

Quantitative and Molecular Genetics, a love story

D.P. Berry¹, R.A. Skuce², M.P. Coffey³

¹Teagasc, Moorepark Dairy Production Research Center, Fermoy, Co. Cork, Ireland, ²Agri-Food and Biosciences Institute (AFBI), Belfast BT4 3SD, United Kingdom, ³Sustainable Livestock Systems, Scottish Agricultural College, Midlothian, EH26 0PH, United Kingdom

Email: donagh.berry@teagasc.ie

Once upon a time, in research centres, universities and breeding companies around the world, there lived two types of scientists, the quantitative geneticist and the molecular geneticist.....

The early years Animal breeding based on the mating of animals of excellent phenotypes has been practiced for many centuries but major advances in animal breeding occurred with the development of BLUP. Although largely unappreciated at the time, Gregor Mendel is credited with providing the genetic understanding of heredity in 1866. DNA was sequenced for the first time in 1977 and in 2001 the first draft of the human genome was released with the first draft of the bovine genome being publicly available in 2006. Throughout this period both disciplines more or less pursued their own paths, each oblivious to the developing love story.

Courtship Flirting between the two disciplines intensified in the early 1990s as animal breeding changed focus from traditional quantitative methods to molecular genetics. Molecular geneticists were to identify regions of the genome associated with performance traits, commonly known as quantitative trait loci (QTLs), and quantitative geneticists were to develop the statistical methodology for incorporating such information into genetic evaluations. The latter step became known as marker assisted selection (MAS). Rumours of “genotype building” circulated where animals would be screened for QTLs and their effects summed to generate true additive breeding values. Quantitative geneticists became anxious when molecular geneticists seemed to imply that they would soon be dumped. However, MAS was not without its shortcomings. It was obvious that the successful exploitation of genomic information in animal breeding needed a stronger relationship between the two disciplines.

Marriage At the start of the millennium, the concept of genomic selection was introduced. Genomic selection is based on relating genetic markers, from dense marker maps of the genome, to accurately recorded phenotypes in a training population. The output is an estimate of the association between each marker and the phenotype under investigation. Animals without phenotypes are then genotyped and their marker effects summed to generate an estimate of their genetic (genomic) merit. This is similar to the “genotype building” alluded to previously except that the markers used in genomic selection are not necessarily causative mutations. The concept of genomic selection became a reality with the first draft sequence of the bovine genome in 2006. This is where the tables were turned and molecular geneticists feared being dumped! They were led to believe that it was no longer necessary to identify the gene or to understand the molecular processes underlying complex traits. All that was needed was to be able to reliably relate the desired phenotype with the genetic markers. The uptake of genomic selection was rapid, and caused a paradigm shift in animal breeding as we knew it. Genomic evaluations in dairy cattle are currently underway in most international genetic evaluations.

The in-laws Molecular geneticists belong to the large family of systems biology. This family is teaching quantitative geneticists the complexity of organisms, including gene regulation and expression. However, to date most quantitative geneticists are ignoring systems biology and are continuing to analyse genomic data from a predominantly statistical perspective. Conversely, quantitative geneticists are trying to teach systems biology researchers the importance of accurately phenotyping large numbers of animals. The quantitative geneticist needs to visit the systems biology household more often to discuss how the technologies and expertise developed can be better harnessed in animal breeding. A cup of tea and a chat should reap great rewards.

Wedding anniversary An anniversary is not only a time of celebration but also a time for reflection. With experience comes wisdom and, with the benefit of hindsight, it is easy to recognise that the complex organisms we are selecting are unlikely to be controlled by just a few major genes. At subsequent anniversaries we will still need to sit back and reflect on what we have learned. One particular lesson to be learned is that in the flush of youth, a development must be rigorously tested to determine whether it becomes a leader or a ‘has been’. The early hysteria of genomics is slowly being replaced by a more sober and realistic assessment of its true commercial value and how it fits into existing breeding programs. Has genomic selection really been tested rigorously? Rigorous testing is important to maintain credibility with industry. Poor concordance between reality and promises made may hinder future scientific endeavour in this area.

Divorce? A continuing and long-term relationship between molecular and quantitative geneticists is vital for sustainable genetic gain for several reasons: 1) linkage disequilibrium exploited between markers on available arrays and functional mutations will break down over generations so greater marker density is required, 2) smaller scale molecular experiments will be needed to elucidate the genetic architecture of difficult to measure traits to provide valuable “prior” information for statistical models, 3) elucidating interactions between genotype and environment may be more easily deciphered with smaller-scale experiments coupled with detailed gene expression analyses, which may be particularly important if marker effects are estimated in nucleus-herd type environments, 4) the impact on prevailing breeding goals on those traits not routinely measured may be more easily quantified using molecular genetics, 5) resolving the phenomenon of the “missing heritability” where the QTL detection studies to date have been unable to explain all the heritability of a given trait. Therefore, this is not the end of this love story, but merely the beginning.....