



The genomics of animal stature

Thirty research groups, including **TEAGASC**, have collaborated to publish a paper in *Nature Genetics* explaining the genetic background of stature in cattle.

One of the largest collaborations to be undertaken in cattle research has successfully explained the genetic basis of a large proportion of the variability in cattle stature. The study, which involved 57 researchers from 30 institutes, identified multiple DNA regions associated with animal stature by analysing the DNA of over 58,000 cattle from 17 populations. These results were published in *Nature Genetics* in February 2018, and have paved the way for researchers to use the same approach to map high value traits such as production and efficiency.

The 1,000 bull genomes project

The 1,000 bull genomes project is a global initiative to provide researchers with access to high-quality whole genome sequences on thousands of key ancestral animals. Whole genome sequencing is the determination of an individual's DNA across all of the possibly three billion sites where subtle changes in the DNA between individuals can exist. Although the cost of sequencing is continuously declining, it remains impractical for individual countries to sequence all animals. Therefore, by pooling data within the consortium, all partners can subsequently use these core sets of animals to accurately predict (often called impute) the whole genome sequence genotypes of other individuals at minimal cost. This is achievable because DNA is transmitted in large chunks across generations, thus allowing the DNA inherited from ancestral bulls to be traced into their relatives. Teagasc submitted whole genome sequence data on 142 influential bulls in Ireland to the database. The whole genome of over 600,000 Irish dairy and beef cattle has since been imputed from the 1,000 bull genomes database, providing a unique resource for genomic characterisation of performance in cattle.

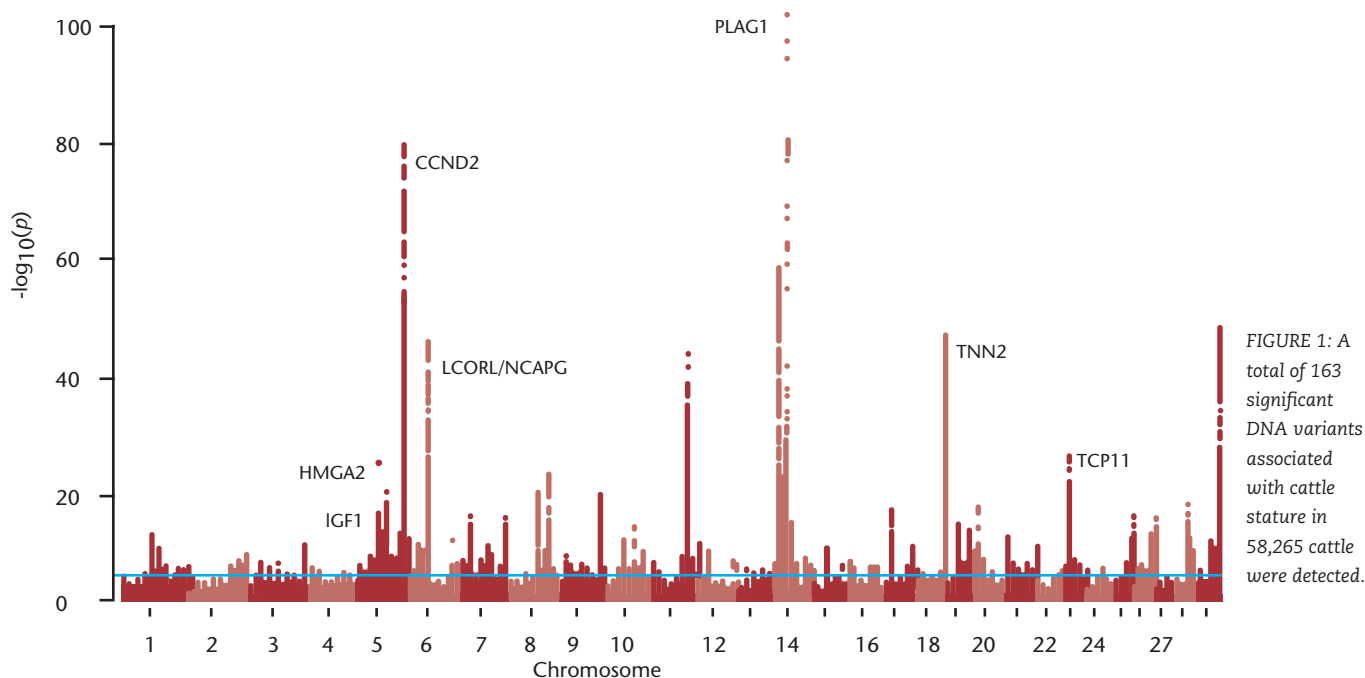
Meta-analysis of stature

Stature was chosen as the trait for initial investigation because it is under strong genetic control, is measured relatively consistently in cattle globally, and is a topic of active research in human genomics. It is also a perfect example of a complex trait, whereby both variability across thousands of DNA sites and environmental conditions contribute to the size and shape of cattle. A total of 5,152 Holstein-Friesian sires with measures of genetic merit for stature in Ireland were analysed by the Teagasc geneticists, and similar analyses were undertaken in each

collaborating country. This involved using the 1,000 bull genomes resource to successfully impute 25.4 million DNA variants into the 5,152 Irish Holstein-Friesian sires. Statistical analyses were undertaken where each DNA variant was associated one by one with stature. Results from each institution were combined to perform one of the largest ever meta-analyses for livestock animals. Results from the combined analyses revealed that the genetic architecture of stature in cattle is influenced by a very large number of DNA variants, and is comparable to that of humans. A total of 163 significant DNA variants associated with stature were detected (**Figure 1**), and cumulatively explained 13.8% of the phenotypic differences between individuals for height. This is similar to humans, where 16% of the phenotypic difference between individuals for height was explained by significant DNA variants. In contrast, however, 13.5% of the phenotypic variation in body size in dogs is explained by just 17 DNA variants. This suggests that the selection for extreme size in dogs has resulted in some DNA variants that have a larger effect on body size than those detected in cattle and humans. The similar genetic architecture in cattle and humans is corroborated by the significant overlap of DNA variants affecting stature in both species; 11 of the 92 genes significantly associated with height in cattle have been previously identified to be associated with stature in humans.

Validation of results

To confirm that the significant DNA variants identified in the study did have a true association with cattle stature, an additional 30,000 cattle, of which 20,000 were from Irish beef herds, were used for validation. The majority of the significant DNA variants identified were validated and could accurately explain between 2.1% and 13.8% of the phenotypic variability in cattle height in the Limousin and Brown Swiss breeds, respectively. In addition, the DNA of miniature cattle from three breeds (Angus, Hereford and Belted Galloway) and a 6,500-year-old wild auroch, an extinct species of large wild cattle, which were the ancestors of modern cattle, were also studied for validation. The DNA from the auroch indicated that many of the significant DNA variants identified in the study actually arose before cattle domestication and breed formation, and that over time, we have selected for shorter stature in cattle relative to wild auroch populations.



Relevance for breeding

This large study confirms that cattle stature, and most likely other complex traits such as fertility and production, can only be explained in part by specific genes. This substantiates the theory underpinning the statistical models of animal breeders, which assumes that there is an infinitely large number of genes, each having an infinitely small effect on performance. Ongoing research by Teagasc geneticists is focusing on further exploiting the 1,000 bull genomes resource to analyse other complex traits such as performance, fertility and health. Ultimately, it is hoped that these large-scale research projects can provide additional knowledge to help improve the accuracy and robustness of prediction equations for animal performance based on DNA variants, and also provide valuable information for the development of tailored management strategies.

Acknowledgements

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Reference

Bouwman, A.C., *et al.* (2018). ‘Meta-analysis of genome-wide association studies for cattle stature identifies common genes that regulate body size in mammals.’ *Nature Genetics*, 50: 362-367.

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