Recent Patents on DNA & Gene Sequences **2008,** *2,* **000-000**

Animal Markers Assisted Selection in South America: a Point of View

Andrés Rogberg-Muñoz[1,3], Alberto Prando[2], Andrés Baldo[2], Pilar Peral-García[1] and Guillermo Giovambattista[1,3,*]

[1]CIGEBA, Facultad de Ciencias Veterinarias, Universidad Nacional de La Plata (UNLP), Calle 60 y 118 S/N, CC 296, B1900AVW La Plata, Argentina. [2]Zootecnia II (Bovinos y Equinos), Facultad de Ciencias Veterinarias, UNLP, Calle 60 y 118 S/N, CC 296, [3]B1900AVW La Plata, Argentina. Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICET), Avda. Rivadavia 1917, C1033AAJ Ciudad de Buenos Aires, Argentina

Received: December 13, 2007; Accepted: December 26, 2007; Revised: January 15, 2008

Abstract: Genetic identification has been continuously evolving during the last century. The recent development of whole-genome projects allowed the discovery and characterization of a large number of single nucleotide polymorphisms (SNP). A number of high-throughput DNA methods has decreased the cost of DNA marker analysis and increased the amount of samples that can be processed at a time. Using this information and methods, many private and governmental laboratories offer a wide range of genetic tests, many of which have been patented. In the field of genetic resources a significant amount of law-making has been developed at the international and regional levels. Many South American countries currently lack jurisprudence in relation to the protection of DNA sequences. In this paper, we compared laws related with life-form patents in some countries from South America. Nowadays, the knowledge and technology leveling many of these countries allows marker assisted selection (MAS) programs to be applied. Herein, we resume the economical value of MAS. Finally, we present a point of view on the pertinence, viability and conditions for developing and applying MAS programs in South America.

Keywords: Genetic markers, DNA test, animal genetic resources, gene patent, marker-assisted selection, genetic identification, genetic disease diagnosis.

INTRODUCTION

Genetic identification is a dynamic research area and has been continuously evolving during the last century. In 1923, Sax [1] was the first to propose that “the effects of individual genes affecting quantitative traits could be statistically isolated via linkage to genetic markers”. Almost 40 years later, Neimann-Sørensen and Robertson [2] applied this design to cattle using blood group polymorphisms as genetic markers. Blood group methods were followed by the analyses of serum and Major Histocompatibility Complex proteins, which had their apogee in the 1970s and 80s. During this period, association studies and QTLs (Quantitative Trait Loci) mapping was limited by the reduced number of isoenzyme and blood group loci that had been characterized. During the 1980s DNA-based methods were developed. RFLP (Restriction Fragment Length Polymorphism) was one of the first techniques to be used for genetic mapping, but this method was too laborious and time consuming. With the generalized use of PCR in the 1990s other techniques were rapidly developed (e.g., RAPD, AFLP, SSCP, ASO, microsatellites). The demonstration of Mendelian inheritance of microsatellite favored the replacement of RFLPs by microsatellites markers for building genetic maps, qualitative and quantitative traits loci detection, and genetic identification in human and other animal species [3-5].

The development of Single Nucleotide Polymorphisms (SNP) was principally made through direct sequencing of a defined DNA region; for example, a region containing candidate genes. This approach was, however, limited to regions for which sequence data was available [6]. This made research very expensive, but important efforts where made to validate the association of few genes. In 2000, the first commercial DNA test for cattle QTL appeared in the market [7] but it took several years for their commercial success, because analyses cost-effective only for selected animals of top commercial value. Furthermore, the first diagnostic test developed used manual typing techniques, such as PCR-RFLP, which limited the amount of samples that could be processed at a given time.

Recently, a number of high throughput SNP genotyping platforms have been developed (Automatic Sequencing, DHPLC, Taqman®, MALDI-TOF MS, Pyrosequencing™, Microarray). These platforms have made genotyping tests massively available because a large amount of samples can be processed quickly and cost effectively [6]. This was the initial step for a successful commercial implementation of Marker Assisted Selection (MAS) programs.

Public access to farm animal genomes started in March 2004 when the first draft of the chicken genome was published [8]. After the bovine genome sequence was deposited in a free public database in October 2004 [9]; the pig whole-genome sequencing began in 2005 and it has been published with <1X coverage [10]; a sheep genetic linkage map has been produced around several regions of interest to individual laboratories, and the sheep complete genome sequence will be finished soon [11]. In addition, there are public databases on many domestic species that include data on PCR primers, and genetic and cytogenetic linkage maps [12]. These databases help researchers to easily identify and

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*Address correspondence to this author at CIGEBA, Facultad de Ciencias Veterinarias, UNLP, Calle 60 y 118 S/N, CC 296, B1900AVW La Plata, Argentina; Tel/Fax #: +54 221 4211799; E-mail: ggiovam@fcv.unlp.edu.ar

1872-2156/08 $100.00+.00

position candidate genes, develop new markers, and perform linkage studies.

The rapid development of multiple DNA markers and the availability of public databases of whole genomes allowed the implementation of MAS programs. DNA markers commonly used in MAS programs include: (1) mutations that are causal of the final phenotype referred to as direct markers; (2) loci in linkage disequilibrium with a functional mutation; (3) loci in linkage equilibrium with a functional mutation of interest, in this case, the equilibrium/ disequilibrium of two markers depends on the population studied. Depending on which kind of marker is used in a MAS program we can also differentiate gene-assisted selection (GAS), linkage disequilibrium MAS (LD–MAS) and linkage equilibrium MAS (LE–MAS) [13]. As an example, we can mention two dairy cattle MAS programs in the German and French Holstein populations [14, 15]. Both programs select young sires using DNA markers for regions in which QTL for economically important traits have been detected. For example, in the French program 12 chromosomal (BTA) segments with putative QTL are analyzed for three major traits: milk production or composition on BTA 3, 6, 7, 14, 19, 20, and 26; mastitis resistance with QTL on BTA 10, 15, and 21; and female fertility with QTL on BTA 1, 7, and 21 [16]. The DNA pre-selected sires are after progeny tested.

South America, the current situation on MAS programs is quite different. In 2006, Argentina, Brazil and Uruguay exported about 40% of the world beef and cattle commercialized [17], and produced 9% of the world's milk [18]. In 2005, Brazil was the fist world exporter of beef and poultry, and the fourth of pork [19]. In spite of the economic importance of animal resources in these countries, there is little investigation on animal genetic markers, and only few producers are applying imported technology, especially due to the high cost of these techniques.

The goal of this review is to present a point of view on the pertinence, viability and conditions for applying MAS programs in South America. We illustrate some of the application, legal and economic aspects related to MAS programs, and their potential benefits for animal production systems in South America.

GENETIC MARKERS IN USE

There are many fields in which DNA markers have been applied successfully. In this paper we will focus on genetic identification, genetic disease detection, and production trait polymorphisms identification. Currently, many private and governmental laboratories offer a wide range of genetic tests, many of which have been patented. We can mention, for example, tests developed by the University of California Davis (www.vgl.ucdavis.edu/service/), Universidad Complutense de Madrid (www.ucm.es/info/genetvet/), Igenity (www.igenity.com), Catapult Genetics (www.geneticsolutions.com.au), and Van Haeringen Laboratorium (www.vhlgenetics.com).

Table **1** outlines the most common genetic tests available for marker assisted selection, which were grouped in the following four categories representing:

Genetic Identification. Genetic identification is one the earliest used genetic markers. Genetic identification was originally developed for allozyme markers and blood groups, but nowadays microsatellites are the most commonly used markers. SNP are becoming highly used and will probably be the marker of choice in the future. The first application of these markers was paternity assignment for Herd Books, but then there have been many different uses such as Identification of Superior Sires in Multi-Sire Breeding Scenarios, resolution of forensic and criminal cases, anti-dopping evaluation, breed assignment, traceability of animals and meat, breed purity (percentage of admix), and inbreeding. Nowadays, more than fifty laboratories participate in the International Society for Animal Genetics (ISAG) Comparison Test for Domestic Animals Identification (www.isag.org.uk).

Genetic diseases. Some genetic diseases are monogenic and, in many cases, the gene responsible for the disease has been detected. Genetic markers can help detecting animals that carry the mutation in early stages so they can be excluded as sires or dams. Sometimes resistance/ susceptibility to some diseases has a genetic origin or component; thus, MAS can be used to improve the maintenance of beneficial variants in the population.

Mendelian Inherited Traits (Qualitative). Most "non-productive" traits genetically inherited can be described by Mendel's laws. Sometimes these traits are very important and may be economically profitable. Coat color and horn/ polled traits are good examples of these qualitative markers.

Production traits (Quantitative). Most traits associated with animal production represent continuous variables that result form the interactions of multiple genes to produce the final phenotype. These traits/genes represent one of the major challenges for MAS programs. In these traits, a major effect can only be seen through the additive effects of many genetic variants.

LEGAL FRAMEWORK

The USA court case Diamond vs. Chakrabarty (1980) represented the first legal precedent for supporting patent protection of genetically modified life forms. The question was whether one particular genetically engineered bacterium could be patented or not, and the Court verdict emphasized that "anything under the sun that is made by man" may be patentable [20].

The Agreement on Trade Related aspects of Intellectual Property Rights (TRIPS) was established in 1994 when the World Trade Organization (WTO, www.wto.org) was founded. The TRIPS does not create a single, universal patent system, but allowed to harmonize, strengthen and expand the scope for patent protection for each of the signing countries in the domestic patent legislation [21]. The TRIPS Agreement allowed member Countries to exempt patent protection of animals other than micro-organisms; and for essentially biological processes (TRIPS Agreement 27, paragraph 3). The World Intellectual Property Organization (WIPO) is an additional important forum under the TRIPS program. With 180 member states, WIPO provided a forum to negotiate standardization of patent criteria in the members' domestic legislation [22]. Finally, the Substantive

Table 1. DNA Tests Commercial Available, which can be Used for MAS Programs

CATEGORY	ANIMAL SPECIES	TESTS AVAILABLE
Genetic Identification	Deer, Equine (horse), Feline (cat), Canine (dog), Caprine (goat), Poultry, Bison (buffalo), Bovine (cattle), Ovine (sheep), Porcine (pig),	Traceability of animals and meat, parentage and sire identification, identification of superior sires in multi-sire breeding scenarios, solve forensic cases, stilling cases, doping cases, breed assignment, breed purity, inbreeding
	Catfish, Chimpanzee, Camelids (llamas, alpacas), Elk, Zebrafish, Antílope, Bear, Wild Rabbit, Birds (most), Mountain Lion, Salmon, Trout	Parentage, breed assignment
Genetic diseases	Cattle	CVM, BLAD, DUMPS, Lrp4 (Mulefoot)
	Pig	RYR (Pork Stress Sindrom), F18 (resistant to the F18 E. coli strain that causes post weaning edema)
	Sheep	Spider lamb syndrome, PRP, resistance to Scrapie
	Poultry	B blood
	Horse	**HYPP, SCID**
	Dog	CLAD, CSNB, MDR1 gene, PARA, PFK
	Cat	PKD
Mendelian Inheritage Traits (Qualitative)	Cattle	MC1R, MGF, MGH (coat color), Polled/Horned
	Pig	c-Kit, MC1R (coat color)
	Horse	MC1R (coat color)
	Dog	MC1R (coat color)
	Cat	MC1R (coat color)
	Bird	Sex determination
Production traits (Quantitative)	Beef	Lep (multiple trait), Calp (Tendernes), Cast (tendernes, growth), Myo (double muscling), Thyr (marbling)
	Dairy	PIT-1, B-Lac, Prol, Caseins, DGAT1, GRH, (Milk yeald and composition), FMO3 (Fishy Off-Flavour)
	Pig	Calp (Tendernes, Growth), RYR1 (meat quality), RN (Drip loss, meat quality), FABP (Fat deposition), MC4R (Feed Intake), IGF-2 (Growth) PRLR (Reproduction), ESR (Reproduction)
	Sheep	Boorola (Reproduction), Inverdale (Reproduction), Cpg (Fat deposition, meat quality), Carwell (rib-eye area)

Patent Law Treaty (SPLT), which, aims to achieve international harmonization on patent applications, core terms, and patent criteria.

Globalization has made food production and trade to increase internationally. As a result, regional and global agreements associated with patent protection and property rights on animal products began to be relevant. In the field of genetic resources a substantial amount of law-making goes on at the international and regional levels [20]. In the WIPO negotiations on the SPLT, the north-south conflict seems very apparent. Even countries with rapid technological development, such as India and Brazil, strongly oppose the aims of the SPLT, whereas industrialized countries are generally in favor. This apparent conflict is generally resolved through bilateral agreements between the parties involved in the trade; i.e., the users and providers of the resources [21].

According to the Food and Agriculture Organization of the United Nations (FAO) definition (www.fao.org), four types of intellectual property rights are relevant in the field of Animal Genetic Resources (AnGR). These include: "geographical indications, trademarks, trade secrets and patents" [23]. One essential difference between patenting industrial inventions and inventions based on modifications of biological material is that the former are wholly made by man, whereas the biological material already exist in nature, at least in a slightly different form. This implies that a product patent relates to something already existing in nature. As a solution, several countries have allowed 'purified' and 'isolated' DNA sequences to be patented as long as a credible use is disclosed [24]. In animals, this creates a potential conflict in terms of prior art and scope of protection, specifically because AnGR are usually under private or communal ownership. Therefore, there is a latent conflict between the owner of the individual animals under consideration (and their genes) and the subsequent patentee [20].

During the last few years, a massive number of DNA sequences with SNP have been reported. As a consequence, the number of patent applications has increased, dramatically; e.g., just in the year 2000 over 355,000 sequences were published as patents [24]. Databases reveal that patent applications claiming SNPs and haplotypes increased 12 times per year from 2000 to 2004. The majority of these patents have been filed by USA research groups, with 4% of these sequences corresponding to pig sequences and 2% to other farm animals [25].

Most commodity producers are located in developing countries. Many countries in South America are good examples of producers/exporters of meat and crops as well as importers of biotechnology. Although Brazil has an important technological development, much of its biotechnology "know-how" is imported. The legal situation in these countries regarding the patenting of plant products is fairly current. However, this seems not to be the case for animal products. Experts however agreed [26] that there is a current lack of jurisprudence for the protection of Expressed Sequence Tags (ESTs), SNPs, and whole Genomes. In Table **2**, we compare the laws associated with life-form patents in some of the major agriculture producer countries of South America.

As it has already done with Plant Genetic resources, South American countries should determine if the upcoming biotechnology related to AnGR has something to offer. Only then, one can develop a rational and effective Intellectual Property Rights (IPR) system on the bases of the economic and social conditions of each country.. In this sense, we agree with Dutfield [24] who argued that "Developed countries should refrain from imposing their interpretation of Art. 27.3(b) based on their own jurisprudence or economic interests".

ECONOMIC SITUATION

Most traits that have an economic impact on animal production (economically important traits), like animal growth, milk production, fat percentage of meat or milk, represent continuous variable traits. These traits are controlled and determined by a large number of genes (polygenic inheritance) and the interaction between genes and the environment. Traditional selection strategies measure both parental and progeny performance. Molecular genetic markers allowed the genotyping of genes contributing to the variation of the trait. However, since markers focus mainly on few genes, these can only explain part of the final phenotype. The absence of markers for other genes involved in the production of the trait and the environmental influence

Table 2. Patent law in South America: Laws Related with the Patenting of Life Forms from Five Major Exporters of Animal Product Commodities in South America. The Internet Links are in their Official National Language (Spanish or Portuguese)

Country	Web	Law Nº	Year	Comment
Argentina	www.inpi.gov.ar/templates/patentes_leycompleta.asp	25.859 Art. 6, 7	2003	Any material preexisting in nature is not considered an invention. Biological and genetic material, as well as biological processes for reproduction, are not patentable
		20.247 and 24.376	1973 and 1994	It is possible to protect (but not patent) any vegetal genera or species.
Brazil	www.inpi.gov.br/	9.279 Art. 18	1996	The totality or partiality of a living organism cannot be patentable. Exceptions include transgenic microorganisms and sequences of DNA when considered as chemical products.
		9.456 Art. 4	1997	Any vegetal genera or species can be protected.
Chile	http://www.ftaa-alca.org/intprop/natleg/chile/L19039sB.asp	19.039 Art. 37	1991	Vegetal varieties or animal breeds are not considered inventions; thus, they are not patentable.
		N° 19.342	1996	Any plant species can be protected, but own produced seeds can only be used (but not commercialized) without interfering with owner right.
Paraguay	http://www.senado.gov.py/index.php?pagina=leyes-anho&prev=2000	1.630/00 Art. 5	2000	Vegetal varieties, animal breeds, and biological processes for animal or plant production are not considered inventions. Exceptions include microorganisms and non biological processes.
Uruguay	http://www.parlamento.gub.uy/leyes/AccesoTextoLey.asp?Ley=17164&Anchor=	17.164 Art. 13, 14	1999	Vegetal varieties, animal breeds, and biological processes for animal or plant production are not considered inventions. Exceptions include microorganisms and non biological processes.

make uncertain to establish if an animal will exactly transmit the desired phenotype following selection [27]. For this reason, MAS should be seen as a tool to assist with rather than a replacement for traditional selection techniques [9].

Implementation of MAS programs require careful consideration of sample collection and storage, genotyping, and data analysis [13]. The value of MAS depends on the specific trait to be selected and on a number of additional factors. For example, in traits with low heritability, MAS can increase the accuracy of breeding values. When the measurement of a trait of interest depends on the sex of the animal,, marker information allows ranking animals. Finally, marker information can be used when a trait is not measurable before the animal reaches sexual maturity, the animal is sacrificed, or the trait is difficult to be measured (e.g., most carcass and reproductive traits) [28].

Despite the kind of marker used, GAS, LD-MAS or LE-MAS can improve performance in farm animals, and accelerate cumulative and permanent genetic improvement of herds. GAS is the most practical and commercially viable system because provides assurance of the inheritance of the trait [9]. LD–MAS is generally influenced by the population used, because of the degree of chromosomal linkage [13]. Finally, LE markers are mostly useful for finding QTLs among breeds [29].

Most evaluations of MAS programs have considered short-time horizons. Comparing MAS with traditional selection strategies, some researchers have found that MAS have greater cumulative response in the short term but traditional selection achieved greater response in the longer term [30]. Other studies [31-35] considered selection on traits that are not measurable in both sexes or on live animals. These studies did not consistently found that longer term responses were less common with MAS than responses from traditional selection methods. However, these studies found that the advantage of MAS over traditional selection tended to decline in later generations and that MAS not necessary maximized responses to selection in the longer term, as well as in the short term [36].

MAS is more useful when combined with reproductive technologies such as artificial insemination (AI), embryo transfer, and in-vitro fertilization (IVF). Combined strategies demonstrated greater genetic gains, with up to 40%. It is obvious that more progeny per top parent allows earlier selection at reasonable accuracy, but also relies heavily on the use of family information, which at times may be lacking [28].

Even though genetic gain is important, most selection programs are aimed at obtaining high economic returns. Hayes and Goddard [37] performed an analysis of MAS economical profits in the breeding program of an integrated pig production enterprise. They concluded that the gain in the index was about 17% for the assumed parameters and MAS was economically viable if the cost per marker decreases to about U$S 0.5. They evaluated increased profit at the production level, which is proportional to extra genetic gain. However, most commercial breeding programs derive profit from increased stock and germplasm [38]. With the increase in the number of available markers and more accurate associations of markers with economically important traits, we can expand the potential application of genetic markers. Examples include Marker Assisted Management (MAM) programs that use markers for management decisions (i.e., feedlot feeding period), and Marker Assisted Marketing (MrktAM) programs, which promote commercialization of better-quality animal/genetics with markers information [39]. It is therefore important that economic analyses are conducted in relation to the specific business, marketing realities, and particular goals a production program.

Some authors think that the establishment of MAS systems in developing countries should be restricted to the public sector. They argue that, although in the short term there may be disadvantages due to limited public funding, the public sector is much more amenable to international collaboration and resource sharing [40]. This debate brings again take us to the north-south conflict, with developing countries producing genetic improvements by MAS programs that are used by developed countries through “international sharing and collaboration”. MAS technology could then be used as a negotiating factor in bilateral trade, as it had happened with property rights laws associated with animal and plant products..

CURRENT & FUTURE DEVELOPMENTS

Nowadays, robotics has considerably decreased the cost of each analysis. Many companies offering tests that contain a group of genes for a target trait rank animals depending on the number of “beneficial” alleles detected. Robotics has also facilitated massive high-throuput genotyping; thus, making the cost of each marker suitable for the implementation of MAS programs in commercial herds. Most marker associations with productive traits have been performed in USA, Europe or Australia, and, in most cases, based on a reduced number of breeds tested. As marker applicability depends on genetic background and environment (weather, production system, health system, etc.), South American countries should if those tools will be useful in their local productive systems. Several factors may prevent the applicability of genetic markers developed in other countries. Some of these factors may result from the fact that: (i) There are differences between the local breeds of each country. The Nelore is the most relevant example. (ii) Some populations within traditional breeds (e.g., native breeds) have great genetic distances with the predominant commercial lines. For example, the Angus breed illustrates this situation very well. (iii) Local production systems may differ from those where the marker was tested. For example, South American production systems are mostly pasture-based, while most markers were developed in feed-lot systems.

Several points should be considered in order to prioritize funding/efforts aimed at MAS programs. First, it should be noticed that only few DNA marker patents are currently commercialized, and that the two ongoing MAS programs have not yet incorporated any of these patents in their programs [16]. We believe therefore that it may be probably more useful to invest in research and development projects for our local production system, rather than relying only in available biotechnology designed for other domestic systems. Second, it is known that most economically important traits have been under high selection. However, selection of secondary traits with low heritability may also be economically valuable and suitable for MAS programs.

Based on the present review of MAS programs and their potential application on the legal and economic aspects of local animal production systems, we propose the the following guidelines for applying MAS programs in South America:

(I). Define a clear jurisprudence in the AnGR area and develop an system that protects the rights of each country to regulate their animal genetic resources.

(II). Increase investments in developing and testing new marker technologies in our production systems. As mentioned earlier, “imported” markers may not be useful, moreover, considering that the feed composition of animals raised on pastures is completely different from those raised in feedlots. For example, there is a possibility that the same animal in both systems can use different metabolic routes, so there could be different genes involved in the final phenotype of the desired trait.

(III). South American countries should promote international cooperation and regional alliances to share markers, MAS programs, implementation experiences, and human resources.

South American countries should establish a program for interactions/association among universities, governmental research institutes, and private companies. Only cooperation between the public sector and the private enterprise will facilitate economic and social growth of local societies.

ACKNOWLEDGMENTS

The present work was supported by grants from Universidad Nacional de La Plata (UNLP) and Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICET). The authors thank Dr. Juan L. Bouzat for suggestions and helpful comments about the manuscript.

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