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A short critical history of the application of genomics to animal breeding ☆

Agustin Blasco [a,*], Miguel Angel Toro [b]

[a] Institute of Animal Science and Technology, Universitat Politècnica de València, P.O. Box 22012, València 46071, Spain
[b] Departamento de Producción Animal, ETS Ingenieros Agrónomos, Ciudad Universitaria, 28040 Madrid, Spain

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ABSTRACT

Two scientific schools have been in coexistence from the beginning of genetics, one of them searching for factors of inheritance and the other one applying biometrical models to study the relationships between relatives. With the development of molecular genetics, the possibilities of detecting genes having a noticeable effect in traits augmented. Some genes with large or medium effects were localized in animals, although the most common result was to detect markers linked to these genes, allowing the possibility of assisting selection programs with markers. When a large amount of simple and inexpensive markers were available, the SNPs, new possibilities were opened since they did not need the presence of genes of large or medium effect controlling a trait, because the whole genome was scanned. Using a large amount of SNPs permits having a prediction of the breeding value at birth accurate enough to be used in some cases, like dairy cattle, to halve its generation interval. In other animal breeding programs, the implementation of genomic selection is less clear and the way in which it can be useful should be carefully studied. The need for large populations for associating phenotypic data and markers, plus the need for repeating the process continuously, complicates its application in some cases. The implementation of the information provided by the SNPs in current genetic programs has led to the development of complex statistical tools, joining the efforts of the two schools, factorial and biometrical, that nowadays work closely related.

1. The long and windy road to genomic selection

1.1. Genetics and animal breeding

From the beginning, there were two scientific traditions in genetics and in its applications to animal breeding. The first, which we can call molecular tradition, starts with Mendel and its aim is to locate and characterize from a biochemical point of view those factors that form the genetic program, hoping to someday manipulate it for our benefit. The second, whose origin can be traced to Galton, and which we can call statistical tradition, studies the manifestation of the genetic program in the quantitative traits through the correlations among relatives with the objective of inducing a genetic–economic change in the productive traits. These two traditions have not been kept as two separate scientific schools but they intermix or separate depending on their respective achievements. Moreover, some prominent animal breeder like Alan Robertson could represent both traditions.

The study of enzymatic polymorphisms through electrophoresis opened new ways, in the 1960s, to investigate the genetic variation of animal populations, which in the case of livestock disposal, until then, of blood groups and

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* Corresponding author. Tel.: +34 963877433.
E-mail addresses: ablasco@dca.upv.es (A. Blasco), miguel.toro@upm.es (M.A. Toro).

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mutants of color as the unique genes of known inheritance (Neimann-Sorensen and Robertson, 1961). The electrophoresis allowed studying of genes independently on whether they show phenotypic variability or not, and revealed an increasing genetic variability. However, only a handful of genetic variants were detected due to the limitations of the technique.

1.2. The QTL explosion and deception

The advent of the new techniques of DNA analysis marks the beginning of the new field of genomics: the scientific discipline of mapping, sequencing and analyzing genomic level of DNA information. Taking advantage of polymorphic markers called microsatellites, spread throughout the genome, researchers were able to build genetic maps of domestic species and to search for regions of the genome harboring genes affecting the performance for economically important traits.

In the 1990s the QTL detection experiment started. Methods to detect these loci were reviewed by Andersson (2001). Initially, two basic designs were used. The first uses the linkage disequilibrium between markers and QTL generated by crosses. Typically, animals are generated by crossing breeds that are highly divergent for the traits of interest (for example European wild boar and domestic Large White or junglefowl and domestic White Leghorn chicken). The second design uses mainly the within-family linkage disequilibrium. This design is especially well suited for commercial populations as dairy cattle where large half-sib families are available. This activity has been very successful. In the data base http://www.animalgenome.org/QTLdb/ the number of reported QTLs are 9862 affecting 653 traits (pigs), 8305 affecting 467 traits (cattle), 3919 for 297 traits (chicken) and 789 for 219 traits (sheep).

After detecting a QTL, the next task is to locate the gene responsible (causal mutation). In QTL detection studies, we can locate one QTL in a chromosome as a region of about 20–40 cM (probably harboring 200–400 genes) which made it difficult to identify the underlying gene responsible. To refine the position several actions can be taken: to increase the number of individuals, to carry out fine mapping or to try the 'candidate gene approach'. All these approaches are difficult, expensive in terms of time and money and success is not guaranteed, thereby making the location of the responsible gene a formidable task. Georges (2007) describes three successful stories: DGAT1 and ABCG2 that affect milk composition in cattle and IGF2 and MSTN influencing muscle mass in pigs and sheep, respectively. Notwithstanding, the difficulties for finding the causal mutations can be illustrated for example by more than 9000 QTLs reported in pigs, of which less than a dozen of causative mutations have been firmly established. Interestingly, the first QTL reported in livestock was FAT1 QTL located in swine chromosome 4 (Andersson et al., 1994); however, its causal mutation is still unknown.

1.3. Marker-assisted selection

One of the main motivations for QTL detection in domestic animals is Marker Assisted Selection (MAS). The usual way of thinking of MAS is a three-step process. First, detect one or several QTLs. Second, find the gene responsible (causal mutation). Third, increase the frequency of the favorable allele either by selection or by introgression. There are some examples as the halothane gene in pigs or the Booroola gene in sheep. This strategy should better be called Gene Assisted Selection. Another approach is to use markers that are in linkage disequilibrium or linkage equilibrium with QTLs. All these applications, from a commercial point of view, were reviewed by Dekkers (2004).

The theory underlying MAS was clarified to a great extent by Lande and Thompson (1990). If the phenotype and the true QTLs for a trait were known, the advantage of QTL-selection response with respect to phenotypic selection would be $1/h$, where h is the square root of the heritability. Thus for heritabilities of 0.10, 0.25 and 0.50 the advantage would be huge: 316%, 200% and 140%, respectively. If markers explain just p percent of the additive variance the advantage would simply be $\sqrt{p}/h$. They also developed selection indices that combine individual and family phenotypic information and molecular scores. In the paper the authors assume that linkage disequilibrium among markers and QTLs is the key factor for the success of MAS and therefore they consider a cross population as the more appropriate one.

The impact of MAS in livestock breeding programs has been modest because the QTL that exceeds the chosen significance thresholds usually accounts only for a minor fraction of the trait variance. However, Smith and Smith (1993) stressed that the number of markers was the only limitation for the success of MAS, even in panmictic populations. They realized that it would be a question of time that enough number of markers were available and urged labs to accomplish the task.

2. Genomic selection

2.1. Many available markers at an affordable cost

Meuwissen et al. (2001) proposed what nowadays is called *genomic selection*. It is rooted it two assumptions that now have been accomplished. The first is that panels with tens of thousands of markers will be available together with cost-effective genotyping procedures, and the second is that marker-density will be sufficient for all responsible genes of a trait to be in linkage disequilibrium with flanking markers. Genomic projects in several domestic species have allowed a large numbers of SNPs to be discovered as a by-product of sequencing or in subsequent re-sequencing. Although we are still far from latest human SNP chips with over 3000,000 SNPs, commercial 'SNP chips' exist for cattle (750,000), dogs (250,000 SNPs), sheep (56,000 SNPs), pigs (60,000 SNPs), horses (55,000 SNPs) and chickens (600,000 SNPs) that can be easily genotyped using the same well-established technology as in human and at a reasonable cost.

In the simplest terms, genomic selection is a two-step process. First, estimate the effects of markers ($>$ 50,000 SNPs) in a reference (training) population that has been phenotyped and genotyped. Second, use this information to predict the

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