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The lactase persistence genotype is associated with body mass index and dairy consumption in the D.E.S.I.R. study

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ABSTRACT

Objective. The T allele of a functional polymorphism (rs4988235: *LCT*-13910 C > T), close to the lactase gene, correlates with lactase persistence (LP) in adults. The LP genotype (TT + TC) has been associated with a higher BMI in European populations in cross-sectional studies. In the French D.E.S.I.R. cohort, a high consumption of dairy products was associated with a lower body weight gain over 9-years, and with a lower incidence of high plasma glucose levels and/or the metabolic syndrome. Our aim was to test in this study, the association of rs4988235 with BMI and related metabolic diseases, in interaction with dairy product consumption.

Methods. Among 5212 subjects from D.E.S.I.R., 3575 Caucasians born in mainland France were genotyped and followed over 9 years.

Results. Those with the LP genotype (frequency: 78.5%) had a higher dairy product consumption, at inclusion and at year-9 ($P < 0.001$). They also had a higher BMI at both time points (difference = 0.3 kg/m^2, $P = 0.05$), but this effect was restricted to medium/high dairy product consumers (difference = 0.5 kg/m^2, $P = 0.006$). This genotype was also associated with the metabolic syndrome (IDF definition), but this association disappeared after adjustment for BMI. In the whole population, the C allele was associated with a higher prevalence of impaired fasting glycemia and/or type 2 diabetes.

Conclusions. The lactase persistence genotype was shown to be associated with a higher BMI in a longitudinal study, mainly in those consuming high amounts of dairy products. The association of the C allele, responsible for lactase non-persistence, with the risk of hyperglycemia needs to be replicated.

Abbreviations: LP, lactase persistence; D.E.S.I.R, Data from the Epidemiological Study on the Insulin-Resistance syndrome; IFG, impaired fasting glycemia; T2D, type 2 diabetes; MetS, metabolic syndrome; IDF, International Diabetes Federation.

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1. Introduction

The lactase enzyme is expressed in enterocytes and digests milk sugar lactose. Lactase activity is high in infancy but declines with age. It is often low in human adults, but sometimes persists at a high level throughout life. Lactase persistence (LP) at an adult age is a dominantly inherited trait. The distribution of lactase phenotypes is highly variable in human populations and is controlled by a functional polymorphism located at −13,910 bp upstream of the lactase gene (rs4988235: *LCT*-13910C > T), within an intron of the adjacent gene, *MCM6*. The T allele is tightly associated with LP in European populations [1], and CC homozygotes have almost undetectable intestinal lactase production. This polymorphism has been shown to be functional in vitro [2–5] and in vivo [6]: the T allele increases the lactase promoter activity after binding transcription factors, while the binding capacity of the C allele is weak. Excellent correlations have been observed between this genotype and results of the lactose hydrogen breath test [7,8]. Nevertheless, some rare exceptions in Europe have been observed which might sometimes but not always, be attributable to difficulties in the diagnosis of lactose intolerance [9,10]. This polymorphism has been proposed to be used as a proxy for milk intake in a Mendelian randomization approach, to study the relationship between milk product intake and diseases [11–13]. However, this approach raises some problems [12], because milk product intake has been associated with the polymorphism in many studies [13–17] but not all [18], or only with a limited effect [11,19], and depends on many non-genetic factors. The LP genotype has been associated with a higher BMI in cross-sectional studies of European populations [16,19,20].This result was found in a meta-analysis of populations from northern Europe where LP is frequent [20], but also in southern Europe [16,19], where the LP frequency is lower. In the study by Corella et al. [19], the association was found only in those consuming more than 8 g lactose per day.

The LP genotype has sometimes been considered as a proxy for dairy intake; it has been associated with a lower BMI and sometimes with a lower frequency of BMI-related metabolic diseases. In the French D.E.S.I.R. (Data from the Epidemiological Study on the Insulin-Resistance syndrome) cohort, a high consumption of milk and dairy products was associated with a lower body weight gain in a 9-year follow-up, and with a lower incidence of impaired fasting glycemia (IFG) or type 2 diabetes (T2D) and/or the metabolic syndrome (MetS) [21]. The aim of this study was to test, in this population, 1) whether the LP genotype was associated with dairy intake; 2) whether and how this genotype was associated with BMI and related metabolic diseases; 3) since we suspect that an association of lactase non-persistence with a low BMI might be due to gastrointestinal problems when consuming dairy products [22], we hypothesized that such problems should be more noticeable in people consuming the highest amounts of dairy products, so we tested the interaction between the genotype and dairy product consumption.

2. Material and methods

2.1. Population

D.E.S.I.R. is a prospective study of 5212 subjects at inclusion (2576 men and 2636 women, aged 30 to 65 years), recruited from volunteers who were offered periodic health examinations free of charge by the French Social Security system in 10 health examination centres from the western part of France. They were clinically and biologically evaluated at 3-yearly visits and the final examination was 9 years after inclusion. Among these 5212 subjects from the D.E.S.I.R. study, 4619 Caucasians born in mainland France were genotyped for the rs4988235 (*LCT* -13910C > T). Among them, 3575 were present both at baseline (T0) and at the end of follow-up (T9), and these are the people we study in our analyses. The clinical and biological measurements have been extensively described in our previous papers [21,23]. Briefly, weight, height, and waist circumferences were measured by trained personnel. Venous blood samples were collected in the morning after subjects had fasted for 12 h. Systolic and diastolic arterial pressures were measured with a mercury sphygmomanometer adapted for arm size after 5 min of rest, with participants in a supine position. Two measures of blood pressure were taken, and means were used for the analysis. A detailed description of laboratory measurements including fasting triglycerides, HDL-C, glucose, and insulin is provided elsewhere [23].

T2D was defined as fasting plasma glucose ≥7 mmol/L or treatment by glucose lowering agents. IFG was defined as fasting plasma glucose between 6.1 and 6.9 mmol/L. In the present work, two definitions for the MetS were used. According to the IDF (International Diabetes Federation) [24], it was defined as waist circumference ≥94/80 cm for men/women plus two of the following factors: 1) triglycerides: ≥1.70 mmol/L or specific treatment for this lipid abnormality; 2) HDL cholesterol (HDL-C): ≤1.03 mmol/L for men and 1.29 mmol/L for women or specific treatment for this lipid abnormality; 3) blood pressure: ≥130/85 mmHg or treatment of previously diagnosed hypertension; 4) fasting glycemia ≥5.6 mmol/L or previously diagnosed T2D (treated by glucose lowering drugs and/or fasting glycemia ≥7.0 mmol/L). According to the NCEP-ATPIII [25], MetS was defined as three of the following factors: 1) waist circumference >102/88 cm for men/women; 2) triglycerides: ≥1.70 mmol/L; 3) HDL-C: ≤1.03 mmol/L for men and 1.29 mmol/L for women; 4) blood pressure: systolic blood pressure ≥130 or diastolic ≥85 mmHg; 5) elevated fasting glycemia ≥6.1 mmol/L. The 9-year prevalent cases of the MetS and/or IFG/T2D were defined as subjects with disease at any time during the follow-up.

A 23-item questionnaire was completed by each participant, to determine the frequency and level of consumption of different foods [21]. This questionnaire has been validated by comparison with the dietary history method, with at least 30 min interviews by trained dieticians. This validation study enabled the determination of multiple linear regression equations to estimate the main nutrient intakes from the questions on the consumption of different foods [26]. Two items concerned dairy products: milk and other dairy products (except cheese), cheese. There were four categories

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