NUTGENEVOL : Deciphering the complex evolution of genes involved in human adaptation to diet

BIOLOGIE & SANTÉ 2011

NUTGENEVOL ANR – Blanc - 2007

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Context

One of the greatest challenges in human evolutionary genetics is to elucidate the evolution of biological polygenic traits. The nutritional transitions that occurred during human evolution have represented important challenges for human adaptation. One of these major transitions is the emergence of agriculture in human societies, for the first time 10,000 yrs ago, when some populations shifted from a meat-based diet to a predominantly cereal-based diet. Before this major transition, genes favouring insulin resistance and gluconeogenesis were certainly selected for, in order to constantly maintain sufficient level of glucose in the blood. These genes may now be detrimental in present societies, because under a high carbohydrate diet, insulin resistance and gluconeogenesis may lead to metabolic disorders such as type 2 diabetes, obesity, and hypertensi

Objectives

In order to understand how metabolic genes involved in alimentary processes and associated with type 2 diabetes have evolved in response to different selective pressures, we study comparatively societies that have lived for thousands of years under contrasted diets. This case study is conducted in Central Asia where pastoral societies and agriculturist societies still coexist. Pastoralists are thought to have a higher input of meat and diary products as compared to agriculturists, whose diet is mainly based on cereals.

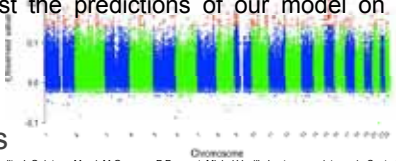
Methods and Results

We have collected phenotypic data (nutritional anthropometry, fasting blood glucose and insulin levels, high density lipoprotein cholesterol and triglycerides), sampled blood for DNA analyses in the two ethnic groups with different food intake (700 sampled individuals– 5 field missions). We used a population genetics approach to detect selection on genes potentially involved in diet adaptation (Lactase, AGXT) and 11 genes known to be involved in type 2 diabetes (TCF7L2, KCNJ11, PPARG, CDKAL1, HHEX, KCNQ1, SLC30A8, IGF2BP2, FABP2, LEPR, PON1). Our results show that **herders have a higher level of insulin resistance (IR): odd ratio of 1.8**. Some genes also show different pattern of selection between the two populations, but **none explain the higher level of IR in herders**. In parallel we have simulated the evolution of complex traits coded by a regulation network like insulin resistance. We show that when these traits are under selection the regulation levels increase and that the genes responding the more to selection are the ones that are the more basal within the network.

Conclusion and Perspective

Thanks to the phenotypical study, we have validated our initial hypothesis that herders would show higher level of “maladaptation” when facing a contemporary high carbohydrate diet. But none of the candidate genes explain this pattern.

In order to find the genes involved in the higher IR in herders we have initiated a **GWAS study** on a subset of our sample. The initial results are highly promising. We will be able also to test the predictions of our model on this dataset.



Publications

E Heyer, L Brazier, L Ségurel, T Hegay, F Austerlitz, L Quintana-Murci, M Georges, P Pasquet, Michel Veuille Lactase persistence in Central Asia: phenotype, genotype and evolution *Human Biology* 2011
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