A new approach to detect non-pleiotropic QTL for correlated traits

S. Casu¹, J.M. Elsen², A. Carta¹

¹ Istituto Zootecnico e Caseario per la Sardegna, Olmedo, Italy
² Station d’Amélioration Génétique des Animaux, Institut National de la Recherche Agronomique, France

Corresponding author: Sara Casu. Istituto Zootecnico e Caseario per la Sardegna. 07040 Olmedo, Italy
Tel: +39 079 387313 – Fax: +39 079 389450 – Email: saracasu@tiscali.it

RIASSUNTO – Un nuovo metodo per l’individuazione di QTL non-pleiotropici nel caso di caratteri correlati. L’approccio si basa sull’analisi dei fenotipi per un carattere d’interesse (A) ottenuti come residui della regressione lineare su un carattere positivamente correlato (B). Il lavoro dimostra, attraverso simulazioni e con un’applicazione a dati reali, che tale approccio aumenta la potenza di individuazione di QTL con solo effetto su A, in misura proporzionale alla correlazione tra caratteri. Esso comporta tuttavia il rischio di concludere erroneamente all’esistenza di QTL non-pleiotropici per A quando il locus influenza B. E’ possibile limitare tale rischio estendendo la ricerca di QTL al carattere correlato. In tal modo, l’effettiva probabilità di false identificazioni si riduce proporzionalmente al rischio di errore di prima specie scelto per B.

KEY WORDS: regression, power, false detection.

INTRODUCTION – In quantitative traits loci (QTL) mapping experiments a number of traits are often recorded. Although most QTL-detection methods are based on single trait analysis, several approaches for multi-trait detection have been proposed (Weller et al., 1996; Knott and Haley, 2000). Those methods mainly focus on either increasing power of detecting pleiotropic QTL or discriminating between pleiotropy and linkage, often with the aim of dissecting unfavourable genetic correlation between traits. Nevertheless, when two traits are positively correlated, the detection of genes only affecting one of them could allow the speeding of its genetic improvement. For instance, although milk yield and milk emission flow are positively correlated in dairy ewes (Marie-Etancelin et al., 2002), indirect response of milk emission flow to the selection on milk yield is not sufficient to contain milking time, which increases with milk production. When two traits are correlated, the genetic variability of one of them can be partitioned in two components: the first one, due to genes showing pleiotropic effects and accounted for the genetic correlation, and the second specific to the trait of interest. The purpose of this paper is to study, through simulations, the power of detection of a non-pleiotropic QTL when the analysis is carried out on the residuals of a linear regression of the trait of interest on the correlated trait. The study focuses on positively correlated traits. Furthermore, an application to real data is presented.

MATERIAL AND METHODS – The simulated population consisted of a daughter design of 10 families with 100 daughters per sire. A QTL, with two isofrequent alleles, was supposed to have effects (a and b) on a trait of interest (A) and a correlated trait (B). The QTL was completely linked to a single fully informative marker locus. Individual values for the 2 traits were generated accounting for QTL genotype and for the positive correlation between phenotypes (r, which included the QTL effects). Different scenarios were investigated assuming r values equal to 0.4, 0.6 or 0.8 and QTL effects ranging from 0.0 to 0.7 standard deviation unit. For each scenario, residuals of the linear regression of A on B were calculated (Ac) using regression coefficient
issued from the imposed r. Significance of the marker contrast at 0.1% threshold level for A, B and Ac was tested by F statistic. Power was calculated from 10000 replicates, simulated, for each scenario, under H₀ and the alternative hypothesis. Real data come from a daughter design consisting of 10 families of around 100 halfsibs. The trait of interest was maximum milk emission flow (MMF), which shows a positive correlation (r=0.47) with milk yield (MY). A single trait interval mapping by within-sire regression analysis was performed on MY, MMF and MMFc, i.e. the residuals of the linear regression of MMF on MY.

RESULTS AND CONCLUSIONS – Simulation results are shown in tables 1 and 2. When the QTL only affects the trait of interest (table 1), detection power is increased if Ac values instead of A are analysed. The proposed approach reduces the variance of residual phenotypes thus increasing the statistic value, as confirmed by the fact that power increases as r increases. The use of other significant markers as cofactors in a univariate analysis of A, exploits the same principle (Zeng, 1994; and Jansen and Stam, 1994).

When the QTL affects B (b≠0) analysing Ac can produce a significant test value even if the QTL does not affect A or if it has a pleiotropic effect (table 2). If the analysis is limited to Ac, the probability to wrongly conclude for the existence of a non-pleiotropic QTL affecting A depends on the combination of the QTL effects. In order to reduce false detection of a non-pleiotropic QTL, the detection analysis should be carried out also on B. This allows bounding the false detection of a non-pleiotropic QTL for A to the cases in which no QTL has been

Table 1. Power of detection of a non-pleiotropic QTL (b = 0) affecting the trait of interest by analysing A (PA) or Ac (PAc). a: QTL effect on A; r: correlation; a=0.001.

| a  | r  | PA | PAc | PA | PAc | PA | PAc |
|----|----|----|-----|----|-----|----|-----|
| .3 | .4 | .251| .365 | .244| .442 | .251| .740 |
| .5 | .6 | .873| .924 | .867| .956 | .877| .991 |
| .7 | .8 | .986| .992 | .987| .995 | .986| .999 |

Table 2. Raw (PAc) and actual (AFD) probability of false detection of a non-pleiotropic QTL affecting A, by analysing regression residuals. AFD = (1-PB)*PAc. PB power of detecting a QTL affecting B. a:QTL effect on A; b:QTL effect on B; r=0.6; α=0.001.

| a  | b  | PAc | PB  | AFD |
|----|----|-----|-----|-----|
| .3 | .3 | .053| .293 | .038 |
| .5 | .5 | .446| .886 | .051 |
| .7 | .7 | .865| .988 | .011 |
| .3 | .3 | .011| .296 | .008 |
| .5 | .5 | .001| .887 | .000 |
| .7 | .7 | .011| .988 | .000 |
| .5 | .5 | .551| .297 | .387 |
| .7 | .7 | .086| .891 | .009 |
| .7 | .7 | .003| .989 | .000 |
| .3 | .3 | .968| .292 | .686 |
| .5 | .5 | .838| .896 | .087 |
| .7 | .7 | .381| .990 | .004 |
detected on B. As shown in table 2, the actual probability of false detection (AFP) can be inferred by the product of type II error for trait B and PAc. This probability stays quite small, except when the power of QTL detection on B is low, as it is the case of low gene effects. Consequently, choosing less stringent significance thresholds for B analysis, leads to a lower risk of false detection of non-pleiotropic QTL affecting A.

Figure 1 reports results of real data analysis. No QTL was detected with the analysis of MMF, whereas the lower variance of MMFc allowed to detect a non-pleiotropic QTL affecting maximum milk emission flow. Considering the high significance level of the test for MMFc (p-value = 0.0002) and that extremely low for MY (p-value = 0.40), the risk to be a false positive for this non-pleiotropic QTL is extremely low. In conclusion, the residuals of a linear regression of the trait of interest on the correlated trait are suitable phenotypes to detect non-pleiotropic QTL in a univariate QTL detection analysis, provided that a detection analysis is also performed on the correlated trait.

Figure 1. Likelihood ratio test profile for the QTL detection analysis on milk yield (MY), maximum milk emission flow (MMF) and regression residuals for maximum milk emission flow (MMFc).

REFERENCES – Marie-Etancelin, C., Arhainx, J., Aurel, M.R., Autran, P., Bibe, B., Jacquin, M., Lagriffoul, G., Pailler, F., Porte, D., Ricard, E., Barillet, F., 2002. Estimates of genetic parameters for milk flow kinetics during machine milking in French Lacaune dairy sheep. Proc. 7th WCGALP, com n. 01-51. Knott, S., Haley, C.S., 2000. Multitraits least squares for quantitative trait loci detection. Genetics 156: 899-911. Jansen, R.C., Stam, P., 1994. High resolution of quantitative traits into multiple loci via interval mapping. Genetics 136: 1447-1455. Zeng, Z.B., 1994. Precision Mapping of Quantitative trait loci. Genetics 136:1457-1468. Weller, J.L., Wiggans, G.R., VanRaden, P.M., Ron, M., 1996. Application of a canonical transformation to detection of quantitative trait loci with the aid of genetic markers in a multi-trait experiment. Theor. Appl. Genet. 92: 998-1002.