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**TITLE:** From Quantitative Trait Loci (QTL) discovery to nutrigenetics

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### **Summary**

The study of the interactions between genetics and nutrition has gained new impetus with the development of high-throughput genomic approaches allowing for a comprehensive approach of the variability of gene sequences or activity. The object of nutrigenetics is to identify the genetic determinants (sequence polymorphisms) of the variability of individual responses to nutrition.

A quantitative trait locus (QTL) is a chromosomal region involved in the control of quantitative phenotypic traits. Based on the knowledge of the chicken genome sequence, numerous positional candidate genes can be proposed within a QTL region, and further evaluation is needed to test the link between polymorphism of those genes, their activity and the expression of the phenotype.

As a proof of principle that such an approach is relevant to nutrigenetics, we identified a polymorphism in the gene encoding the enzyme  $\beta$ -carotene 15,15'-monooxygenase 1 (BCMO1), which affected the response to dietary intake of  $\beta$ -carotene in term of plasma, liver and duodenal concentrations of lutein.

Another project aims to identify the genetic determinants of digestive ability through the development and characterization of two experimental lines of chickens divergently selected for this trait. Recently, chromosomal regions controlling this trait have been identified, and further studies of sequence polymorphisms and gene expression (functional genomics) data in extreme animals issued from a cross population are underway.

Eventually, the tools of nutrigenetics will predict the potential for adaptation of genotypes to various feeds. Nutrigenomics, allowing a better understanding of the mechanisms by which nutrition affects gene activity, is expected to propose new nutritional strategies to guide phenotypes and new selection strategies to improve birds' ability to adapt to different diets. The combination of both approaches should permit to identify genes controlling those phenotypes.

### **Main text**

Interactions between genetics and nutrition are old concerns which can now be studied in more details, thanks to the development of high-throughput genomic approaches. The object of nutrigenetics is to identify the genetic determinants (sequence polymorphisms) of the variability

of individual responses to nutrition. While this opens great promises in term of personalized nutrition for humans, its potential application in animal nutrition and selection deserves some thoughts. Broilers have been intensively selected for growth rate and carcass conformation in a relatively standard environment including standard diets mainly based on corn and soybean. There is ample evidence that those animals do not express their full genetic potential for growth when fed alternative feedstuffs, even if their nutritional requirements are matched. Although genetic selection does not result in complete homogeneity of the animals on the market, some alleles are more frequent in selected populations and sometimes even fixed (Hayes et al, 2009). Identification of those alleles which are associated with the ability of birds to cope with particular feedstuffs would permit to choose the most appropriate strain or candidate to selection for a given objective, taking into account the context of available feedstuffs. Besides, this could also allow the breeders to develop specifically adapted strains on demand. The present paper will attempt to illustrate the feasibility of identifying such alleles and the potential application for the selection of broilers

#### Polymorphism at the BCMO1 locus identifies a nutrigenetic control of carotenoid metabolism

Experimentally selected broiler lines with High and Low growth rate have been used as a model to identify the mechanisms controlling growth, body composition and meat quality traits. After several studies comparing the lines, a cross population was constructed to identify the QTL that governed the corresponding traits. At the time, only a limited number of polymorphic microsatellite markers, around 130, could be used. Nevertheless, many QTL were identified and among them, one that controlled meat yellowness was the strongest (Nadaf et al, 2007). Following further studies implying finer mapping and bioinformatics, the BCMO-1 gene was identified as a double positional and functional candidate gene for the QTL (Le Bihan-Duval et al, 2011). An allelic polymorphism at the BCMO1 locus, within the promoter region, conferred a differential transcriptional activity to the gene in the breast muscle which was negatively correlated with the intensity of breast meat yellow color and its content in carotenoid pigments. A genetic test based on HRM of a PCR product was developed to genotype the chickens at this locus, and was also validated in unrelated broiler lines, and patented. It permitted to produce and select birds homozygous for one allele or the other, and exhibiting a high or a low BCMO-1 gene activity (High BCMO vs Low BCMO), within the same genetic background, for use in further studies (Jlali et al, 2012). Supplementation with  $\beta$ -carotene was provided to dissect the mechanisms underlying this genetic difference. Genotype by diet interactions were observed for retinol accumulation which increased following  $\beta$ -carotene supplementation in the duodenum of chickens with the High BCMO allele, and for xanthophyll's and vitamin E accumulation which decreased in duodenum, liver and plasma of chickens with the Low BCMO allele (Jlali et al, 2014). Carotenoid metabolism is therefore under a nutrigenetic control at the BCMO1 locus, which could be identified following observations made during a QTL analysis.

#### Towards the identification of alleles controlling broiler adaptation to various feedstuffs

With the objective of developing more sustainable poultry production schemes, the availability of broilers which could adapt to variable feedstuffs is a priority. The between-birds variability in digestibility had been shown to depend on the wheat varieties (Carré et al, 2002, Choct et al, 2009)

and the demonstration that chicken digestive ability was an heritable trait was first made by Mignon-Grasteau et al (2004), by comparing birds fed a wheat based diets incorporating Rialto wheat, a hard and viscous variety selected for its low digestibility values. They also demonstrated the possibility of divergently selecting broilers on this trait and created an experimental model of good and bad digesters, which they subsequently used for further characterization of the underlying physiological and genetic mechanisms of adaptation to feed. These two lines differ for their response to dietary variations such as the incorporation of different wheat varieties (Péron et al, 2006) and to the incorporation of xylanase or antibiotics (Garcia et al, 2007). They also show marked differences in the relative development of their digestive organs – the good digesters showing a more developed gastric compartment (gizzard and proventriculus) and a lesser developed intestine (Péron et al, 2006, Garcia et al, 2007, Rougière et al, 2009, de Verdal et al, 2010), and a slower transit (Rougière and Carré, 2010). Broilers with enhanced digestive abilities also perform better on a more classical corn soybean diet, although the difference is less pronounced (Mignon-Grasteau et al, 2010; 5-10 % instead of 30-40 % in AMEn with wheat based diet). To evaluate their robustness against pathogens, the experimental lines were subjected to challenge by *E. coli*. While lesion scores did not differ between the two lines, mortality and bacterial loads were lower in the good digesters than in the bad digesters (Calenge et al, 2014).

A reference population resulting from the cross between the two lines was constructed and used for the identification of QTLs controlling numerous traits of importance for broiler production. The F2 population was genotyped with 3000 informative SNPs markers (Tran et al, 2014). A strong QTL controlling digestive use of starch and of dry matter was identified on chromosome 20 (Tran et al, 2014). Further QTL controlling feed intake, feed efficiency, growth, body composition, anatomy and excretion traits were also described (Mignon-Grasteau et al, 2015-a). Co-localisation of QTL controlling feed efficiency and development of the gastro-intestinal tract suggest a functional or even causal relationship between these traits. Functional candidates could be proposed and discussed for several of these traits. In their most recent paper, Mignon-Grasteau et al (2015-b) used extreme animals from the crossed population to examine the relationship between digestive ability and microbiota composition through the determination of cecal content of targeted bacterial species by quantitative PCR. This study demonstrated a link between host genetics, microbiota composition and feed efficiency or digestive efficiency. *Lactobacillus* and *E. coli* were more frequent in the less efficient birds. The digestive use of dry matter was positively correlated to the levels of *L. crispatus*, *C. leptum* and *C. coccoides*. Moreover, QTL controlling *C. leptum* and *Lactobacillus* were identified. The most significant QTL controlling *C. leptum* was on chromosome 6 in a region which includes gene involved in inflammatory responses of the gut and the motility of the digestive tract.

The next objective is to validate genetic markers which could be used for selection in commercial populations. The identification of the genes that control the traits would be the ultimate goal for both fundamental and applied purposes. Some of the underlying physiological mechanisms, have also been unravelled, which opens perspective for nutritionists.

## Conclusions and perspectives

Our recent data obtained using experimental lines of chickens show that some responses to diet are genetically determined and therefore, that chickens can be selected on this criterion. In the case of carotenoids in the diet, an allelic variation in a single gene has been identified as a key determinant of the response. The same allele as detected in the experimental cross can be tracked in commercial populations and used for selection purposes. In the case of digestive ability for various feedstuffs, the feasibility of selection has been demonstrated and correlated responses and some of the underlying physiological mechanism have been described. A number of genomic regions controlling this trait and related traits of interest have been identified. Further studies are underway to identify the genes controlling those traits and their alleles. This will provide new tools for selecting birds with an increased adaptability for more various feedstuffs, which in a longer term could improve the sustainability of broiler production schemes.

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