genome constructs have gone through several stages of improvement, it must be pointed out that they are still not fully annotated and they contain contigs (contiguous sequences of DNA created from overlapping sequenced fragments) that are unassigned to chromosomes. The incomplete annotation of these genomes limits accurate genome expression analysis (72). As mentioned above, disease phenotypes may be associated with differential gene expression between tolerant and susceptible animals, and the more complete the genome annotation the better.

Several next-generation sequencing platforms, such as the Roche 454, Illumina and SOLiD, have been developed. Each of these platforms has a specific sequencing chemistry and pipeline (reviewed in Bai *et al*. [72] and Metzker [73]). The progressive improvement in terms of read length, sequencing speed and genotyping accuracy will facilitate the improvement of reference genome annotation in the future. Recently, a company in the United Kingdom (Oxford Nanopore Technologies) has developed a new advanced sequencing technology called 'nanopore-based sequencing'. This technology, reviewed by Branton *et al*. (74), is based on nanopores embedded within a synthetic membrane, which single-stranded DNA molecules will pass through and be translated into sequence data. Although no data have yet been published that allow a critical examination of the accuracy of its sequence outputs, nanopore sequencing has several advantages over the currently used sequencing platforms, e.g. long DNA reads (25–50 kilobases), short processing time and low sequencing cost. It may therefore be expected that the coming years will see the availability of new and/or updated livestock genomes, and also an increasing number of re-sequenced livestock genomes, which will facilitate the understanding of the genetic mechanisms behind disease resistance and tolerance in livestock.

Application of genomics for the improvement of disease tolerance/resistance (marker-assisted selection and genomic selection)

Genomic approaches will not only contribute to our understanding of the mechanism of disease tolerance/resistance, but they may also be expected to facilitate

breeding improvement programmes for disease tolerance/resistance traits. Three avenues may be envisaged:

– marker-assisted selection (MAS)

– marker-assisted introgression (MAI)

– genomic selection.

All use genetic markers in linkage disequilibrium (LD) with the QTL of interest. None requires the identification of the causative mutation. However, to be worthwhile, the implementation of both MAS and MAI programmes requires that the mapped QTL explain a substantial proportion of the phenotypic variance of the trait of interest (75, 76, 77). Also, MAI, which involves the introgression of a chromosomal fragment of interest into a different breed or population from that in which it originated, has the added constraint that the expression of the QTL of interest may be dependent on the genomic background of the recipient populations (78).

Genomic approaches allow these limitations to be addressed, to some extent. More particularly, a new approach to marker-assisted genetic improvement programmes has been proposed, which has been called 'genomic selection' (79). The main idea is to use tens to hundreds or thousands of genetic markers distributed across the genome, typically SNPs, and to look for associations between these and the phenotype of interest. Rather than looking for a specific single marker–phenotype association, genome-wide selection relies on using the overall genetic make-up of the animals as a proxy for the phenotype (80, 81). Genomic selection assumes an infinitesimal model of inheritance (i.e. a very large [effectively infinite] number of loci) for the traits of interest.

Application of genomic selection requires large numbers of animals to be genotyped and their phenotypes recorded accurately, to estimate marker effects on the trait of interest. Animals of unknown phenotypes may then be genotyped with the same markers and the expected SNP or haplotype effects will be summed across the whole genome to predict the expected genomic estimated breeding values (GEBVs). These GEBVs can be used as a selection criterion to define candidate breeding animals (79, 80, 82).

Breeding programmes using genomic selection are being carried out for production-related traits, such as milk yield, in cattle and sheep (83, 84). Genomic selection programmes for dairy cattle breeds are now implemented in several countries, including Australia, New Zealand, the United States and the Netherlands. In all cases, GEBVs showed higher accuracy and reliability than the parental average estimated breeding value based on progeny testing (85, 86). Fertility has also been included in genomic selection programmes; however, the low heritability of the trait is an issue that limits the reliability of GEBV in such cases (86).

So far, to the best of the authors' knowledge, there are no ongoing genomic selection programmes aimed at improving vector-borne disease tolerance of livestock. However, given the increasing evidence that, rather than involving a few loci with major effects, tolerance of vector-borne disease is polygenic (e.g. see Hanotte *et al.* [10]), such an approach may represent a promising new avenue (but see below).

It is important to recognise that genomic selection does not take into account any epigenetic effects. Also, it is necessary to understand the heritability of the trait and the distribution of the associated QTL effects to estimate the number of animals for which phenotypes must be obtained. If the QTL show medium-to-large effects on the trait of interest, a low number of phenotypic records might be sufficient to reach an acceptable level of GEBV accuracy (86). This may facilitate the application of genome-wide selection to increase the tolerance/resistance to parasitic diseases.

The challenges of applying genomic selection for the improvement of disease tolerance/resistance

The application of genomic selection approaches in breeding programmes to improve vector-borne disease tolerance and/or resistance faces a major challenge: the lack of availability of large reference populations with recorded phenotypes. This issue, which is critical to accurate estimation of the genomic marker effect, is particularly challenging in developing countries and in extensive husbandry systems, where large amounts of standardised phenotype records may be difficult to collect in the absence of relevant infrastructure and/or long-term financial support. Also, the evidence so far indicates that genomic estimation of breeding value might be breed or population specific, because variation has been observed in the LD between markers in different breeds. More specifically, the predictive equation used to estimate the GEBV from the genotyped markers derived from one breed will be of lower accuracy in other breeds (81). Such variation in LD between markers in different breeds is one of the major reasons why genomic selection has not been implemented on a large scale in breeds of beef cattle and sheep. It could be a major issue for the tropics, where many breeds and/or livestock populations are often found in a small geographical area (23).

Conclusions and future prospects

Despite decades of research, the mechanisms of genetic control of vector-borne disease tolerance and/or resistance remain largely unknown. The complexity of the phenotypes and the polygenic nature of their expression complicate the identification of all genetic factors involved. However, these constraints are not specific to disease resistance/tolerance traits. The expression of many productivity traits is also under complex genetic control and shows genome × environment interactions. However, through genomics selection programmes the livestock industry has been able to apply new genomics tools to the improvement of productivity. There is no reason to believe that such an approach may not be equally possible for the improvement of tolerance or resistance to vector-borne disease challenges in the future. However, the complexity of the phenotypes and of the environmental challenges means that it is necessary first to identify ways to summarise the expression of tolerance and resistance in 'simple' phenotypes. For studies on farms and under natural conditions, the recording of survivability and/or disease episodes could represent a shortcut (59). However, recording these phenotypes still requires close monitoring of animals and, more particularly, their health status. The challenges ahead are many, but are not impossible to address.

Résistance génétique : la tolérance aux maladies à transmission vectorielle, perspectives et défis de la génomique

H. Bahbahani & O. Hanotte

Résumé

Les maladies à transmission vectorielle affectant les bovins et les petits ruminants (par exemple la trypanosomose, la fièvre de la vallée du Rift et la théilériose due à *Theileria parva*) entraînent souvent des pertes économiques importantes dans les pays tropicaux, en particulier sur le continent africain. Diverses stratégies de contrôle (par exemple la gestion des vecteurs, la vaccination et/ou les traitements acaricides) sont mises en œuvre pour minimiser ces impacts négatifs. Ces stratégies comportent parfois des inconvénients de nature environnementale, technique et/ou économique. En revanche, il a été constaté que certaines populations d'animaux d'élevage de race locale présentent une tolérance ou une résistance d'origine génétique lorsqu'elles sont exposées à ces maladies (c'est le cas par exemple des bovins de race N'Dama et des ovins Djallonké, qui sont trypanotolérants). L'utilisation de ces populations représente une solution durable pour minimiser l'impact négatif de ces infections et infestations pour l'élevage. Les auteurs résument l'état actuel des connaissances sur le contrôle génétique de ces mutations : les lacunes sont identifiées et les perspectives offertes par les méthodes de la génomique pour améliorer les facteurs de tolérance et/ou de résistance aux maladies à transmission vectorielle font l'objet d'un examen critique.

Mots-clés

Gène candidat – Gène marqueur – Locus de caractères quantitatifs – Maladie à transmission vectorielle – Phénotype – Sélection assistée par un marqueur – Sélection génomique – Trypanotolérance.

Resistencia genética: tolerancia a las enfermedades transmitidas por vectores y perspectivas y problemas de la genómica

H. Bahbahani & O. Hanotte

Resumen

Las enfermedades transmitidas por vectores que afectan al ganado bovino y a pequeños rumiantes (p.ej. tripanosomosis, fiebre del Valle del Rift o fiebre de la Costa Este [teileriosis]) provocan importantes pérdidas económicas en los países tropicales, especialmente en el continente africano. Para reducir al mínimo posible sus efectos negativos se utilizan diversas estrategias de lucha (gestión, vacunación y/o tratamientos con acaricidas), estrategias que suelen presentar inconvenientes de orden ambiental, técnico y/o económico. Sin embargo, en diversas poblaciones de ganado autóctono se ha descrito un cierto nivel de resistencia o tolerancia genética a estas enfermedades (p.ej. bovinos N'Dama y ovinos Djallonké tripanotolerantes). El uso de tales poblaciones constituye una alternativa sostenible para reducir al mínimo los efectos negativos sobre la producción ganadera de tales infecciones o infestaciones. Los autores resumen lo que hasta la fecha se sabe acerca del control genético de esas adaptaciones, señalan las lagunas existentes al respecto y examinan, desde una perspectiva crítica, lo que la genómica podría aportar a la mejora genética de la tolerancia y/o resistencia a las enfermedades transmitidas por vectores.

Palabras clave

Enfermedad transmitida por vectores – Fenotipo – Gen candidato – Locus de un carácter cuantitativo – Marcador genético – Selección asistida por marcadores – Selección genómica – Tripanotolerancia.

References

1. Robinson P.M. (1982). – *Theileriosis annulata* and its transmission: a review. *Trop. Anim. Hlth Prod.*, **14**, 3–12.

2. Mukhebi A.W., Perry B.D. & Kruska R. (1992). – Estimated economics of theileriosis control in Africa. *Prev. Vet. Med.*, **12**, 73–85.

3. Chanie M., Adula D. & Bogale B. (2013). – Socio-economic assessment of the impacts of trypanosomiasis on cattle in Girja District, Southern Oromia Region, Southern Ethiopia. *Acta Parasitol. Global.*, **4** (3), 80–85.

4. Rogers D.J. (2000). – Satellites, space, time and the African trypanosomiases. *Adv. Parasitol.*, **47**, 129–171.

5. Palmer S.R., Soulsby L., Torgerson P. & Brown D. (2011). – Oxford textbook of zoonoses: biology, clinical practice, and public health. Oxford University Press, Oxford, 423–424.

6. Munyua P., Murithi R.M., Wainwright S., Githinji J., Hightower A., Mutonga D., Macharia J., Ithondeka P.M., Musaa J., Breiman R.F., Bloland P. & Njenga M.K. (2010). – Rift Valley fever outbreak in livestock in Kenya, 2006–2007. *Am. J. Trop. Med. Hyg.*, **83** (2 Suppl.), 58–64.

7. Eisler M.C., Torr S.J., Coleman P.G., Machila N. & Morton J.F. (2003). – Integrated control of vector-borne diseases of livestock – pyrethroids: panacea or poison? *Trends Parasitol.*, **19** (8), 341–345.

8. Di Giulio G., Lynen G., Morzaria S., Oura C. & Bishop R. (2009). – Live immunization against East Coast fever: current status. *Trends Parasitol.*, **25** (2), 85–92.

9. Noyes H., Brass A., Obara I., Anderson S., Archibald A.L., Bradley D.G., Fisher P., Freeman A., Gibson J., Gicheru M., Hall L., Hanotte O., Hulme H., McKeever D., Murray C., Oh S.J., Tate C., Smith K., Tapio M., Wambugu J., Williams D.J., Agaba M. & Kemp S.J. (2011). – Genetic and expression analysis of cattle identifies candidate genes in pathways responding to *Trypanosoma congolense* infection. *Proc. Natl Acad. Sci. USA*, **108** (22), 9304–9309.

10. Hanotte O., Ronin Y., Agaba M., Nilsson P., Gelhaus A., Horstmann R., Sugimoto Y., Kemp S., Gibson J., Korol A., Soller M. & Teale A. (2003). – Mapping of quantitative trait loci controlling trypanotolerance in a cross of tolerant West African N'Dama and susceptible East African Boran cattle. *Proc. Natl Acad. Sci. USA*, **100** (13), 7443–7448.

11. Maillard J.C., Berthier D., Thevenon S., Quere R., Piquemal D., Manchon L. & Marti J. (2004). – Use of the serial analysis of gene expression (SAGE) method in veterinary research: a concrete application in the study of the bovine trypanotolerance genetic control. *Ann. N.Y. Acad. Sci.*, **1026**, 171–182.

12. Hill E.W., O'Gorman G.M., Agaba M., Gibson J.P., Hanotte O., Kemp S.J., Naessens J., Coussens P.M. & MacHugh D.E. (2005). – Understanding bovine trypanosomiasis and trypanotolerance: the promise of functional genomics. *Vet. Immunol. Immunopathol.*, **105** (3–4), 247–258.

13. Glass E.J. & Jensen K. (2007). – Resistance and susceptibility to a protozoan parasite of cattle: gene expression differences in macrophages from different breeds of cattle. *Vet. Immunol. Immunopathol.*, **120** (1–2), 20–30.

14. Jensen K., Paxton E., Waddington D., Talbot R., Darghouth M.A. & Glass E.J. (2008). – Differences in the transcriptional responses induced by *Theileria annulata* infection in bovine monocytes derived from resistant and susceptible cattle breeds. *Int. J. Parasitol.*, **38** (3–4), 313–325.

15. Chaussepied M., Janski N., Baumgartner M., Lizundia R., Jensen K., Weir W., Shiels B.R., Weitzman J.B., Glass E.J., Werling D. & Langsley G. (2010). – TGF-b2 induction regulates invasiveness of *Theileria*-transformed leukocytes and disease susceptibility. *PLoS Pathog.*, **6** (11), e1001197.

16. Medzhitov R., Schneider D.S. & Soares M.P. (2012). – Disease tolerance as a defense strategy. *Science*, **335** (6071), 936–941.

17. Stewart J.L. (1937). – The cattle of the Gold Coast. *Vet. Rec.*, **49**, 1289–1297.

18. Murray M. & Trail J.C.M. (1984). – Genetic resistance to animal trypanosomiasis in Africa. *Prev. Vet. Med.*, **2** (1–4), 541–551.

19. Akole G.W.O., Audie M., Pinder S.K., Roelants G.E. & Murray M. (1986). – Susceptibility and immune responses of zebu and taurine cattle of West Africa to infection with *Trypanosoma congolense* transmitted by *Glossina morsitans centralis*. *Vet. Immunol. Immunopathol.*, **11**, 361–373.

20. Mattioli R.C., Jaitner J., Clifford D.J., Pandey V.S. & Verhulst A. (1998). – Trypanosome infections and tick infestations: susceptibility in N'Dama, Gobra zebu and Gobra × N'Dama crossbred cattle exposed to natural challenge and maintained under high and low surveillance of trypanosome infections. *Acta Trop.*, **71** (1), 57–71.

21. Naessens J., Leak S.G., Kennedy D.J., Kemp S.J. & Teale A.J. (2003). – Responses of bovine chimaeras combining trypanosomosis resistant and susceptible genotypes to experimental infection with *Trypanosoma congolense*. *Vet. Parasitol.*, **111** (2–3), 125–142.

22. Naessens J. (2006). – Bovine trypanotolerance: a natural ability to prevent severe anaemia and haemophagocytic syndrome? *Int. J. Parasitol.*, **36** (5), 521–528.

23. DAGRIS (2007). – Domestic Animal Genetic Resources Information System (S. Kemp, Y. Mamo, B. Asrat & T. Dessie, eds). International Livestock Research Institute (ILRI), Addis Ababa, Ethiopia.

24. Orenge C.O., Munga L., Kimwele C.N., Kemp S., Korol A., Gibson J.P., Hanotte O. & Soller M. (2012). – Trypanotolerance in N'Dama × Boran crosses under natural trypanosome challenge: effect of test-year environment, gender, and breed composition. *BMC Genet.*, **13**, 87–102.

25. Glass E.J., Preston P.M., Springbett A., Craigmile S., Kirvar E., Wilkie G. & Brown C.G. (2005). – *Bos taurus* and *Bos indicus* (Sahiwal) calves respond differently to infection with *Theileria annulata* and produce markedly different levels of acute phase proteins. *Int. J. Parasitol.*, **35** (3), 337–347.

26. Davis G. (1993). – Genetic parameters for tropical beef cattle in northern Australia: a review. *Aust. J. Agric. Res.*, **44** (2), 179–198.

27. Porto Neto L.R., Jonsson N.N., D'Occhio M.J. & Barendse W. (2011). – Molecular genetic approaches for identifying the basis of variation in resistance to tick infestation in cattle. *Vet. Parasitol.*, **180** (3–4), 165–172.

28. Utech K.B.W., Wharton R.H. & Kerr J.D. (1978). – Resistance to *Boophilus microplus* (Canestrini) in different breeds of cattle. *Aust. J. Agric. Res.*, **29** (4), 885–895.

29. Piper E.K., Jackson L.A., Bagnall N.H., Kongsuwan K.K., Lew A.E. & Jonsson N.N. (2008). – Gene expression in the skin of *Bos taurus* and *Bos indicus* cattle infested with the cattle tick, *Rhipicephalus (Boophilus) microplus*. *Vet. Immunol. Immunopathol.*, **126** (1–2), 110–119.

30. Machado M.A., Azevedo A.L., Teodoro R.L., Pires M.A., Peixoto M.G., de Freitas C., Prata M.C., Furlong J., da Silva M.V., Guimaraes S.E., Regitano L.C., Coutinho L.L., Gasparin G. & Verneque R.S. (2010). – Genome wide scan for quantitative trait loci affecting tick resistance in cattle (*Bos taurus* × *Bos indicus*). *BMC Genomics*, **11**, 280.

31. Griffin L. & Allonby E.W. (1979). – Trypanotolerance in breeds of sheep and goats with an experimental infection of *Trypanosoma congolense*. *Vet. Parasitol.*, **5** (2–3), 97–105.

32. Griffin L. & Allonby E.W. (1979). – Studies on the epidemiology of trypanosomiasis in sheep and goats in Kenya. *Trop. Anim. Hlth Prod.*, **11** (3), 133–142.

33. Goossens B., Osaer S., Kora S. & Ndao M. (1998). – Haematological changes and antibody response in trypanotolerant sheep and goats following experimental *Trypanosoma congolense* infection. *Vet. Parasitol.*, **79** (4), 283–297.

34. Gutierrez C., Corbera J.A., Morales M. & Buscher P. (2006). – Trypanosomosis in goats: current status. *Ann. N.Y. Acad. Sci.*, **1081**, 300–310.

35. Chochlakis D., Ioannou I., Sharif L., Kokkini S., Hristophi N., Dimitriou T., Tselentis Y. & Psaroulaki A. (2009). – Prevalence of *Anaplasma* sp. in goats and sheep in Cyprus. *Vector Borne Zoonotic Dis.*, **9** (5), 457–463.

36. De la Fuente J., Atkinson M.W., Hogg J.T., Miller D.S., Naranjo V., Almazan C., Anderson N. & Kocan K.M. (2006). – Genetic characterization of *Anaplasma ovis* strains from bighorn sheep in Montana. *J. Wildl. Dis.*, **42** (2), 381–385.

37. Razmi G.R., Dastjerdi K., Hossieni H., Naghibi A., Barati F. & Aslani M.R. (2006). – An epidemiological study on *Anaplasma* infection in cattle, sheep, and goats in Mashhad Suburb, Khorasan Province, Iran. *Ann. N.Y. Acad. Sci.*, **1078**, 479–481.

38. Ziapour S.P., Esfandiari B. & Youssefi M.R. (2011). – Study of the prevalence of babesiosis in domesticated animals with suspected signs in Mazandaran Province, North of Iran, during 2008. *J. Anim. Vet. Adv.*, **10** (6), 712–714.

39. Nagore D., García-Sanmartin J., García-Pérez A.L., Juste R.A. & Hurtado A. (2004). – Identification, genetic diversity and prevalence of *Theileria* and *Babesia* species in a sheep population from northern Spain. *Int. J. Parasitol.*, **34** (9), 1059–1067.

40. Li Y., Guan G., Ma M., Liu J., Ren Q., Luo J. & Yin H. (2011). – *Theileria ovis* discovered in China. *Experim. Parasitol.*, **127** (1), 304–307.

41. Altay K., Dumanli N., Holman P.J. & Aktas M. (2005). – Detection of *Theileria ovis* in naturally infected sheep by nested PCR. *Vet. Parasitol.*, **127** (2), 99–104.

42. Luo J. & Yin H. (1997). – Theileriosis of sheep and goats in China. *Trop. Anim. Hlth Prod.*, **29** (4), 8S–10S.

43. Daniel A.D., Joshua R.A., Kalejaiye J.O. & Dada A.J. (1994). – Prevalence of trypanosomiasis in sheep and goats in a region of northern Nigeria. *Rev. Elev. Méd. Vét. Pays Trop.*, **47** (3), 295–297.

44. Agyemang K. (2005). – Trypanotolerant livestock in the context of trypanosomiasis intervention strategies. PAAT Technical and Scientific Series No. 7. Food and Agriculture Organization of the United Nations, Rome.

45. Goossens B., Osaer S. & Kora S. (1997). – Long-term effects of an experimental infection with *Trypanosoma congolense* on reproductive performance of trypanotolerant Djallonke ewes and West African dwarf does. *Res. Vet. Sci.*, **63** (2), 169–173.

46. Goossens B., Osaer S., Ndao M., Van Winghem J. & Geerts S. (1999). – The susceptibility of Djallonke and Djallonke-Sahelian crossbred sheep to *Trypanosoma congolense* and helminth infection under different diet levels. *Vet. Parasitol.*, **85** (1), 25–41.

47. Geerts S., Osaer S., Goossens B. & Faye D. (2009). – Trypanotolerance in small ruminants of sub-Saharan Africa. *Trends Parasitol.*, **25** (3), 132–138.

48. Hoeven E., Fidalis M.N., Leak S., Geerts S., Hanotte O. & Jianlin H. (2007). – Introgression of the Sahelian breed into West African dwarf goats. *In* Proc. 28th Meeting of the International Scientific Council for Trypanosomiasis Research and Control, 26–30 September 2005, Addis Ababa, Ethiopia, 622–626.

49. Bishop S.C. & Morris C.A. (2007). – Genetics of disease resistance in sheep and goats. *Small Ruminant Res.*, **70** (1), 48–59.

50. Baker R.L., Audho J.O., Aduda E.O. & Thorpe W. (2001). – Genetic resistance to gastro-intestinal nematode parasites in Galla and Small East African goats in the sub-humid tropics. *Anim. Sci.*, **73**, 61–70.

51. Beh K.J., Hulme D.J., Callaghan M.J., Leish Z., Lenane I., Windon R.G. & Maddox J.F. (2002). – A genome scan for quantitative trait loci affecting resistance to *Trichostrongylus colubriformis* in sheep. *Anim. Genet.*, **33** (2), 97–106.

52. Baker R.L. & Gray G.D. (2004). – Appropriate breeds and breeding schemes for sheep and goats in the tropics. *In* Worm control for small ruminants in tropical Asia (R.A. Sani, G.D. Gray & R.L. Baker, eds). *ACIAR Monograph*, **113**, 63–95.

53. Marshall K., Mugambi J.M., Nagda S., Sonstegard T.S., Van Tassell C.P., Baker R.L. & Gibson J.P. (2013). – Quantitative trait loci for resistance to *Haemonchus contortus* artificial challenge in Red Maasai and Dorper sheep of East Africa. *Anim. Genet.*, **44** (3), 285–295.

54. Coltman D.W., Wilson K., Pilkington J.G., Stear M.J. & Pemberton J.M. (2001). – A microsatellite polymorphism in the gamma interferon gene is associated with resistance to gastrointestinal nematodes in a naturally-parasitized population of Soay sheep. *Parasitology*, **122** (5), 571–582.

55. Ingham A., Reverter A., Windon R., Hunt P. & Menzies M. (2008). – Gastrointestinal nematode challenge induces some conserved gene expression changes in the gut mucosa of genetically resistant sheep. *Int. J. Parasitol.*, **38** (3–4), 431–442.

56. Periasamy K., Pichler R., Poli M., Cristel S., Cetra B., Medus D., Basar M., Thiruvenkadan A.K., Ramasamy S., Ellahi M.B., Mohammed F., Teneva A., Shamsuddin M., Podesta M.G. & Diallo A. (2014). – Candidate gene approach for parasite resistance in sheep: variation in immune pathway genes and association with fecal egg count. *PLoS ONE*, **9** (2), e88337.

57. Dayo G.K., Thevenon S., Berthier D., Moazami-Goudarzi K., Denis C., Cuny G., Eggen A. & Gautier M. (2009). – Detection of selection signatures within candidate regions underlying trypanotolerance in outbred cattle populations. *Molec. Ecol.*, **18** (8), 1801–1813.

58. Dayo G.K., Gautier M., Berthier D., Poivey J.P., Sidibe I., Bengaly Z., Eggen A., Boichard D. & Thevenon S. (2012). – Association studies in QTL regions linked to bovine trypanotolerance in a West African crossbred population. *Anim. Genet.*, **43** (2), 123–132.

59. Murray G.G., Woolhouse M.E., Tapio M., Mbole-Kariuki M.N., Sonstegard T.S., Thumbi S.M., Jennings A.E., van Wyk I.C., Chase-Topping M., Kiara H., Toye P., Coetzer K., Dec Bronsvoort B.M. & Hanotte O. (2013). – Genetic susceptibility to infectious disease in East African shorthorn zebu: a genome-wide analysis of the effect of heterozygosity and exotic introgression. *BMC Evol. Biol.*, **13** (1), 246–253.

60. De Clare Bronsvoort B.M., Thumbi S.M., Poole E.J., Kiara H., Auguet O.T., Handel I.G., Jennings A., Conradie I., Mbole-Kariuki M.N., Toye P.G., Hanotte O., Coetzer J.A. & Woolhouse M.E. (2013). – Design and descriptive epidemiology of the Infectious Diseases of East African Livestock (IDEAL) project, a longitudinal calf cohort study in western Kenya. *BMC Vet. Res.*, **9**, 171–192.

61. Mbole-Kariuki M.N., Sonstegard T., Orth A., Thumbi S.M., Bronsvoort B.M., Kiara H., Toye P., Conradie I., Jennings A., Coetzer K., Woolhouse M.E., Hanotte O. & Tapio M. (2014). – Genome-wide analysis reveals the ancient and recent admixture history of East African shorthorn zebu from Western Kenya. *Heredity*, **113**, 297–305.

62. Matukumalli L.K., Lawley C.T., Schnabel R.D., Taylor J.F., Allan M.F., Heaton M.P., O'Connell J., Moore S.S., Smith T.P., Sonstegard T.S. & Van Tassell C.P. (2009). – Development and characterization of a high density SNP genotyping assay for cattle. *PLoS ONE*, **4** (4), e5350.

63. Rincon G., Weber K.L., Eenennaam A.L., Golden B.L. & Medrano J.F. (2011). – Hot topic: performance of bovine high-density genotyping platforms in Holsteins and Jerseys. *J. Dairy Sci.*, **94** (12), 6116–6121.

64. Decker J.E., McKay S.D., Rolf M.M., Kim J., Molina Alcala A., Sonstegard T.S., Hanotte O., Gotherstrom A., Seabury C.M., Praharani L., Babar M.E., Correia de Almeida Regitano L., Yildiz M.A., Heaton M.P., Liu W.S., Lei C.Z., Reecy J.M., Saif-Ur-Rehman M., Schnabel R.D. & Taylor J.F. (2014). – Worldwide patterns of ancestry, divergence, and admixture in domesticated cattle. *PLoS Genet.*, **10** (3), e1004254.

65. Utsunomiya Y.T., Perez O'Brien A.M., Sonstegard T.S., Van Tassell C.P., do Carmo A.S., Meszaros G., Solkner J. & García J.F. (2013). – Detecting loci under recent positive selection in dairy and beef cattle by combining different genome-wide scan methods. *PLoS ONE*, **8** (5), e64280.

66. Gautier M. & Naves M. (2011). – Footprints of selection in the ancestral admixture of a New World Creole cattle breed. *Molec. Ecol.*, **20** (15), 3128–3143.

67. Gautier M., Flori L., Riebler A., Jaffrezic F., Laloe D., Gut I., Moazami-Goudarzi K. & Foulley J.L. (2009). – A whole genome Bayesian scan for adaptive genetic divergence in West African cattle. *BMC Genomics*, **10**, 550.

68. Utsunomiya Y.T., do Carmo A.S., Carvalheiro R., Neves H.H., Matos M.C., Zavarez L.B., Perez O'Brien A.M., Solkner J., McEwan J.C., Cole J.B., Van Tassell C.P., Schenkel F.S., da Silva M.V., Porto Neto L.R., Sonstegard T.S. & García J.F. (2013). – Genome-wide association study for birth weight in Nellore cattle points to previously described orthologous genes affecting human and bovine height. *BMC Genet.*, **14**, 52.

69. Kijas J.W., Lenstra J.A., Hayes B., Boitard S., Porto Neto L.R., San Cristobal M., Servin B., McCulloch R., Whan V., Gietzen K., Paiva S., Barendse W., Ciani E., Raadsma H., McEwan J. & Dalrymple B. (2012). – Genome-wide analysis of the world's sheep breeds reveals high levels of historic mixture and strong recent selection. *PLoS Biol.*, **10** (2), e1001258.

70. Johnston S.E., McEwan J.C., Pickering N.K., Kijas J.W., Beraldi D., Pilkington J.G., Pemberton J.M. & Slate J. (2011). – Genome-wide association mapping identifies the genetic basis of discrete and quantitative variation in sexual weaponry in a wild sheep population. *Molec. Ecol.*, **20** (12), 2555–2566.

71. Tosser-Klopp G., Bardou P., Bouchez O., Cabau C., Crooijmans R., Dong Y., Donnadieu-Tonon C., Eggen A., Heuven H.C., Jamli S., Jiken A.J., Klopp C., Lawley C.T., McEwan J., Martin P., Moreno C.R., Mulsant P., Nabihoudine I., Pailhoux E., Palhiere I., Rupp R., Sarry J., Sayre B.L., Tircazes A., Jun W., Wang W. & Zhang W. (2014). – Design and characterization of a 52K SNP chip for goats. *PLoS ONE*, **9** (1), e86227.

72. Bai Y., Sartor M. & Cavalcoli J. (2012). – Current status and future perspectives for sequencing livestock genomes. *J. Anim. Sci. Biotechnol.*, **3** (1), 8.

73. Metzker M.L. (2010). – Sequencing technologies: the next generation. *Nat. Rev. Genet.*, **11** (1), 31–46.

74. Branton D., Deamer D.W., Marziali A., Bayley H., Benner S.A., Butler T., Di Ventra M., Garaj S., Hibbs A., Huang X., Jovanovich S.B., Krstic P.S., Lindsay S., Ling X.S., Mastrangelo C.H., Meller A., Oliver J.S., Pershin Y.V., Ramsey J.M., Riehn R., Soni G.V., Tabard-Cossa V., Wanunu M., Wiggin M. & Schloss J.A. (2008). – The potential and challenges of nanopore sequencing. *Nat. Biotechnol.*, **26** (10), 1146–1153.

75. Lande R. & Thompson R. (1990). – Efficiency of marker-assisted selection in the improvement of quantitative traits. *Genetics*, **124** (3), 743–756.

76. Davis G.P. & DeNise S.K. (1998). – The impact of genetic markers on selection. *J. Anim. Sci.*, **76** (9), 2331–2339.

77. Dekkers J.C. (2004). – Commercial application of marker- and gene-assisted selection in livestock: strategies and lessons. *J. Anim. Sci.*, **82** (E-Suppl.), E313–E328.

78. Lecomte L., Duffe P., Buret M., Servin B., Hospital F. & Causse M. (2004). – Marker-assisted introgression of five QTLs controlling fruit quality traits into three tomato lines revealed interactions between QTLs and genetic backgrounds. *Theoret. Appl. Genet.*, **109** (3), 658–668.

79. Meuwissen T.H., Hayes B.J. & Goddard M.E. (2001). – Prediction of total genetic value using genome-wide dense marker maps. *Genetics*, **157** (4), 1819–1829.

80. Goddard M.E. & Hayes B.J. (2007). – Genomic selection. *J. Anim. Breed. Genet.*, **124** (6), 323–330.

81. Hayes B.J., Lewin H.A. & Goddard M.E. (2013). – The future of livestock breeding: genomic selection for efficiency, reduced emissions intensity, and adaptation. *Trends Genet.*, **29** (4), 206–214.

82. Goddard M.E. & Hayes B.J. (2009). – Mapping genes for complex traits in domestic animals and their use in breeding programmes. *Nat. Rev. Genet.*, **10** (6), 381–391.

83. Pryce J.E. & Daetwyler H.D. (2012). – Designing dairy cattle breeding schemes under genomic selection: a review of international research. *Anim. Prod. Sci.*, **52** (3), 107–114.

84. Duchemin S.I., Colombani C., Legarra A., Baloche G., Larroque H., Astruc J.M., Barillet F., Robert-Granie C. & Manfredi E. (2012). – Genomic selection in the French Lacaune dairy sheep breed. *J. Dairy Sci.*, **95** (5), 2723–2733.

85. VanRaden P.M., Van Tassell C.P., Wiggans G.R., Sonstegard T.S., Schnabel R.D., Taylor J.F. & Schenkel F.S. (2009). – Invited review: reliability of genomic predictions for North American Holstein bulls. *J. Dairy Sci.*, **92** (1), 16–24.

86. Hayes B.J., Bowman P.J., Chamberlain A.J. & Goddard M.E. (2009). – Invited review: genomic selection in dairy cattle – progress and challenges. *J. Dairy Sci.*, **92** (2), 433–443.