HAL open science

Intérêt de l'approche eQTL (QTL d'expression) pour l'identification de gènes responsables de la variabilité de caractères quantitatifs

Sandrine Lagarrigue, Michel Jacques M.J. Duclos

To cite this version:

Sandrine Lagarrigue, Michel Jacques M.J. Duclos. Intérêt de l'approche eQTL (QTL d'expression) pour l'identification de gènes responsables de la variabilité de caractères quantitatifs. Séminaire AGENAE/GENANIMAL 2007, Oct 2007, Paris, France. hal-02755223

HAL Id: hal-02755223

https://hal.inrae.fr/hal-02755223v1

Submitted on 3 Jun 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

E-QTL

Evaluation of the eQTL (expression QTL) approach to identify genes responsible for quantitative trait variation

Coordinator: S.LAGARRIGUE INRA Rennes

Partners: M. DUCLOS INRA Nouzilly

Start : July 2004 for 3 years
One additional year granted due to the late availability of chicken 20K microarrays (2006)

Background and objectives

Although many QTL for various traits have been mapped in livestock species, identification of causative mutations remains laborious, therefore limiting their use in animal breeding. The aim of the current programme is to improve location as well as biological functions of a QTL region using new information get after transcriptome analyses. Two approaches can be used : i) the eQTL identification (an eQTL region controls the expression variability of a gene or a gene cluster). So When searching for mutations underlying a (usual) QTL, a co-located eQTL may bring new functional information about the QTL mutation subject to the relationship with the studied trait has been evidenced. ii) the second approach is the splitting up of the trait of interest: gene expression patterns of F2 individuals used in (usual) QTL analysis can lead to identify genetically homogeneous sub-groups. A second QTL analyses on such sub-groups can allow to increase QTL significance and then its location.

We plan to apply these two concepts to two meat-type chicken experimental design, otherwise submitted to (usual) QTL studies.

First design

It is made of three sire-families obtained by crossing two experimental lines divergently selected on abdominal fat pad. The sires have been identified as heterozygous for at least one fat QTL (chr 1,5,7).

Results

In 2007, hepatic transcriptome profiles for ~50 offsprings from each of the 3 sires were obtained using a chicken 20K oligochip (ARK-genomics). Liver has been chosen as the main tissue regarding the lipid metabolism in the chicken. In collaboration with the SIGENAE team we ascertained and enriched annotations of the 20460 oligo-set.

We first studied the progeny of one sire heterozygous at the GGA5 QTL because of the high effect of this QTL. Transcriptome profiles were individually assessed and three study strategies have been undertaken.

1- We identified the genes differentially expressed between the two groups defined according to the QTL haplotype (Q vs q) received from their sire. A new synthetic variable combining the expression of these genes was defined on the basis of a principal component analysis (PCA) results. A linkage analysis on this synthetic variable was then performed with 10 markers along GGA5 using the QTLMaP software. As expected, an eQTL for this new expression variable co-localized with the QTL region with a very high likelihood ratio test (LRT). However, we did not prove its relation with fatness, except by its location.

2- We then identified the genes differentially expressed between the fat versus lean progenies defined according to the phenotype. As above, a new synthetic variable of the expression of these genes was constructed on the basis of the PCA first axis. Interestingly, this axis also very well separated the two Q versus q groups, thus confirming that the GGA5 QTL has a high effect on the trait. Linkage analysis on this gene synthetic variable showed an eQTL region co-localizing with the fat GGA5 QTL with a higher LRT. It is to emphasize that, among these genes, a gene subset diffferentially expressed between the Q vs q groups allowed identification of an eQTL at the same location as the fat QTL with an even more higher LRT. This results allowed to more precisely locate the GGA5 fatness QTL.

3- In addition to the above analyses, we performed a hierarchical ascendant classification (HAC) of the 48 offsprings with the 113 gene expressions. HAC allowed to split the F2 population in three sub-populations more homogeneous. A linkage analysis on fatness with some of these sub-groups allowed to increase the LRT of the fat GGA5 QTL and then to precise again its location.

Conclusion and perspectives

Ours results show the feasibility of this strategy in livestock species: a trans e-QTL which is related by construction to the fatness trait, co-localizes with the fat GGA5 QTL. This e-QTL region, through the genes that it controls, gives new information about the function of the mutation responsible for fatness variability in chickens. The biological interpretation of these genes is in progress, exploiting Gene Ontology (GO) annotations through the human orthologs (detected for roughly 50% of the avian genes present on the microarray). Standard tools are used as GOTM as well as tools recently developed in the present project (Chabelier et al., 2007).

References

1. J. Chabalier, J. Mosser and A. Burgun 2007. A transversal approach to predict gene product networks from ontology-based similarity, BMC Bioinformatics.; 8: 235
2. G. Le Mignon, F. Pitel, O. Demeure, S. Leroux, M. Douaire, B. Abasht,, P. Le Roy and S. Lagarrigue, 2008. eQTL mapping allows to refine abdominal fatness QTL in chicken. PAG, SanDiego, USA, 12-16 January 2008
3. C. Klopp, F. Moreews, M. Aubry and S. Lagarrigue, 2008. Contribution to the annotations of the chicken 20K oligo microarray of ARK-genomics, PAG, SanDiego, USA, 12-16 January 2008

Second design

It was constituted by two divergently selected lines of broiler chickens with high (HG) or low (LG) growth rates for which various QTL for growth and body composition were detected. These two lines were used for a transcriptional profiling study at different ages (using a 14 K cDNA chips from UDel). This was an opportunity for testing whether genes differentially expressed between parental lines could be linked to QTLs. Because of this gene selection step, the expressional study could be limited to RTPCR quantification of expressional/positional candidates in F2 offsprings issued from the cross of the parental lines.

Results

The transcriptional data showed that about 80 genes showed a consistent difference at least across two of six stages between 1 and 11 weeks of age (Jenkins et al, 2006). In this study, the amplitudes of the differences were small (fold change between 1.2 and 2, except one gene). Only two genes were confirmed (out of five showing the highest fold change difference) by quantitative RTPCR. The gene with the largest difference encoded for a retroviral envelope protein (Pr57env), which was largely over-expressed in LG chickens (up to 10 fold). Expression of the alpha enolase gene was also higher in LG chickens (about 2 fold). The other genes (Aldolase A and C, ATP synthase), which were not confirmed could be false positive in the microarray analysis. Alternatively, the discrepancy between microarray and RTPCR could result from a complex pattern of cross hybrization of the cDNAs with several transcripts. These results designated Pr57env and AENO as the first candidates to be measured on individuals from the F2 population, although they were not closely associated with QTL loci. The measures are underway on all F2 offsprings issued from one sire family shown to be heterozygous for several QTL controlling growth and meat quality, and on extreme animals with high or low body weight from the other 4 families. An expressional/functional candidate, IGF-1 and a functional/positional candidate are also currently tested. In the mean time further classical QTLs controlling meat quality traits have been detected (Nadaf et al, 2007), providing further candidates will be considered based on their status of functional/positional or expressional/positional candidates (up to 10).

Conclusion and perspectives

The relatively limited variation in the transcription profiles between genotypes, despite their marked phenotypic differences, has lowered the potential for detecting expressional/positional candidates. The study of functional/positional candidates could be an interesting alternative approach to better characterise the phenotypes underlying the QTL.

References

1. Jenkins C., Le Bihan-Duval E., Berri C., Simon J., Cogburn L., Duclos M.J., 2007. 7èmes Journées de la *Recherches Avicoles*, Tours, France, 28-29 mars 2007.
2. Nadaf J., Gilbert H., Pitel F., Berri C., Feve K., Beaumont C., Duclos M. J., Vignal A., Porter T. E., Simon , Aggrey , Cogburn L.A. and Le Bihan-Duval E., 2007. Identification of QTL controlling meat quality traits in an F2 cross between two chicken lines selected for either low or high growth rate. BMC Genomics, 8:155