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Role of rs9939609 FTO gene variant in weight loss, insulin resistance and metabolic parameters after a high monounsaturated vs a high polyunsaturated fat hypocaloric diets

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Abstract

Introduction: common polymorphisms (rs9939609) of the fat mass and obesity associated gene (FTO) have been linked to obesity.

Objectives: our aim was to investigate the role of this polymorphism on insulin resistance, metabolic changes and weight loss secondary to a high monounsaturated fat vs a high polyunsaturated fat hypocaloric diets.

Material and Methods: a sample of 233 obese subjects was enrolled in a prospective way. In the basal visit, patients were randomly allocated during 3 months to; Diet M (high monounsaturated fat hypocaloric diet) or Diet P (high polyunsaturated fat hypocaloric diet).

Results: after treatment with two diets and in both genotypes, weight, fat mass and waist circumference decreased. Lower levels of body mass index (BMI), weight and fat mass were detected after Diet P in A allele carriers than TT genotype subjects. With the diet type P and in both genotypes (TT and AT + AA), total cholesterol levels (-15.3 + 35.1 mg/dl vs. -11.6 + 32.1 mg/dl: p > 0.05) and LDL cholesterol levels (-11.5 + 34.1 mg/dl vs. -8.5 + 30.1 mg/dl: p > 0.05) decreased. In A allele carriers a significant decreased was detected in insulin levels (-2.8 + 2.1 UI/L vs. -1.3 + 8.0 UI/L: p < 0.05), too. With the diet M and in both genotype groups, leptin levels (-8.0 + 17.1 ng/ml vs. -4.9 + 18.7 ng/ml: p > 0.05) decreased.

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PAPEL DE LA VARIANTE DEL GEN FTO rs9939609 EN LA PÉRDIDA DE PESO, RESISTENCIA A LA INSULINA Y PARÁMETROS METABÓLICOS TRAS DOS DIETAS HIPOCALÓRICAS, RICAS EN GRASAS MONOINSATURADAS VS POLINSATURADAS

Resumen

Introducción: un polimorfismo común (rs9939609) del gen de la masa grasa y la obesidad (FTO) se ha relacionado con la obesidad.

Objetivos: nuestro objetivo fue investigar el papel de este polimorfismo en la resistencia a la insulina, los cambios metabólicos y la pérdida de peso secundarios a una dieta hipocalórica con alto contenido en grasas monoinsaturadas vs. una dieta hipocalórica con alto contenido en grasas poliinsaturadas.

Material y métodos: fue estudiada una muestra de 233 sujetos obesos de forma prospectiva. En la visita basal, los pacientes fueron asignados al azar durante tres meses a Dieta M (dieta hipocalórica con alto contenido en grasa monoinsaturada) o dieta P (dieta hipocalórica con alto contenido en grasas poliinsaturadas).

Resultados: después del tratamiento con las dos dietas y en ambos genotipos, la circunferencia de la cintura, el peso, la masa grasa y la cintura disminuyeron. Se detectaron niveles más bajos de índice de masa corporal (IMC), peso y masa de grasa después de la dieta P en los portadores del alelo A comparados con los sujetos de genotipo TT. Con la dieta P y en los dos genotipos (TT y AT + AA), los niveles de colesterol total (-15,3 + 35,1 mg/dl vs. -11,6 + 32,1 mg/dl: p > 0,05) y los niveles de colesterol LDL (-11,5 + 34,1 mg/dl vs. -8,5 + 30,1 mg/dl: p > 0,05) disminuyeron. En los portadores del alelo A se detectó una disminución significativa en los niveles de insulina (-2,8 + 2,1 UI/L vs. -1,3 + 8,0 UI/L: p < 0,05) y el índice HOMA-IR (-1,0 + 1,3 vs. -0,2 + 2,1: p > 0,05). Con la dieta M y en los dos genotipos, los niveles de leptina (-8,0 + 17,1 ng/ml vs. -4,9 + 18,7 ng/ml: p > 0,05) disminuyeron.
Introduction

Obesity and overweight are major public health problems that are estimated to affect a high percentage of the population and have been linked as risk factors for many common diseases. However, obesity has multiple causes and is determined by the interaction between genetic and environmental factors. Common polymorphisms of the fat mass and obesity associated gene (FTO) have been linked to obesity in some populations. One of these genetic variants (rs9939609) has been related to an increased risk for both obesity and type 2 diabetes mellitus.

The exact function of FTO gene could affect body mass index (BMI) is not clear, possible role in determination of energy expenditure or energy intake were suggested. Moreover, the effect of FTO variants on body weight response after dietary intervention remains unclear. Some of the studies are based on cross-sectional data and evaluate relationship between lifestyle influences and the rs9939609 DNA variant on body weight changes. Few intervention studies have explored the interaction between dietary intervention and FTO gene variant on adiposity indices or metabolic parameters. Two studies performed on obese subjects with diabetes mellitus did not find any association. Moreover, Razquin et al. showed that, although at baseline the A allele was associated with higher body weight, after 3 years of nutritional intervention with a Mediterranean-style diet, A-allele carriers had lower body weight gain than wild type subjects. In other study, carriers of the risk allele had a greater reduction in weight in response to 2-year high-protein diet. Other interventional study during 3 months with a low fat hypocaloric diet showed a better metabolic improvement secondary to weight loss in A carriers. The AA genotype was associated with a higher initial body weight and did influence success of weight stabilization during 40 weeks.

In attempting to understand the influential role of rs9939609 DNA variant, we decide to investigate the role of this polymorphism on insulin resistance, metabolic changes and weight loss secondary to a high monounsaturated fat vs a high polyunsaturated fat hypocaloric diets in obese subjects.

Subjects and methods

Subjects

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the Hospital Universitary Rio Hortega ethics committee. A sample of 233 obese subjects was enrolled in a prospective way. These patients were recruited in a Nutrition Clinic Unit. All participants provided informed consent. Inclusion criteria were body mass index > 30. Exclusion criteria included history of cardiovascular disease or stroke during the previous 24 months, total cholesterol > 200 mg/dl, triglycerides > 250 mg/dl, blood pressure > 140/90 mmHg, fasting plasma glucose >110 mg/dl, as well as the use of sulphonylurea, thiazolidinedions, insulin, glucocorticoids, antineoplastic agents, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and psychoactive medications.

Procedure

Patients were randomly allocated to one of two diets for a period of three months. Diet M (high monounsaturated fat hypocaloric diet) consisted in a diet of 5614.9 kJ with the next distribution of percentage of macronutrients: 46.6% of carbohydrates, 34.1% of lipids and 19.2% of proteins. The distribution of fats was; 21.7% of saturated fats, 67.5% of monounsaturated fats and 10.8% of polyunsaturated fats. Diet P (high polyunsaturated (PUFAs) fat hypocaloric diet) consisted in a diet of 6104.5 kJ, 45.7% of carbohydrates, 34.4% of lipids and 19.9% of proteins. The distribution of fats was; 21.8% of saturated fats, 55.5% of monounsaturated fats and 22.7% of polyunsaturated fats.
fats (7 g per day of w-6 fatty acids, 2 g per day of w-3 fatty acids and a ratio w6/w3 of 3.5) The exercise program consisted of an aerobic exercise at least 3 times per week (60 min each). The adherence of these diets was assessed each 7 days with a phone call by a dietitian in order to improve compliance of the calorie restriction and macronutrient distribution. National composition food tables were used as reference13.

Fasting glucose, c-reactive protein (CRP), insulin, insulin resistance (HOMA index), total cholesterol, LDL-cholesterol, HDL-cholesterol, plasma triglycerides concentration and adipokines (leptin, adiponectin, resistin, TNF alpha, and interleukin 6) levels were measured at basal time and three months after dietary intervention. Weight, height, fat mass by tetrapolar bioimpedance and blood pressure measures were realized at the same times. Genotype of rs9939609 FTO gene polymorphism was studied.

**Weight and anthropometric measurements**

Body weight was measured to an accuracy of 0.5 Kg and body mass index computed as body weight/(height²). Waist (narrowest diameter between xiphoid process and iliac crest) and hip (widest diameter over greater trochanters) circumferences to derive waist-to-hip ratio (WHR) were measured, too. Tetrapolar body electrical bioimpedance was used to determine body composition with an accuracy of 5 g14. An electric current of 0.8 mA and 50 kHz was produced by a calibrated signal generator (Biodynamics Model 310e, Seattle, WA, USA) and applied to the skin using adhesive electrodes placed on right-side limbs. Blood pressure was measured twice after a 10 minutes rest with a simple mercury sphygmomanometer, and averaged.

**Biochemical Assays**

Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, Ltd., New York, N.Y., USA), while HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate-magnesium. LDL cholesterol was calculated using Friedewald formula. CRP was measured by immunoturbimetry (Roche Diagnostics GmbH, Mannheim, Germany), with a normal range of 0-7 mg/dl and analytical sensivity 0.5 mg/dl.

Plasma glucose levels were determined by using an automated glucose oxidase method (Glucose analyser 2, Beckman Instruments, Fullerton, California). Insulin was measured by RIA (RIA Diagnostic Corporation, Los Angeles, CA) with a sensitivity of 0.05mUI/L (normal range 0.5-30 mUI/L) and the homeostasis model assessment for insulin sensitivity (HOMA index) were calculated using these values15. Leptin was measured by ELISA (Diagnostic Systems Laboratories, Inc., Texas, USA) with a sensitivity of 0.05 ng/ml and a normal range of 10-100 ng/ml16. Adiponectin was measured by ELISA (R&D systems, Inc., Mineapolis, USA) with a sensitivity of 0.246 ng/ml and a normal range of 2.07-24.3 ng/ml17. Interleukin 6 and TNF alpha were measured by ELISA (R&D systems, Inc., Mineapolis, USA) with a sensitivity of 0.7 pg/ml and 0.5 pg/ml, respectively. Normal values of IL6 were (1.12-12.5 pg/ml) and TNF-alpha (0.5-15.6 pg/ml)18.

**Genotyping of rs9939609 FTO gene polymorphism**

Oligonucleotide primers and probes were designed with the Beacon Designer 5.0 (Premier Biosoft International19, LA, CA). The polymerase chain reaction (PCR) was carried out with 50 ng of genomic DNA, 0.5 ul of each oligonucleotide primer (primer forward: 5’-GGCTCTTGAATGAATAGG-3’ and reverse 5’-GACTGTTACATTTAACTTTAG-3’) and 0.25 uL of each probes (wild probe: 5’-Fam-AGTGCATCACAAATTCACAGC-BHQ-2-3’ and (mutant probe: 5’-Texas red-AGTGCATCACAAATTCACAGC-BHQ-2-3’) in a 25 uL final volume (Termociclador iCycler IQ (Bio-Rad®), Hercules, CA). DNA was denatured at 95°C for 3 min; this was followed by 45 cycles of denaturation at 95°C for 15 s, and annealing at 59.3°C for 30 s. The PCR were run in a 25 uL final volume containing 12.5 uL of IQTM Supermix (Bio-Rad®), Hercules, CA) with hot start Taq DNA polymerase. Hardy Weinberger equilibriuim was assessed.

**Statistical analysis**

Sample size were calculated to detect differences between 2 groups by genotype in each of 2 groups by diet, with 90% power and 5% significance (n=110, in each diet group). The results were expressed as average+/standard deviation. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables were analyzed with a 2-way ANOVA model. In this model, we have introduced covariates such as age, sex, BMI , variation of BMI, menopausal status and decrease of energy intake. Qualitative variables were analyzed with the chi-square test, with Yates correction as necessary, and Fisher’s test. A Chi square test was used to evaluate the Hardy–Weinberg equilibrium. Non-parametric variables were analyzed with the Wilcoxon test. The statistical analysis was performed for the combined TA and AA as a group (mutant group) and wild type TT as second group, with a dominant model. A p-value <0.05 was considered significantly.

**Results**

Two hundred and thirty three patients gave informed consent and were enrolled in the study. The mean
Anthropometric characteristics of participants at baseline and at month 3 of intervention are shown in table I. With the diet type M (high monounsaturated fat hypocaloric diet) and in both genotype groups (TT vs AT+AA), body mass index (BMI) (-1.5+1.2 kg/m² vs -1.7+1.8 kg/m²; p>0.05), weight (-3.4+2.9 kg vs -4.2+4.8 kg; p>0.05), fat mass (-2.6+3.2 kg vs -3.4+3.4 kg; p>0.05) and waist circumference (-5.2+5.8 cm vs -4.3+4.5 cm; p>0.05) decreased. There were no significant differences between the effects (on weight, BMI, waist circumference, fat mass) in either genotype group. With the diet type P (high polyunsaturated fat hypocaloric diet) and in both genotypes, BMI (-1.7+1.6 kg/m² vs -1.9+1.6 kg/m²; p>0.05), weight (-3.0+3.3 kg vs -4.7+3.6 kg; p>0.05), fat mass (-2.9+4.4 kg vs -4.3+3.7 kg; p>0.05) and waist circumference (-3.2+2.8 cm vs -3.3+3.7 cm; p>0.05) decreased. There were significant differences between the effects (on weight, BMI and fat mass) in either genotype group with diet P. Lower levels of BMI (-1.1+1.2 kg/m² vs -2.0+1.4 kg/m²; p>0.05), weight (-2.0+2.1 kg vs -5.1+3.9 kg; p>0.05) and fat mass (-3.0+2.8 kg vs 4.2+2.9 kg; p>0.05) were detected after Diet P in A allele carriers than TT genotype subjects.

Table II shows the biochemical parameters. With the diet type M and in both genotype group, no significant changes were detected before weight loss. With the diet type P and in both genotypes (TT and AT+AA), total cholesterol levels (-15.3+35.1 mg/dl vs -11.6+32.1 mg/dl; p>0.05) and LDL cholesterol levels (-11.5+34.1 mg/dl vs -8.5+30.1 mg/dl; p>0.05) decreased. There were no significant differences between the effects on lipid parameters with diet P in either group. In A allele carriers a significant decreased was detected in insulin levels (-2.8+2.1 UI/L vs -1.3+8.0 UI/L; p>0.05) and HOMA index (-1.0+1.3 vs -0.2+2.1; p>0.05) without a statistical effect in subjects with TT genotype. No differences were detected among basal and post-treatment values of biochemical variables between both genotypes.

Table I

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DIET M</th>
<th>DIET P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TT (n=36)</td>
<td>TA or AA (n=83)</td>
</tr>
<tr>
<td></td>
<td>0 time</td>
<td>At 3 months</td>
</tr>
<tr>
<td>BMI (kg)</td>
<td>36.7 (5.6)</td>
<td>35.2 (5.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93.6 (14.6)</td>
<td>90.2 (13.7)</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>39.8 (10.5)</td>
<td>37.2 (10.1)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>113.1 (14.6)</td>
<td>107.9 (15.5)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.90 (0.07)</td>
<td>0.89 (0.06)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>127.9 (14.8)</td>
<td>123.3 (11.7)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.4 (8.5)</td>
<td>80.4 (4.1)</td>
</tr>
</tbody>
</table>

DBP: Diastolic blood pressure. SBP: Systolic blood pressure. WHR: Waist to hip ratio. WC: Waist circumference. (*) p<0.05, between genotypes in each diet. No statistical differences between genotypes in different diet groups.
Table II
Changes in metabolic parameters (mean S.D.)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DIET M</th>
<th>DIET P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TT (n=36)</td>
<td>TA or AA (n=83)</td>
</tr>
<tr>
<td></td>
<td>0 time</td>
<td>At 3 months</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>98.6 (10.2)</td>
<td>97.1 (11.5)</td>
</tr>
<tr>
<td>Total ch. (mg/dl)</td>
<td>206.3 (31.8)</td>
<td>199.2 (34.1)</td>
</tr>
<tr>
<td>LDL-ch. (mg/dl)</td>
<td>121.1 (27.1)</td>
<td>117.0 (12.9)</td>
</tr>
<tr>
<td>HDL-ch. (mg/dl)</td>
<td>56.7 (12.1)</td>
<td>55.4 (13.5)</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>130.1 (53.1)</td>
<td>134.9 (50.4)</td>
</tr>
<tr>
<td>Insulin (mUI/L)</td>
<td>14.8 (9.1)</td>
<td>14.7 (8.1)</td>
</tr>
<tr>
<td>HOMA index</td>
<td>3.9 (2.8)</td>
<td>3.8 (2.3)</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>5.2 (4.3)</td>
<td>4.7 (3.7)</td>
</tr>
</tbody>
</table>

Chol: Cholesterol. Lp (a): lipoprotein a. TG: Triglycerides CRP: c reactive protein. HOMA index: Homeostasis model assessment. (*) p<0.05, in each group with basal values. No statistical differences between genotypes in each diet or in different diet groups.

Discussion

Our results showed an association between the FTO variant rs9939609 and weight loss after a high polyunsaturated fat hypocaloric diet. Also, a relationship between the type of the hypocaloric diets and metabolic changes secondary to weight loss was observed.

The results of different type of studies with this polymorphism of FTO gene have shown inconsistent data. There are some cross-sectional studies confirming the association19-20, but there is contradictory information about the influence of lifestyle factors on this association in intervention studies6-12. For example, Razquin et al11 reported that, after 3 years of nutritional intervention with a Mediterranean-style-diet, A-allele carriers had lower body weight gain than wild type subjects. In other study10, carriers of the A allele had a greater reduction in weight in response to 2-year high-protein diet, whereas an opposite genetic effect was observed on changes in fat distribution in response to a low-protein diet. In other interventional study11 during 3 months with a low fat hypocaloric diet showed a better metabolic improvement secondary to weight loss in A carriers. In this previous study11, the improvement of insulin levels and HOMA index was statistically significant in TT subjects with both interventional diets (low fat vs low carbohydrate) and only in A allele participants with low fat diet. Moreover, in this last group, total cholesterol, LDL cholesterol and C reactive proteins levels decreased, too. On the other hand, leptin levels decreased more in A allele carriers group secondary to a low fat diet than in TT genotype with both diets and in A allele carriers with the low carbohydrate diet, too11. However, a contradictory effect on HOMA index has been detected in other study11, participants with TT showed the greatest reduction in HOMA-R. In other interventional trial12, the AA genotype was associated with a higher initial body weight and did influence success of weight stabilization during 40 weeks, no metabolic effects were reported. In other study, a trend towards lower weight loss was observed for AA carriers in a young population with a mean age of 10 years19. Finally, a surgical study with bariatric procedure22 has shown a higher initial weight loss at 3 months in TT genotype carriers of rs9939609 DNA variant. However, the weight loss at 9 and 12 months of bariatric surgery was similar in both genotypes with a significant improvement in biochemical parameters and cardiovascular comorbidities.

Our present finding suggests that having a hypocaloric diet (high monounsaturated (M) or high polyunsaturated (P) hypocaloric diet) is beneficial for both groups of subjects (TT or AT+AA genotype) of the rs9939609 DNA variant. However, A allele carriers showed the greatest reduction of weight with an additional improvement of HOMA index, insulin and leptin levels after P diet. These different results in weight loss in the literature could be secondary to the duration and style of dietary intervention in the protocols or differences on background characteristics in the study populations (basal weight, sex distributions, average age and so on). Some specific reasons could explain
these contradictories results. Firstly, the distribution of macronutrients in the prescribed diets and the type of dietary fat may influence on secondary metabolic responses and weight loss. For example, distribution of macronutrients and percentage of dietary fat were not reported in some study9,10,12. In other study11, low fat diet had the next distribution of macronutrients; 53% carbohydrates, 27% fats and 20% proteins) and the percentage of polyunsaturated fatty acids was around 18%, a percentage close to that used in our study and percentage of dietary fat may influence on secondary metabolic responses to weight loss. Moreover, there are investigations reporting the relationship between FTO mRNA expression and metabolic changes secondary to weight loss was observed. Metabolic improvement was better in A carriers with a weight loss secondary to a P hypocaloric diet.

The presence of other types of polymorphisms in FTO gene could be explained these inconsistent results, too. For example, a recent study have demonstrated that in overweight healthy females, FTO gene variants (rs17817449 and rs17818902) have no effect on BMI and cardiovascular risk factors over time of short lifestyle intervention19.

The most relevant data of our study is that changes in the dietary fat composition secondary to a hypocaloric diet may interact with the polymorphism and confer to A allele carriers some advantages to body weight loss. Moreover, there are investigations reporting associations of dietary fat with some gene variants23-24. In our study, the improvement of insulin levels and HOMA index was statistically significance only in A allele carriers with diet P. Moreover, in this last group, total cholesterol and LDL cholesterol levels decreased, too. On the other hand, leptin levels decreased more in this group secondary to weight loss with the same diet (P) than in TT genotype. This better metabolic result in A allele carriers with diet P could be secondary to an interaction of the macronutrient distribution of the diet with the A variant of this FTO SNP or could be due to the greatest weight loss of this group. Interestingly, an interaction between rs9939609 and insulin sensitivity has been described, too. A study found that insulin sensitivity was significantly decreased in homozygous carriers (AA) and that the impact of the rs9939609 DNA variant on BMI levels was highly influenced by insulin sensitivity25. The biological function of FTO is largely unknown. However, FTO could be related with a lot of metabolic pathways. Some studies have confirmed the relationship between FTO mRNA expression and expression of the proinflammatory molecules serum leptin14, CRP26, adiponectin27 and TNF-alpha28.

In conclusion, our design showed an association between the rs9939609 DNA variant and weight loss after a high polyunsaturated fat hypocaloric diet. Also, an interaction with the type of the hypocaloric diets and metabolic changes secondary to weight loss was observed. Metabolic improvement was better in A carriers with a weight loss secondary to a P hypocaloric diet.

**Table III**

| Characteristics | DIET M | | DIET P | | |
|-----------------|-------|-----|-------|-----|
|                 | TT (n=36) | TA or AA (n=83) | TT (n=28) | TA or AA (n=86) |
| IL 6 (pg/ml)    |       |     |       |     |
| 0 time          | 1.4 (0.9) | 1.3 (2.8) | 0.9 (1.0) | 0.8 (1.7) |
| At 3 months     | 1.2 (3.1) | 1.0 (3.1) | 2.7 (4.1) | 2.4 (3.2) |
| TNF-α (pg/ml)   |       |     |       |     |
| 0 time          | 1.4 (0.9) | 1.7 (1.3) | 1.6 (1.1) | 1.8 (2.1) |
| At 3 months     | 1.9 (3.1) | 1.8 (2.3) | 2.7 (2.5) | 2.9 (1.5) |
| Adiponectin (ng/ml) | 10.6 (6.9) | 10.1 (5.7) | 11.4 (6.6) | 10.5 (4.1) |
| 0 time          | 10.6 (5.8) | 10.0 (6.1) | 11.3 (6.6) | 10.4 (7.3) |
| Leptin (ng/ml)  |       |     |       |     |
| 0 time          | 44.8 (24.4) | 36.6 (33.1) | 36.3 (30.2) | 31.7 (28.1) |
| At 3 months     | 35.5 (27.6) | 31.3 (22.1) | 45.9 (35.1) | 36.2 (31.7) |

IL-6: interleukin 6. (*) p<0.05, in each group with basal values. No statistical differences between genotypes in each diet or in different diet groups.

**References**

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rs9939609 gene variant and two different hypocaloric diet


