QUANTITATIVE GENETICS

A lean feat —
microRNAs and
muscle mass

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Domestic animals have been bred for thousands of years for specific phenotypic traits. Meatiness in sheep and cattle is a good example of such an economically important trait. Michel Georges and colleagues have now identified the molecular basis of meatiness in Texel sheep — their impressive muscles are a result of a point mutation which creates an illegitimate microRNA target in the 3' UTR of myostatin (*MSTN*), resulting in downregulation of its expression.

The hunt for a molecular determinant of the QTL responsible for large muscles in Texel sheep began with a whole-genome scan. A QTL with a major effect on muscle mass was mapped to chromosome 2 and subsequently fine mapped to a region around the *MSTN* locus. Loss of *Mstn* in mice, cattle and humans leads to a 'double-muscle' phenotype, but although the gene seemed a

perfect candidate to account for the phenotype in sheep the authors did not find any mutation candidates within its ORE. One SNP, located in the 3' UTR, was present in Texel sheep but was found in only 1% of other breeds. On close examination it turned out to create an illegitimate miRNA target for three previously characterized miRNAs, two of which the authors show are abundantly expressed in sheep muscles.

One way in which miRNAs regulate gene expression is to block mRNA translation. In agreement with this, the authors show that *MSTN* protein levels are reduced in Texel sheep. They demonstrate that inserting 80 bp around the newly created miRNA target, or the complete 3' UTR from Texel sheep, downstream of a reporter gene reduces its expression by 2.5-fold to 3.5-fold in cell culture. These results indicate that the 1-bp substitution which creates the new miRNA target site disrupts muscle homeostasis and results in the build up of extra muscle fibres.

Struck by their findings, the authors wondered how widespread

such point mutations that either create or destroy miRNA target sites might be. By comparing human and chimpanzee sequences, they identify almost 4,000 SNPs that fall into this category. These data, as well as those for the mouse, have been collected in a new web site called **Patrocles**.

The results of this elegant research not only reveal the molecular basis of a striking quantitative trait but also indicate that the polymorphic miRNA-mediated regulation of gene expression could be widespread. In addition, they identify a new class of regulatory mutations that underlie QTLs.

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ORIGINAL RESEARCH PAPER Clop, A. et al. A mutation revealing a potential illegitimate miRNA target site in the myostatin gene is a quantitative trait nucleotide with major effect on muscularity in sheep. *Nature Genet.* 4 June 2006 (doi:10.1038/ng1810)

FURTHER READING Andersson, L. & Georges, M. Domestic-animal genomics: deciphering the genetics of complex traits. *Nature Rev. Genet.* 5, 202–212 (2004) | Bartel, D. P. & Chen, C.-Z. Micromanagers of gene expression: the potentially widespread influence of metazoan microRNAs. *Nature Rev. Genet.* 5, 396–400 (2004)

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