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NEWS AND COMMENTARY

Quantitative genetics

Detecting selection

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Finding out which loci throughout the genome are affected by selection is important to our understanding of evolution and of huge interest to livestock geneticists. Now Luis Gomez-Raya *et al* (2002) have used artificial selection in cattle to demonstrate a method for measuring the genomic response to selection.

Evolution, driven by selection, depends on changes in gene frequency. However, it is often difficult to demonstrate this change at specific genes or nucleotides. Often natural selection is weak and the large number of neutral or nearly neutral polymorphisms mask variation that is selectively significant. Therefore, it is not surprising that some of the most crucial insights into evolution, even as far back as Darwin, have come from observations of artificial selection of livestock. In this tradition, Gomez-Raya *et al* studied the genomic response in Norwegian cattle to selection for high growth in the male offspring of elite sires (bulls).

Gomez-Raya *et al* use an experimental design very similar to that used to map quantitative trait loci (QTLs) in which a large number of offspring of one or more sires are typed for a genetic marker at which their sire is heterozygous (say Aa) and measured for the trait of interest. If there is a heterozygous QTL affecting the trait linked to the marker, the offspring that inherit sire allele A will differ in the trait from the offspring that inherit marker allele a. By using genetic markers covering all chromosomes at about 30 cM spacing, QTLs anywhere in the genome can be detected, provided their effect on the trait is large enough.

Often, in wild animals and in livestock, only the selected animals are available to the researcher. In the new study, Gomez-Raya *et al* estimated the frequency of each sire's alleles in his sons, which have been selected by the cattle breeder at 282 marker loci spread evenly throughout the genome. They found that the frequency of sire alleles differed significantly from the expected 1:1 ratio at some markers, indicating selection at genes linked to these markers.

Apart from artificial selection, this distortion of segregation could be because of natural selection among the zygotes or selection among gametes. Gomez-Raya *et al* addressed the former possibility by examining the segregation distortion in the culled offspring compared to the selected group; the latter by estimating the gene frequency of sire alleles in individually genotyped sperm. Their analyses of all these data clearly suggested that artificial selection caused the distorted gene frequencies in selected offspring. The significant effect the markers had on growth rate was an additional evidence in favour of this conclusion.

However, the novelty of this new study comes more from the way in which Gomez-Raya *et al* were able to detect selection rather than the simple fact that they detected it.

This experiment used six sires with 70–110 sons per sire genotyped for 282 markers. In such designs, the cost of genotyping is high. QTL mapping experiments often reduce the cost by only genotyping animals at the high and low phenotypic extremes of the trait of interest. An allele frequency difference at a marker locus between these extremes indicates a QTL linked to this marker. By contrast Gomez-Raya *et al* propose to detect a QTL by genotyping only one extreme (eg the selected offspring). Their strategy is to target marker alleles in the selected animals with a frequency significantly different from the 0.5 expected from random segregation. This is a powerful test provided the gene frequency over all offspring is 0.5. Gomez-Raya *et al* test this by estimating the sire allele frequency in the culled offspring and by typing individual sperm from the sire.

This approach could be useful for QTL mapping in other circumstances. It is often the case that only a selected group of offspring is available and this severely reduces the power to detect QTL if the conventional analysis is used. However, by assuming that the marker allele frequency in an unselected group of offspring is 0.5, a powerful test for a QTL can still be made. For markers that show an apparently significant effect, it would be wise to confirm this assumption as Gomez-Raya *et al* have done. A common design for mapping genes affecting human disease is the affected sib pair, for which the analysis is based on the same principle of comparing observed allele sharing with an expected allele sharing of 50%. Again, differential survival of marker genotypes could cause greater than expected allele sharing in sibs whether they both suffer from the disease or not.

A second novel feature of this new study is that they do not select the highs and lows for a single trait, as is usual for selective genotyping, but consider all selected animals. A QTL might affect the trait under selection but exhibit no change in gene frequency because such a change could incur a fitness cost associated with other traits the QTL influences. Thus Gomez-Raya *et al* focus on the outcome of selection, a gene that is changing in frequency, rather than detecting a gene for a particular trait.

Could this approach be used to detect selection in wild populations? Only in rare situations I suspect. Power in QTL mapping requires large families and a gene with a moderate to large effect. Thus, one would need a species where at least one parent of each individual is known and where that parent has many (>100) offspring. Even then, Gomez-Raya *et al* show that there is only a 50% probability of detecting a gene with an effect of 0.6 phenotypic standard deviations. Bee species, where there is only one queen per hive, might be an example where many known offspring of one mother occur.

The need for large families arises because the Gomez-Raya *et al*. approach is based on linkage and not on a population-wide association study. Within a family a marker is inherited together with many genes on the same chromosome, so 200 markers or even less can detect QTLs anywhere in the genome. In the absence of known family structure one can still test individual genes to see if they affect the trait of interest but to cover the whole genome would require a very dense set of markers so that every gene was in strong linkage disequilibrium with one or more markers. At least one company is applying this design to humans, using people who have survived to old age as a selected group in which to find genes affecting longevity. Of course, in this design a control group is needed in which to estimate the gene frequencies in early life.

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Gomez-Raya L *et al* (2002). *Genetics* **162**: 1381–1388.