Journal homepage: http://www.sasas.co.za/journals

South African Journal of Animal Science 2018, 48 (No. 5)

Invited Paper: 50th SASAS Congress 2017

Genomics for the advancement of livestock production: A South African perspective

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(Received 11 December 2017; Accepted 3 July 2018; First published online 26 September 2018)

Abstract

Most of the growth of human populations worldwide will be in developing countries, including South Africa. Natural resources are under immense pressure and animal scientists are faced with the challenges for increased efficiency and long-term sustainability of livestock production. Since the completion of the Human Genome Project, animal genomes have been mapped with genomics, enabling new opportunities for application in farm animal species. The use of microsatellite markers has made significant contributions to the insight in genetic characterisation of indigenous and local developed breeds in most farm species in South Africa and Africa. The single nucleotide polymorphic (SNP) marker discovery and development of commercial SNP arrays made genomic selection possible and genomic enhanced breeding values (GEBVs) are used widely in the First World. In South Africa, genomic programmes for beef and dairy cattle were established in 2015 and 2016, with the focus on building training populations for genomic selection. The SA Bonsmara breed was the first to receive GEBV. The availability of hard-to-measure phenotypes is limited, and these are the traits that hold the most potential for genomic selection and answering to the challenges of methane (CH_4) emissions and higher efficiency. Genome editing, which involves zinc-finger nucleases (ZFNs), transcription-activators such as endonucleases (TALEN) and RNA-programmable genome editor (CRISPR/CAS9), includes the most recent technology for application in precision genetics. Welfare and ethical concerns will be an important consideration in the acceptability of genome editing to consumers. Applications that benefit the animals are more acceptable to the public. The use of genome editing to produce polled cattle is one of the first applications with a direct welfare impact as it nullifies the need for painful dehorning. In this paper, genomic technology is reviewed with the focus on the most recent research trends and commercial application of genomics towards the genetic improvement of livestock with specific reference to South Africa.

Keywords: Genetic diversity, genomic selection, gene editing, microsatellite markers, SNP
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Introduction

The expected growth of the world human population has been well documented, with a projected world population of approximately 9.6 billion people by 2050 (United Nations, 2012; Telegu *et al.*, 2017). Most of the growth is expected to take place in developing countries and on the African continent (Telegu *et al.*, 2017). A human population growth surge is also anticipated in South Africa, with an expected population size of approximately 70 million people by 2050 (Worldometers, 2017). Furthermore, global warming is likely to alter environmental conditions, with extreme changes expected for developing countries south of the equator (Scholtz *et al.*, 2013). Natural resources will come under pressure and livestock production will have to be performed with higher efficiency and long-term sustainability, using less land and water, and with greater awareness of global climate change and animal welfare (Thornton, 2010). To answer these challenges, technologies in the animal science domain, including genomic technologies, need to be investigated.

URL: http://www.sasas.co.za
ISSN 0375-1589 (print), ISSN 2221-4062 (online)
Publisher: South African Society for Animal Science
http://dx.doi.org/10.4314/sajas.v48i5.2

Almost three decades have passed since the first papers highlighting the potential of hypervariable regions in human DNA were published by Tautz (1989). During the first decade of molecular exploration, fundamental research demanded an understanding of DNA markers, the discovery of new markers and theoretical simulations to forecast their application. At the same time, molecular technologies had to be developed and the Human Genome Project (HGP) proved to be instrumental in the development of genome sequencing technologies and marker discoveries (Venter *et al.*, 2001). The HGP commenced in 1990 and was completed in 13 years, involving 14 research groups (Venter *et al.*, 2001).

The first markers to prove useful in livestock and poultry breeding were microsatellite markers. These multi-allelic markers proved their superiority compared with multi-locus markers, such as DNA fingerprinting (DFP), for application in population genetics studies, genetic characterization and genetic conservation of indigenous farm animal resources (Van Marle-Köster & Nel, 2003). Several studies using microsatellite markers were also performed in South African animal science research, including local chicken breeds (Van Marle-Köster *et al.*, 2008), Nguni cattle (Sanarana *et al.*, 2016), South African sheep breeds (Buduram, 2004) and commercial and indigenous goats (Visser *et al.*, 2004; 2011; Pieters *et al.*, 2009).

In the early 2000s, microsatellite markers were applied to search for genome fragments in which quantitative trait loci (QTL) affecting performance of traits of economic importance were located (Blasco & Toro, 2014). Owing to the relatively small number of markers available at that time, only a small fraction of the trait variance could be explained, limiting the application of QTL detection (Blasco & Toro, 2014). Despite several microsatellite-based QTL studies in a wide range of species, including SA Angora goats (Visser *et al.*, 2011; 2013), the wider application in marker assisted selection (MAS) remained limited (Hill, 2014). In 2001, Meuwissen *et al.* (2001) published a visionary paper demonstrating the need for a large number of evenly spread markers to predict the genetic merit of animals. This formed the foundation for the current principles of genomic selection. The mapping of various farm animal genomes paved the way for SNP discovery that answered the requirements set by Meuwissen and colleagues. These efforts resulted in the development of high-throughput technology and of methodologies and tools for genetic improvement and advancement of livestock production on a commercial level. In this paper, genomic technology is reviewed with the focus on the most recent research trends and commercial application of genomics towards the genetic improvement of livestock with specific reference to South Africa.

Genomic research in farm animals

Whole genome sequencing has made a major contribution to the generation of genomic data (Druet, *et al.*, 2014). The chicken genome was the first farm animal to be sequenced in 2004 (Groenen *et al.*, 2009), followed by the sheep, cattle, pig and goat genomes in 2007, 2009 and 2013, respectively (Fan *et al.*, 2010). Since the completion of the genome maps of most of the farm animals, DNA markers and genomic studies have domated genetic research in farm animals that covers a wide range of topics. Initially, molecular research was directed to identifying major genes with beneficial effects as well as genes associated with genetic defects (Montaldo & Meza-Herrera, 1998; Dekkers & Hospital, 2002; Dekkers, 2004; Cohen-Zinder *et al.*, 2005). Diagnostic tests were developed for genetic defects such as bovine leucocyte adhesion deficiency syndrome (Danishuddin *et al.*, 2013), deficiency of uridine-monophosphate synthase (Kaya *et al.*, 2016), complex vertebral malformation (Noordhuizen *et al.*, 2013) and Curly calf syndrome (Whitlock, 2010) which makes early detection possible and enables breeders to make informed selection decisions.

One of the most important contributions of DNA marker technology was the development of parentage verification panels. Incorrect or incomplete parentage recording has a negative effect on the accuracy of estimated breeding value (EBV) and selection progress. Several studies confirmed the importance of accurate parentage for EBV estimation and demonstrated significant re-rankings (Visser *et al.*, 2011; Kios *et al.*, 2012; Garritsen *et al.*, 2015) using DNA-based verification. Incorrect parentage results in a decrease in selection accuracy and a significant loss in rate of genetic improvement (Van Eenennaam *et al.*, 2014).

The availability of DNA markers such as microsatellites provided the opportunity to perform population studies and contributed to knowledge of genetic diversity of farm animals, especially indigenous genetic resources (Hassen *et al.*, 2009; Qwabe *et al.*, 2012; Greyvenstein *et al.*, 2016; Makina *et al.*, 2016; Mdladla *et al.*, 2016). In 1998 the Food and Agricultural Organisation (FAO) documented guidelines for conservation of farm animal genetic resources and listed the recommended microsatellite marker panels from the International Society for Animal Genetics (ISAG) for the evaluation of genetic diversity in farm animal species (FAO, 1998). Currently, microsatellite markers and genetic diversity studies may seem trivial compared with the power of SNP markers and high-throughput genotyping, but these studies made significant contributions to scientific knowledge and created awareness of the potential of indigenous breeds. Indigenous breeds represent a large portion of the total livestock populations in many countries and their contribution to food security cannot be ignored (Mwai *et al.*, 2015; Nyamushamba *et al.*, 2016).

Tables 1 and 2 provide a summary of the research published over the past two decades in which DNA marker technology was used in various studies on indigenous resources in South Africa and other African countries.This is not an exhaustive list, but it demonstrates the diversity of these genetic resources and potential for sustainable production.

Table 1 Summary of research using DNA marker technology in indigenous livestock and poultry in South Africa

Species	Main focus	DNA Marker	Breed(s)	Reference
Cattle	Genetic diversity	Microsat.	Nguni	Sanarana *et al.* (2016)
			Afrikaner	Pienaar (2014)
		SNP	Afrikaner, Drakensberg, Nguni	Makina *et al.* (2014); Makina *et al.* (2016); Zwane *et al.* (2016)
	Evaluation of the BovineSNP50	SNP	Nguni	Qwabe *et al.* (2013)
	Detection of selection signatures	SNP	Afrikaner, Drakensberg, Nguni	Makina *et al.* (2015a)
	LD and effective population size	SNP	Afrikaner, Drakensberg, Nguni	Makina *et al.* (2015b)
	Parentage verification	Microsat.	Boran	Kios *et al.* (2012)
Goat	Genetic diversity	Microsat.	SA Boer goat, Savanna, Kalahari Red	Visser *et al.* (2004) Pieters *et al.* (2009)
		SNP	Boer goat	Huson *et al.* (2014)
		SNP	Boer goat, Savanna, Kalahari Red & Tankwa	Mdladla *et al.* (2016)
Sheep	Genetic diversity	Microsat.	Namaqua Afrikaners	Qwabe *et al.* (2012)
		SNP	Namaqua Afrikaners	Sandenbergh *et al. (*2016); Molotsi *et al.* (2017)
	Identify genomic regions	SNP	Damara	Greyvenstein *et al.* (2016)
Pig	Frequency of MH gene	SNP	Kolbroek	Soma *et al.* (2014)
Chicken	Genetic diversity	Microsat.	Naked-neck, Ovambo, Koekoek & Venda	Van Marle-Köster & Nel (2000); Van Marle-Köster *et al.* (2008)

The establishment and availability of molecular tools such as radiation hybrid maps, reference genome sequences and subsequent high-throughput systems and genotyping platforms accelerated research and made commercialization possible. Developments of commercial SNP arrays provided opportunities to improve on the limitations faced by traditional and quantitative studies to accelerate genetic progress. High-density SNP panels have been shown to be very useful for analyses of genetic diversity and population structure for a range of livestock species (e.g. Bovine HapMap Consortium, 2009; Kijas *et al.*, 2009; 2013). Currently a wide range of commercial SNP beadchips is available for the various livestock species, as shown in Table 3.

More recently, research has been performed by applying SNP markers to population genetics. Genetic diversity, inbreeding and effective population size estimates have been reported in South African farm animals, including cattle (Makina *et al.*, 2014; Makina *et al.*, 2015b), goats (Lashmar *et al.*, 2015; Mdladla *et al.*, 2016; Visser *et al.*, 2016) and sheep (Sandenbergh *et al.*, 2016; Molotsi *et al.*, 2017).

Table 2 Summary of research using DNA marker technology in indigenous livestock and poultry in Africa

Species	Main Focus	DNA marker	Breed(s)	Reference
Cattle	Genetic diversity	Microsats	Angone, Landim & Bovino de Tete	Bessa *et al.* (2009)
			Red Bororo, White Fulani, Banyo Gudali, Ngaoundere Gudali, Sokoto Gudali, Adamwa Gudali, Wadara, Namchi, Muturu & N`Dama	Ibeagha-Awemu *et al.* (2004)
			Arab Shuwa, Ngaoundere Gudali, Namchi & White Fulani	Ema *et al.* (2014)
			Malawi Zebu	Changadeya *et al.* (2012)
		RAPD	Angoni, Barotse, Tonga & Baila	Zulu (2008)
	SNP identification	SNP	Afikaner & Tuli	Barris *et al.* (2012)
Sheep	Genetic diversity	Microsats	Balami, Uda, Yankasa & West Afican Dwarf	Agaviezor *et al.* (2012); Agaviezor *et al.* (2013)
			Hamra, Ouled-Djellal, Béni-Ingil, D`men, Corse, Lacaune & Foro-Foro	Gaouar *et al.* (2014)
			Djallonke	Wafula *et al.* (2005)
		RAPD	Barbarine, Queue Fine & D'man	Khaldi *et al.* (2010)
Goat	Genetic diversity	Microsats	West African Dwarf & Maradi	Adebambo *et al.* (2011)
			Tswana Goat	Maletsanake *et al.* (2013)
			Ovambo-, Kavango-, Kunene- & Caprivi- ecotypes	Els *et al.* (2004)
			Maasai, Kigezi, Mubende, North West Highland, Arsi-Bale, Ndebele, Pafuri, West African Dwarf, Maure, Djallonke	Chenyambuga *et al.* (2004)
			Pafuri, Tete, Maputo, Cabo Delgado	Garrine (2007)
		SNP	Boer Goat	Huson *et al.* (2014)
Chicken	Genetic diversity	SNP	Tilili, Gelilia, Debre-Elias, Melo-Hamusit & Gassay/Fatra	Hassen *et al.* (2009)

Application of Genomic Selection

Since the first studies were published by Schaeffer (2006) on the potential use of genomic information in dairy cattle, genomic selection (GS) has been well established and routinely used in the dairy industry in most first-world countries (Bouquet & Juga, 2013; Boichard *et al.*, 2015). The dairy industry had the advantage of having access to DNA repositories owing to the wide use of artificial insemination, which accelerated the building of training populations (Wiggans *et al.*, 2009). In most European countries and North America, genomics are included in routine genetic evaluations of dairy cattle, with international AI bulls being marketed with GEBV (Silva *et al.*, 2014). A number of beef cattle breeds has also invested in genomics with large numbers genotyped in North and South American countries as well as in the UK and on the European continent (Berry *et al.*, 2016). The need for establishment of training populations in each country for specific breeds have been demonstrated by Saatchi *et al.* (2013) to perform national and international evaluations in Hereford cattle from North and South American countries. Minimum population sizes for training populations have been reported, but generally approach at least 1000 animals in livestock (Blasco & Toro, 2014) with recent studies indicating the benefits of even larger populations. The decrease in the cost of genotyping and the availability of lower density chips have resulted in a preference for larger training populations and continuous updating of these populations to ensure high accuracies (Berry *et al.*, 2016). The creation of these breed-specific training populations remains one of the largest stumbling blocks in the implementation of genomic selection in developing countries.

In South Africa, genomics for beef and dairy cattle was initiated only in 2015 and 2016, respectively, as state-funded programmes over a ten-year period (Livestock Genomics (online)). The main aim of these programmes is the establishment of training populations for the participating beef (13) and dairy (3) breeds.

Table 3 Summary of available Single Nucleotide Polymorphism (SNP) arrays for livestock species

Platform	Species	SNP chips	Size
Affymetrix®	Cattle	Axiom® Genome--wide BOS1	648 875
	Pigs	Axiom® Porcine genotyping array	658 692
Geneseek®	Cattle	GGP-LD version3	26151
	Cattle	GGP HD	76 879
	Cattle	GGP150K	139 480
	Pigs	GGP Porcine LD	10 000 - 34 000
	Pigs	GGP Porcine HD	70 000
Ilumina®	Cattle	Bovine LD	7931
	Cattle	Bovine SNP 150	54 609
	Cattle	Bovine HD	777 962
	Goat	Goat SNP 50	53 347
	Pigs	Porcine SNP 60	64 232
	Sheep	Ovine SNP 50	54 241
	Sheep	Ovine HD array	600 000
	Sheep	Ovine LD beadchip	15 000
Igenity®	Dairy cattle	Igenity Elite, Igenity Prime, Igenity Select, Igenity Essential, Igenity Basic	5 000 - 140 000
	Beef cattle	Igenity Gold, Igenity Angus Gold, Igenity Silver, Igenity Angus Silver, Igenity beef dashboard, Seek sire	50 000 - 200 000

Since 2015, more than 3500 genotypes have been generated for the beef cattle breeds and close to 1000 for dairy cattle. The first GEBVs, which were estimated using the single-step model MIX 99 (Lidauer *et al.*, 2015), have been published for the SA Bonsmara (Van der Westhuizen *et al.*, 2017) indicating an improvement in prediction accuracy of 36% for a trait such as inter-calving period. The Bonsmara and Beefmaster have training populations of approximately 2200 and 800 animals, respectively, with genotypes and phenotypes of traits of economic importance. Preliminary reports indicated that accuracies for genotyped animals have improved on average between 15% and 30% (depending on the trait), in which traditional EBV accuracies for the trait were lower than 50%. The highest impact on accuracy values was seen on traits with low heritabilities and hard-to-measure phenotypes, such as maternal traits and feed conversion ratio.

The validation of genotype imputation as a method of inferring high density *in silico* genotypic data to allow genomics-based breed improvement of the SA Drakensberger is currently under way. Genotype imputation is a statistical method that involves the prediction and simulation of missing marker genotypes from observed or non-missing genotypes through model-based approaches (Marchini *et al.*, 2007). This is based on the assumption that a reference population and test population of the same breed, if they are related in some way, should have the same underlying LD pattern (Pei *et al.*, 2008). The shared haplotype structure between the reference and test populations can therefore be used to infer missing haplotypes in the test population from the haplotype structure of the reference population. If high-density genotypes can be reliably imputed from low density SNP arrays with sufficient accuracy, this will allow the opportunity to genotype more animals with more affordable low-density arrays (García-Ruiz *et al.*, 2015). This method would enable South African researchers to have access to genetic marker information of sufficient density, which would allow applications such as genome-wide association studies (GWAS) and GS in indigenous cattle breeds.

A number of factors influence the uptake of new technologies and the adoption phase differs among industries. Van Eenennaam *et al.* (2014) referred to the wide range of breeds and the limited use of artificial insemination (AI) as some of the most important factors that have resulted in the slow uptake of genomic selection in the USA beef industry, as opposed to the dairy cattle industry. The relative value of a beef cattle bull that will be used in natural mating systems is significantly less than that of a dairy cattle seed stock bull that can produce thousands of offspring. This same situation is valid in South Africa. The relative value of small stock is even less, and a large number of numerically small sheep and goat breeds are found in Africa.

No national South African strategy for the implementation of GS in small stock has yet been developed, and the uptake of the technology by breeders is expected to be limited. On the other hand, vertically integrated industries with well-defined breeding goals, such as the poultry and pig industries, have realised maximum genetic progress, but are facing challenges such as already short generation intervals and a multitude of breeds or lines (Van Eenennaam *et al.*, 2014).

The need for continuous phenotyping is another challenge for effective use of genomic selection. The largest benefit of genomic selection is expected to be in difficult-to-measure phenotypes, sex-limited traits and traits with low heritability (Blasco & Toro, 2014). Traits such as feed efficiency, disease resistance and methane emissions are highlighted as those in which phenotypes are required for genomic selection in both beef and dairy cattle (Van Eenennaam *et al.*, 2014). Gonzales-Reico *et al*. (2014) also emphasized the value of phenotypes for effective use of genomics in dairy cattle populations. Often product quality traits such as milk fatty acid composition in dairy cattle and meat quality traits in beef cattle are not recorded owing to costs and difficulties in measuring, and these contribute little to the overall selection objective of the industries. Adoption of technology will depend on the benefit to the producer weighed against the investment. Scientists have a huge challenge in communicating genomics to the breeder/farmer and the consumer as the end-user of the product.

Future genomics

Genomic selection has been accepted globally as a new technology with a range of benefits for animal breeding and selection, but genetic engineering and gene editing of livestock remain controversial topics. Although selective breeding and even genomic selection of animals modify the genomes of animals, they are not capable of manipulating, isolating or transferring specific traits or alleles of interest (Telugu *et al.*, 2017). However, advances in the field of genome editing and genetic engineering have opened new possibilities for livestock production.

Genome editing is a precise way of introducing sequence changes by cutting DNA (Plastow, 2016), using molecular scissors. These scissors include zinc-finger nucleases (ZFNs), transcription-activator-like endonucleases (TALEN) and the most recent highly effective RNA-programmable genome editor (CRISPR/CAS9). They are all capable of precise sequence deletions, replacements and insertions by gene and SNP targeting (Petersen & Niemann, 2015). However, CRISPR has the added advantage of being simple to generate, easy to handle, efficient and cost-effective (Petersen, 2017).

Genome editing in the agricultural industry was first introduced in the early 1990s in commercial crop species (oilseed rape, soya and maize) and has been accepted with relatively little consumer resistance (Bruce, 2017). The traits that were targeted were mostly herbicide tolerance and insect resistance. On the other hand, consumer perceptions of the editing and modification of large mammal genomes are generally more negative. No genetically modified (GM) food animals are yet available for human consumption. Salmon that was modified for faster growth, however, was approved by the United States Food and Drug Administration (FDA) in 2015, paving the way for marketing of GM food animal products (Bruce, 2017).

Welfare and ethical concerns for animals play an important role in the acceptability of genome editing to consumers. Applications that benefit the animal are much more acceptable to consumers than those with production advantages. The use of genome editing to produce polled cattle is one of the first applications that will have a direct welfare impact as it nullifies the need for painful dehorning. The polled allele was recently successfully introduced into dairy cows (Carlson *et al.*, 2016). Increased disease resistance is also perceived as a welfare benefit to animals. In this regard, pigs have been on the forefront of research, with genome-edited animals resistant to African Swine Fever and Porcine Reproductive and Respiratory Syndrome (PRRS) (Bruce, 2017; Petersen, 2017). The *NRAMP1* gene has been introduced into the bovine genome, providing cattle with increased resistance to bovine tuberculosis (Petersen, 2017).

More consumer resistance is expected if genome editing should be used purely for increased production, such as double-muscled livestock, which are produced by the genetic knockout of the myostatin (*MSTN*) gene (Petersen, 2017). Muscular animals, however, often suffer from calving difficulties and increased mortalities, with a clear negative effect on animal welfare (Bruce, 2017). Modified animal products with an improved impact on human health might be more acceptable. Milk composition has been altered by knocking out the bovine whey protein β-lactoglobulin, which is a major allergen, in both cattle and goats (Petersen, 2017). In the same vein, gene coding for the two dominant allergenic components in egg white, namely ovalbumin and ovomucoid, was knocked out (Oishi *et al.*, 2016).

While these applications are still under scrutiny, the livestock industry is facing new challenges, and should consider novel solutions. To be able to tackle issues such as the growing world population, pressure to increase production while considering animal welfare and the risk of global pandemics affecting animals (Telugu *et al.*, 2017) innovative thinking and embracing new technologies will become paramount.

Conclusion

Genomic technology has been well established in first-world countries. In South Africa genomics should be seen as a tool not only for genomic selection but for gaining insights into the adaptive mechanisms, disease tolerance and unique traits in indigenous livestock resources. The livestock production landscape in South Africa for implementation of genomic technology is fragmented and producers must explore ways to ensure optimal use on different levels of production in order to contribute to sustainable production. Research and industry will have to make a concerted effort to ensure that the benefits of genomic technology is demonstrated and implemented for advancement of sustainable livestock production.

Authors' Contributions

The manuscript was drafted, written and edited by both authors (EVMK and CV).

Conflict of Interest Declaration

The authors declare that there are no conflicts of interest.

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